CRANFIELD UNIVERSITY

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Glycaemic control: The role of nutritional intake, postprandial glycaemia, nutrition therapy adherence and diabetes complications

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Abstract

Introduction: A proper nutrition can contribute to adequate glucose control in patients with type 2 diabetes. The analysis of the association between glycaemia and socio-demographic characteristics, nutrition recommendations compliance and meal composition can contribute to the discussion of the optimal nutrition therapy for patients with type 2 diabetes.

Aims: This thesis analysed the associations between several clinical and psychometric variables that can determine glycaemic control: nutritional intake, barriers to nutrition therapy adherence, postprandial glycaemia, and diabetes complications perception.

Methods: A group of 66 patients previously diagnosed with type 2 diabetes mellitus was recruited and categorized into patients with HbA1c below 7% (proper glycaemic control) and patients with HbA1c of 7% or above (poor glycaemic control).

All subjects were interviewed and offered a nutritionally controlled breakfast. Glucose response to the experimental breakfast was monitored for 120 minutes after the meal.

Results: The results show that subjects with adequate glycaemic control have a better compliance of nutrition recommendations, but all patients have excess intakes of energy, total cholesterol, saturated fatty acids, and sugars.

There are no significant differences in postprandial glycaemia between patients with adequate glycaemic control and those with poor glycaemic control,

Patients with poor glycaemic control have a more biased opinion of their likelihood of personal disease risk.

Younger age, high body mass index, and biased personal disease risk perceptions are important predictors of glycaemic control.

Discussion: This work identified several determinants of glucose control and shows that some patients are unaware that they exceed the recommended rise in postprandial glucose, and thus may be at a higher than expected risk for macro and microvascular events.

Conclusions: As self-monitoring is the only practical way to detect postprandial hyperglycaemia, efforts should be made to promote regular glucose self-monitoring. Health professionals need to consider specific patient characteristics in order to provide proper continued medical care, and nutrition education should be structured and tailored to the perceptions of patients.

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Abbreviation

AADE:	American Association of Diabetes Educators
ACD:	Academy of Nutrition and Dietetics
ACES:	*Agrupamentos de Centros de Saúde*
ADA:	American Diabetes Association
AHEAD:	Action for Health in Diabetes
ANOVA:	One-Way Analysis of Variance
ATP:	Adenosine Triphosphate
BMI:	Body Mass Index
CCK:	Cholecystokinin
CI:	Confidence Interval
CVD:	Cardiovascular Disease
DAWN:	Diabetes Attitudes Wishes and Needs
DGS:	*Direção Geral de Saúde*
DRI:	Daily Recommended Intake
EASD:	European Association for the Study of Diabetes
ER:	Environmental Risk
ERS:	*Entidade Reguladora da Saúde*
FAO:	Food and Agriculture Organization
FFA:	Free Fatty Acids
GDM:	Gestational Diabetes *Mellitus*
GDP:	Gross Domestic Product
GI:	Glycaemic Index
GIP:	Glucose–Dependent Insulinotropic Peptide
GLP:	Glucagon-Like Peptides
GUIDANCE:	Guideline Adherence to Enhance Care
HbA1c:	Glycated Haemoglobin
IDF:	International Diabetes Federation
IFG:	Impaired Fasting Glucose
IGT:	Impaired Glucose Tolerance
IOM:	Institute of Medicine
IPAQ:	International Physical Activity Questionnaire
KATP:	ATP-sensitive potassium
M:	Mean
MET:	Metabolic equivalents
Mdn:	Median
NCI:	National Cancer Institute
NICE:	National Institute for Health and Clinical Excellence
OADA:	Oral Anti-Diabetic Agents
OB:	Optimistic Bias
OD:	Odds Ratio
OECD:	Organisation for Economic Co-operation and Development

OGTT:	Oral Glucose Tolerance Test
PD:	Personal Disease
PP:	Pancreatic Polypeptide
PPG:	Postprandial Glycaemia
PPHG:	Postprandial Hyperglycaemia
PREPARE:	Physical Activity Recommendation and Encouragement
RDA:	Recommended Dietary Allowances
RPS-DM:	Risk Perception Survey for Diabetes Mellitus
RR:	Relative Risk
SD:	Standard Deviation
SFA:	Saturated Fatty-Acids
SGLT2:	Sodium-Glucose Cotransporter 2
T2DM:	Type 2 Diabetes *Mellitus*
TCI:	Total Caloric Intake
TFA:	*Trans* Fatty-Acids
UK:	United Kingdom
UKPDS:	The UK Prospective Diabetes Study
UNESCO:	United Nations Educational, Scientific and Cultural Organization
VDL:	Very Low Density Lipoprotein Cholesterol
WC:	Waist Circumference
WtH:	Waist-To-Height
WHO:	World Health Organization
YPLL:	Years of Potential Life Lost

Chapter 1: Literature review

1.1. Background and significance

Osteoporosis, type 2 diabetes *mellitus* (T2DM), several types of cancer, and coronary disease are considered high-prevalent diseases, related with obesity and overweight (WHO/FAO 2003). There is a growing concern with the burden associated with these non-communicable diseases and T2DM may even be considered the greatest epidemic in human history, with over 190 million affected individuals worldwide and an estimated 300 million more with pre-diabetes (Zimmet 2005). The mortality attributed to diabetes in the year 2000 was around 2.9 million deaths (5.2% of all-causes mortality), placing diabetes as the fifth leading cause of death (Roglic et al. 2005). Diabetes is also responsible for 2-7% of the expense of health services in Western countries (ADA 2003a).

Treatment and prevention approaches for T2DM focus on achieving glycaemic control, in order to manage the disease and to prevent or slow down its complications. General management of diabetes consists of patient education, medical nutrition therapy, physical activity, and pharmacological therapy combined with oral hypoglycaemic agents or insulin (Nyenwe et al. 2011).

Recently, the role of postprandial glycaemia (PPG) in overall glycaemic control and as a risk factor for cardiovascular complications has been discussed, as patients with good glycaemic control can show elevated postprandial hyperglycaemia (PPHG). According to the American Diabetes Association (ADA), glycated haemoglobin (HbA1c) levels below or around 7% are associated with long-term reduction in macro-vascular disease (ADA 2013a), and a reasonable goal in HbA1c for T2DM adult patients is 7%. HbA1c reflects the average plasma glucose concentration over prolonged periods of time and a 2009 review (Peter et al. 2009) suggests that the relative contribution of PPG for the overall glycaemic control is around 70% in patients with HbA1c below 7.3%, independently of the timing of the meal during the day.

PPHG seems to be common in T2DM patients, even in those who are considered to have good overall glycaemic control, and achievement of target HbA1c and fasting plasma glucose levels does not necessarily indicate that good glycaemic control is continuous

throughout the day (Ceriello 2010). A meta-analysis by Coutinho and colleagues (Coutinho et al. 1999) reports an exponential relationship between the incidence of cardiovascular events and elevated glycaemia two hours after a meal, resulting in an increased mortality risk, that is also reported in a large European patient sample (Ning et al. 2010). A 2010 review (Ceriello 2010) suggests that PPG values one hour after breakfast are predictive of all-cause mortality and reports that PPHG is associated with increased cardiovascular risk, independent of fasting hyperglycaemia. This adds to the evidence indicating that PPG may be a more dominant cardiovascular risk factor than fasting hyperglycaemia.

The International Diabetes Federation (IDF) has developed specific clinical guidelines for PPG and recommends that two hour post-meal glucose levels are kept below 140 mg/dl (IDF 2007), and that the difference between pre-prandial and post-prandial glycaemia should normally be between 30 and 50 mg/dl (Slama et al. 2006). Furthermore, the management and treatment of T2DM must consider PPG (Tibaldi 2009), as its variations throughout the day and between different meals are influenced by the blood glucose level before the meal, the nature and quantity of carbohydrate consumed, or the anti-diabetic treatment (Ceriello 2010).

Although the goals and objectives for treating T2DM are known, their translation into a daily routine seems difficult. Studies that have evaluated adherence do dietary recommendations have shown poor results, especially those with T2DM patients (Thanopoulou et al. 2004; Toeller et al. 1996), who appear to have high intake of calories and saturated fat, accompanied by low intake of fibre (Rivellese et al. 2008). Self-reported adherence to treatment in T2DM is higher for pharmacological therapy than for a proper diet, even if weight loss trough diet and exercise also results in an improved glycaemic control (Vijan et al. 2005). Despite the recognized success of medical nutrition therapy, patients treated with diet alone, in a general practice setting, have significant rates of complications, and are less likely than those on medication to be adequately monitored (Julia and Pringle 2004). This can imply that compliance with dietary

recommendations can be improved in a general practice setting, and that patient education strategies should be assessed.

A proper patient education is something that needs to be addressed as to overcome barriers to chronic disease self-management (Jerant et al. 2005). Daly and collaborators, (Daly et al. 2009), identified the type and duration of diabetes, other illnesses or conditions, psychosocial factors, medication use, following of meal and exercise plans, and also glucose testing at home as factors that influence diabetes treatment and management. Research with a focus group design (Gazmararian et al. 2009) identified as barriers to diabetes care the emotional toll following diagnosis and the lifestyle changes needed to treat the disease. The same study also reports that patients fail to recognize the risks and consequences of a condition that is asymptomatic for most of its natural history, but believe that there is a lack of follow-up on patient education interventions (refresher courses and support group discussions, for example), and that different education modalities could be available.

The Diabetes Attitudes Wishes and Needs (DAWN) (Martha M Funnell 2006) and DAWN2 studies (Peyrot et al. 2013), which include a large international sample of patients and analysed psychosocial issues in diabetes and person-centred diabetes care, showed that patients with diabetes report low rates of self-management behaviours, especially for diet and exercise, allowing to conclude that there are still significant challenges in self-management, adherence, access to support and involvement in care. Results from these studies show that patient distress with the disease is common and interferes with self-management (Peyrot et al. 2005a). The DAWN2 study shows that patients report important prevalences of negative impact of diabetes in all life and lifestyle aspects investigated, ranging from 20.5% on relationship with family/friends to 62.2% on physical health. Only 48.8% of subjects had participated in diabetes educational programs to help manage the disease (Nicolucci et al. 2013).

Few studies have specifically examined the reasons for the low adherence to dietetic recommendations or examined how patients view dietary restrictions, but it is known that interventions aimed at improving patients ability to modify their diet need to

consider preferences and barriers when setting goals for treatment (UKPDS Study Group 1995b).

This knowledge, together with the multiple determinants of food intake make the case for the need of further research, in order to successfully translate the benefits of interventions in controlled research environment to individuals in the community (Vijan et al. 2005).

The health risks of poor diabetes care are well known by the scientific community, but the general population is yet to fully appreciate the hazards of this condition (Nyenwe et al. 2011). Assessing patients' characteristics and their motives and motivations to comply with nutrition therapy may offer some insight into the skills and adjustments needed to promote the adequacy of current nutrition therapy guidelines in a clinical, on the field, setting. Additionally, considering the effect of PPG in glycaemic control, the fact that it provides immediate feedback on the effect of foods and meals, and its role as a cardiovascular risk factor (Jovanovic 2009), an investigation analysing the associations between PPG and socio-demographic characteristics, nutrition recommendations compliance and meal composition, could contribute to the discussion of the optimal nutrition therapy in T2DM and to the design of strategies to reduce the burden of diabetic complications. A comparison of PPHG using a case-control design, with patients who believe they currently have achieved a good glycaemic control and patients who fall above the HbA1c cut point defined for this metabolic state, may help to understand the role of HbA1c in the education, counselling, and treatment of T2DM, and also to quantify the odds of achieving good glycaemic control based on different risk factors.

1.2. Overview of diabetes, insulin secretion and insulin action

Diabetes *mellitus* is a condition that encompasses a group of metabolic diseases characterized by hyperglycaemia (ADA 2013b). Its clinical features have been documented since antiquity, with records from around 1550 BC detailing references to a condition now believed to be diabetes *mellitus* (Sanders 2002). The term diabetes has been traced to Egypt, in 230 BC, when *Apollonius* of Memphis used the Greek word meaning siphon or "to pass through" to describe patients' symptoms. Around 150 AD, *Aretaeus* of Cappadocia provided a clinical description of a condition characterized by increased urine flow, thirst and weight loss, noting that the onset commonly followed acute illness, injury or emotional stress (Bilous et al. 2010). Although physicians in India, contemporary of *Apollonius* of Memphis, named this condition "*madhumeha*" or "honey urine" after observing that urine from patients attracted ants and flies, the term *mellitus*, from the Greek and Latin for honey, was only firmly established after 1769, on account of an elaborate classification on human diseases published by William Cullen, a British physician. This was the first time a distinction was made between "diabetes *mellitus*", which was applied to cases were the urine presented sweet smell and flavour, and "diabetes *insipidus*", applied to cases with limpid but not sweet urine (Bilous et al. 2010; Sanders 2002).

Currently, diabetes *mellitus* is considered a heterogeneous multi-etiologic disorder, characterized by chronic hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism, caused by pathophysiological mechanisms linked to insulin synthesis, insulin metabolic regulation or both (ADA 2013b).

Insulin is a hormone synthesised within the β-cells of the islets of Langerhans in the endocrine part of the pancreas and is essential for the regulation of carbohydrate and fat metabolism. Carbohydrate metabolism plays a major role in energy production and glucose, a monosaccharide naturally occurring in its D-form and metabolized by nearly all known organisms, is considered the most important carbohydrate. Glucose and fat (in the form of fatty acids) can provide energy for all the body's needs (Holt et al. 2011).

Glucose comes directly from food intake by breakdown of glycogen in the liver, or by the formation of glucose in the liver and kidneys, from other carbon compounds such as lactate, pyruvate, amino acids, or glycerol. Although glucose is used by all cells, free fatty acids act as the main fuel for most organs, due to the greater energy yield potential of fatty acids: when oxidized, one gram of fatty acids produces approximately nine kilocalories, while the same weight in carbohydrate produces approximately four kilocalories. The brain constitutes the exception to this fuel predominance, as glucose serves as the only metabolic fuel for this organ under normal physiologic conditions. The brain's inability for synthesizing glucose or to store more than a relatively small amount of glycogen, together with the limitations of transport across the blood-brain barriers and with the low circulating concentration of alternative substrates, signify that a continuous supply of glucose is needed to maintain normal organ function (Szablewski 2011).

Glucose is extremely important in muscle cells, as its conversion into energy is faster than energy production from fatty acids; this can account for the need for a steady concentration of glucose, managed by a process of glucoregulation that aims to maintain glycaemic homeostasis. Homeostatic arterial glucose levels is achieved by a regulatory mechanism involving insulin, that acts in skeletal muscle, adipose tissue, and liver, promoting uptake and storage of carbohydrate, fat, and amino acids, while simultaneously antagonizing the catabolism of these nutrients (Holt et al. 2011).

In skeletal muscle, insulin induces glucose transport and glycogen storage, as well as glycolysis and tricarboxylic acid cycle activity. In the liver, insulin lowers glucose output by inhibiting glycogenolysis and gluconeogenesis, and also promotes glycogen synthesis. In adipocytes, insulin promotes glucose uptake, glycerol synthesis, and triglyceride formation (Holt et al. 2011).

In healthy individuals, glucose homeostasis maintains glycaemia at an average of approximately 90 mg/dl within a 24h period, with a maximal concentration usually not exceeding 165 mg/dl, after a meal. A decrease in plasma glucose to around 70 mg/dl will signal for the suppression of insulin release and will also lead to a decrease in glucose

uptake in certain areas in the brain where glucose sensors are located; this, in turn, will activate the release of counter regulatory hormones. Conversely, a 10 mg/dl increment in plasma glucose will stimulate insulin release. Glycaemia below 55 mg/dl impairs cerebral function, while more severe and prolonged hypoglycaemia causes convulsions, permanent brain damage, and even death (Szablewski 2011).

The regulatory neuro-hormonal system depends on adequate insulin secretion, controlled by the function of the islets of Langerhans in the pancreas. The β-cells in this organ detect changes in circulating nutrients and respond by initiating an insulin secretory response.

The pancreas is mainly an exocrine gland, responsible for the secretion of digestive enzymes, but its endocrine part regulates nutrient homeostasis and metabolism. The endocrine portion of the pancreas accounts for approximately 2% of the total organ's mass and comprises approximately two million clusters of cells of at least four types: α-cells, β-cells, δ-cells, and pancreatic polypeptide (PP) cells. These cells can be classified by their secretion: α-cells secrete glucagon, β-cells secrete insulin, δ-cells secrete somatostatin, and PP cells secrete pancreatic polypeptide (Shrayyef and Gerich 2010).

Insulin is synthesized only within the β-cells and consists of two polypeptide chains linked by disulfide bonds. It regulates carbohydrate and fat metabolism by direct and indirect actions, in order to maintain nutrient homeostasis. Insulin, through binding to its receptors in the liver, kidney, muscle, and adipose tissue, enables a signalling pathway which involves a number of protein kinases and regulatory proteins and causes suppression of glucose release from the liver and kidneys, the translocation of glucose transporters in muscle and adipose tissue to increase their glucose uptake, and the inhibition of free fatty acids (FFA) release due to the suppression of lipase activity and a simultaneous increase in their clearance. Insulin also promotes glycogen accumulation by inhibiting glycogenolysis and stimulating glycogen synthase, the key enzyme in glycogen synthesis. Besides these actions, glucose levels are also lowered by the suppression of glucose output from the liver through inhibition of gluconeogenesis,

which has an effect on circulating FFA levels, since FFA promote gluconeogenesis and reduce glucose transport into the cells (Gerich 2000).

Insulin secretion is characterized by dephosphorylation and phosphorylation that, in specific sites, create recognition domains that will allow the formation of multimolecular complexes. At the same time, scaffolding or adaptor proteins are formed that target enzymes to specific intracellular locales where critical substrates reside (Shrayyef and Gerich 2010).

Insulin secretion occurs in two phases – a fast first secretory response, lasting for about 10 minutes, in which insulin secretion rises rapidly, followed by a prolonged and steady secretion second phase, that lasts for as long as the blood glucose remains elevated. The first phase involves the plasma membrane fusion of a readily releasable pool of insulin granules that discharge their contents in response to nutrient and non-nutrient secretagogues. Second-phase secretion is promoted exclusively by nutrients, mainly glucose, directed into β-cells by transporters (GLUT 1, GLUT 2 and GLUT 3) that enable an equilibrium between extracellular and intracellular concentrations. In the cells, glucose is phosphorylated by glucokinase, which modulates insulin secretion to the glucose levels (Holt et al. 2011). Glycolysis and mitochondrial metabolism produce adenosine triphosphate (ATP), which closes ATP-sensitive potassium (KATP) channels. This, in turn, causes depolarization of the β-cell plasma membrane, which leads to an influx of extracellular calcium that triggers granule translocation and exocytosis (Ciaraldi 2010). Glucose levels below 5 mmol/L (90 mg/dL) do not affect insulin release and glucose must be metabolised within the β-cell to stimulate secretion (Szablewski 2011).

When there is no extracellular glucose, the β-cell membrane potential is maintained in potassium equilibrium by the efflux of potassium ions through ATP sensitive potassium channels. The presence of ATP in the cytosolic surface of β-cell membrane result in rapid, reversible inhibition of resting membrane permeability to potassium ions. ATP generation following glucose metabolism, along with lowering ADP levels, leads to closure of the ATP sensitive potassium channels which promotes depolarization of the β-cell membrane and influx of calcium ions. The increase of calcium ions starts the

insulin secretory response, with the exocytosis of insulin secretory granules. Intracellular calcium is a principal effector of the nutrient induced insulin secretory response, linking depolarization with exocytosis of insulin secretory granules. Elevations in intracellular calcium are sufficient to initiate insulin secretion, and conditions that elevate intracellular calcium usually stimulate insulin release. Conversely, preventing calcium influx by removal of extracellular calcium or by pharmacologic blocking calcium channels inhibits nutrient induced insulin secretion (Codario 2010; Holt et al. 2011).

Insulin secretion is mainly determined by the concentration of nutrients in plasma, mainly glucose, but some amino acids, such as leucine, lysine and arginine, can stimulate insulin secretion in the absence of glucose (Szablewski 2011). Leucine enters islets by a sodium independent transport system and affects β-cell membrane potential and ion fluxes, resulting in an insulin secretion similar to those of glucose, albeit in a smaller scale. Lysine and arginine cross the β-cell plasma membrane via a specific transport system for cationic amino acids and is believed that the accumulation of these positively charged molecules directly depolarizes the β-cell membrane, leading to a calcium influx (Holt et al. 2011).

Insulin secretion in response to nutrient concentrations can be enhanced or inhibited by the action of several neurotransmitters and different hormones. Islets are innervated by cholinergic, adrenergic and peptidergic autonomic nerves and it is know that the autonomic innervation of the islets is important in regulating insulin secretion. An increased insulin output follows the activation of parasympathetic nerves and decreased insulin secretion follows increased sympathetic activity (Codario 2010).

The autonomic nervous impact on hormone secretion is thought to be involved in insulin secretion during feeding, in coordinating islets to generate oscillations of hormone secretion, and in the regulation of secretory responses to metabolic stress. The parasympathetic nerve fibres that innervate islets are postganglionic, and acetylcholine, the major postganglionic parasympathetic neurotransmitter, stimulates the release of insulin and glucagon. In β-cells, acetylcholine ultimately amplifies the effects of glucose by elevating cytosolic calcium and activating the enzyme protein kinase C. Acetylcholine

also depolarizes the plasma membrane by affecting sodium ions' conductivity, causing an increase in cytosolic calcium (Opara 2005).

Islets also have an extensive sympathetic innervation, and norepinephrine, the major sympathetic neurotransmitter, has both secretion stimulatory (due to β_2-adrenoreceptors) and inhibitory effects (via α_2-adrenoreceptors), depending on the relative levels of expression of the receptor subtypes (LeRoith et al. 2004).

Pancreatic islets have a complex innervation and capillary network, receiving signals from other hormones and allowing islets to integrate the hormonal response and function as a coordinated secretory unit. The influence of other islet endocrine cell secretions has been studied and it is known that glucagon, a peptide hormone secreted by pancreatic α-cells, and somatostatin, secreted by δ-cells, have important effects on insulin secretion. The physiologic action of pancreatic polypeptide, which is the secretion of the fourth type of islet cell, is not completely know, although PP levels seem to rise after a meal composed of mixed nutrients, and its secretion is often elevated in patients with pancreatic tumours (Holt et al. 2011).

Glucagon acts almost exclusively in the liver and plays an opposite role to insulin in glucose and nutrient homeostasis, promoting catabolism and making energy available to tissues when nutrients from food are less available. Glucagon activates adenylate cyclase, resulting in an intracellular cAMP increase, enhancing glycogenolysis as a result of phosphorylase stimulation. This response diminishes after several hours and is followed by an increase in gluconeogenesis. In the liver, a low insulin to glucagon ratio signals energy utilization, resulting in glycogenolysis, gluconeogenesis, and fatty acid oxidation (Giugliano et al. 2008). Glucagon is a potent stimulator of hepatic glucose production and its secretion is influenced by hypoglycaemia, by sympathetic nervous input, by cholecystokinin secretion and by the presence of arginine and alanine (Ramnanan et al. 2011).

The glucagon precursor, proglucagon, produces several peptides with different receptors and biologic activities. Among these, two glucagon-like peptides (GLP-1 and GLP-2) are identified. GLP-1 is produced in intestinal L-cells by cleavage of proglucagon

and secreted in response to carbohydrates, lipids and protein in the intestinal lumen. GLP-1 stimulates production and secretion of insulin and somatostatin, and inhibits glucagon (Szablewski 2011).

GLP-2 is produced by the same process that results in GLP-1 and promotes growth of the intestinal mucosa and nutrient absorption, while inhibiting motility in the intestine.

GLP-1 in classified as an incretin, referring to a group of intestinally secreted peptides released in response to the presence of nutrients, which enhance glucose-stimulated insulin secretion (Amori Re 2007).

GLP-1, glucose–dependent insulinotropic peptide (GIP), and cholecystokinin (CCK) were identified as the main incretins associated with an elevated insulin response to nutrients after food intake and, currently, it is know that GIP is released from K-cells in the duodenum and jejunum in response to the absorption of glucose, to other actively transported sugars, amino acids, and long-chain fatty acids. Although GLP-1 and GIP both enhance insulin output, GIP stimulates glucagon secretion and inhibits GLP-1 release. CCK is released in the gastrointestinal tract in response to fat and protein but its role in insulin secretion has not been completely explained due to the fact that high concentrations are required to assess its effects, and it is possible that its main function is in digesting nutrients in the duodenum (Rijkelijkhuizen et al. 2010).

As stated, homeostatic regulation of body energy primarily involves insulin actions in skeletal muscle, adipose tissue, and liver. Generally, insulin promotes carbohydrate, fat and amino acid uptake and storage at the same time it antagonizes catabolism. Insulin promotes glycogen synthesis in muscle, adipocytes, and liver by activating glycogen synthase, which adds activated glucosyl groups to growing polysaccharide chains, enhancing the final step in glycogen synthesis (Szablewski 2011). Nonetheless, tissue-specific insulin action occurs, mainly due to different expression of effector systems in target cells (Holt et al. 2011).

In skeletal muscle, which accounts for the majority of glucose uptake, insulin stimulates the glucose transport effector system, promoting glucose storage as glycogen, as well

as promoting glycolysis and tricarboxylic acid cycle. Glucose transport proteins allow the creation of pores in cell membranes that allow for facilitative diffusion of monosaccharides, although each of the identified transporter isoforms has a specific role in glucose metabolism, determined by physiologic conditions and by substrate specificity and affinity (Szablewski 2011).

In the liver, insulin lowers glucose output through modifications of enzymes, such as phosphorylation, and through changes in gene expression; hepatic metabolism inhibits glycogenolysis and gluconeogenesis and enhances glycogen synthesis, all of which determine glucose output (Holt et al. 2011).

Insulin augments availability of both glycerol and fatty acids for triglyceride synthesis and activates lipogenic and glycolytic enzymes. This means that, in adipocytes, insulin promotes glucose uptake, glycerol synthesis, and triglyceride formation, while at the same time having an antilipolytic effect. Lipolysis in adipose tissue is regulated to assure that metabolic fuels are adapted to energy needs so that, during fasting, lipolysis is enhanced to allow that FFA will be available for oxidative fuel for the liver, the heart, and skeletal muscle. FFA are metabolized by the liver into ketones that replace glucose as the main fuel for the nervous system tissue. After nutrient intake, lipolysis is decreased and adipocytes store triglycerides, regulated by the antilipolytic action of insulin in adipose tissue (Opara 2005).

The final responses in insulin action are directed at glucose transport and glycogen synthesis, while glucose entry into the primary insulin target tissues occurs by facilitated diffusion, mediated by the glucose transport proteins. The most important transporters with regard to insulin action appear to be GLUT1 and GLUT4. GLUT1 exists in all target tissues, residing primarily on the cell surface, and GLUT4 exists in some intracellular vesicles present in adipose tissue and cardiac and skeletal muscles. There is a recycle of GLUT4 between the plasma membrane and intracellular vesicles and insulin increases the rate of GLUT4 exocytosis at the same time transporter endocytosis is slowed (Bilous et al. 2010; Ciaraldi 2010).

The tissue selectivity of insulin responsiveness is modulated, in large part, by cell-specific expression of different elements of the signalling pathways or of final effectors. Despite this, there are several principles in the organization of insulin action. These principles include the phosphorylation/dephosphorylation cascades initiated by the insulin receptor kinase, the formation of multimolecular complexes involving specific recognition domains on adapter proteins, and the targeting of signalling and effector molecules to appropriate intracellular locales. Impaired insulin action in diabetes most often involves defects in insulin receptor kinase and kinase activation but it is unlikely that mutations in individual elements of insulin signalling are responsible for the majority of instances of insulin resistance (Bilous et al. 2010).

Each of the elements involved in insulin action can represent a site of possible defects that lead to insulin-resistant states, which can be caused by alterations in protein turnover, activity or expression.

In diabetic patients, the initial events in insulin signalling, hormone recognition, and receptor kinase activation are impaired and can contribute to insulin resistance (Ciaraldi 2010). An example of this is the reduction in insulin receptor binding that has been found in skeletal muscle and adipose tissue in diabetic patients (Hunter and Garvey 1998). This may be an acquired defect, resulting from hyperinsulinemia, as reductions were also recorded in obese, non-diabetic individuals, but it is common for the insulin-stimulated kinase activity of the receptor to be impaired in diabetes (Ciaraldi 2010).

Several nucleotide polymorphisms have also been linked to diabetes pathophysiology. Polymorphisms in GLUT1 and in GLUT4, linked to the regulation of protein expression, appear to be significant in obese (Bonadonna 2004). The total cellular complement of GLUT4 appears to be reduced in 40-50% in subcutaneous adipocytes of diabetic patients and this impairment seems to be sufficient to account for the reduction in maximal insulin-stimulated adipocyte glucose transport. In muscle tissue, an impairment in insulin-stimulated GLUT4 translocation is also documented (Bonadonna 2004; Ciaraldi 2010).

1.3. Diabetes classification, epidemiology and pathogenesis

Due to the fact that diabetes *mellitus* is a group of diverse metabolic disorders characterized by hyperglycaemia and different complications, classification of the disease has evolved from a classification based on clinical findings such as age of onset or treatment modalities (insulin-dependent and non-insulin-dependent diabetes) to a classification based on the cumulative knowledge of the aetiology and pathogenesis of these metabolic disorders.

The current classification of diabetes *mellitus*, adopted and endorsed by the ADA (2013a), IDF and World Health Organization (WHO) (WHO/IDF 2006), includes four types of clinical manifestations, according to their different aetiology. These types are type 1 diabetes, type 2 diabetes, other specific types of diabetes, and gestational diabetes *mellitus* (GDM).

1.3.1. Type 1 diabetes *mellitus*

Type 1 diabetes results from a progressive destruction of the pancreatic islet cells in susceptible individuals, leading to complete insulin deficiency and thus requiring lifelong treatment with insulin. The underlining pathophysiologic mechanisms trigger autoimmunity from islet cell autoantibodies that gradually kill β-cells. Following the loss of first-phase insulin release, autoimmunity impairs secretory function of β-cell, leading to glucose intolerance and hyperglycaemia. This type of diabetes, where circulating islet cell antibodies suggest autoimmune destruction of β-cells, is classified as type 1 autoimmune diabetes *mellitus*. Around 10% of all cases of type 1 diabetes seem strongly inherited and, despite presenting β-cell destruction, have no evidence of autoimmunity or detectable islet cell autoantibodies. These cases constitute a type 1 diabetes subtype labelled “idiopathic” (ADA 2013b).

Younger patients often present ketoacidosis as the first manifestation of the disease (Kitabchi et al. 2009). This results from a metabolic imbalance due to the combination of insulin deficiency and the increase in counter regulatory hormones, like

catecholamines, cortisol and glucagon, which leads to metabolic acidosis, hyperglycaemia and high total body ketone concentration. In diabetic ketoacidosis, hyperglycaemia besides resulting from impaired insulin action, develops as a consequence of increased gluconeogenesis and glycogenolysis (Kitabchi et al. 2006). The combination of insulin deficiency and increased counter regulatory hormones also leads to the release of free fatty acids into the circulation, and to their oxidation into ketone bodies of hepatic fatty acid, originating the ketonemia and metabolic acidosis (Kitabchi et al. 2006; Kitabchi et al. 2009). Due to the metabolic work required to compensate for the hyperglycaemia and the acidosis, diabetic ketoacidosis is life-threatening, with patients experiencing vomits, dehydration, difficulties in breathing, confusion, and coma.

While some patients with type 1 diabetes present ketoacidosis as the first manifestation of the disease, others have fasting hyperglycaemia that can change to severe hyperglycaemia or ketoacidosis in the presence of some form of stress, like an infection. In some patients, islet cell function is retained at a sufficient degree as to prevent ketoacidosis for many years (Holt et al. 2011).

Susceptibility to type 1 diabetes is influenced by genetic factors, particularly human leukocyte antigen genes, and it is believed that a link exists to environmental factors and that some gene-environment interactions occur, although its role in the onset of this type of diabetes is yet unknown. Genetic factors may help to accelerate the failure of β-cell secretion in response to exogenous environmental factors and there are reported associations between type 1 diabetes and viral infections, toxins, nutritional factors, perinatal factors, and postnatal growth. However, no definite causal environmental factor for type 1 diabetes has yet been identified (Bilous et al. 2010).

Type 1 diabetes can occur at any age, but its highest incidence rates are reported during childhood and adolescence, increasing steadily from birth to peak at around puberty (10-15 years). The incidence rate in most populations is lower among 15 to 29 year-olds than among younger individuals. The peak in incidence rate occurs slightly earlier in girls

than it does in boys, suggesting an eventual influence of puberty (Diamond Project Group 2006; IDF 2011).

A multicentre prospective registration study in 17 countries, during the 15-year period between 1989 and 2003 (Patterson et al.), showed significant yearly increases in incidence, ranging from 0.6% to 9.3%, with an overall annual increase of 3.9% (95% CI 3.6–4.2). The reported increases in the 0–4 years, 5–9 years, and 10–14 years groups were 5.4% (4.8–6.1), 4.3% (3.8–4.8), and 2.9% (2.5–3.3), respectively. The authors of this study also report that mean (M) age of onset is decreasing and estimate that if present trends continue, by 2020 there will be a doubling of incidence in children under the age of 5 and a more even distribution of incidence across age groups below 15 years of age. Furthermore, this study reports that prevalence under 15 years of age is predicted to rise 70% between 2005 and 2020.

Evidence also suggests that there is a significant worldwide variation in standardized incidence among 0-14 year-olds. During the period of 1990-1999, the age-adjusted incidence ranged from 0.1/100,000 in Zunyi (China) to 37.8 in Sardinia and 40.9 in Finland (Diamond Project Group 2006). In Europe there is an approximately 10-fold difference between highest and lowest incidence countries, with the lowest rate being reported as of 3.6/100,000 in Macedonia during 1989–1994 and the highest being 30/100,000, reported in Sweden (Patterson et al. 2005). In Portugal, France, Italy and Spain, age-adjusted incidence rates ranged from 10 to 15/100,000 (Diamond Project Group 2006; Macedo et al. 2003; Serrano Ríos et al. 1990).

In the Portuguese region of Algarve, the age-adjusted incidence rate between 1985 and 2005 was estimated as being 15/100,000. Based on this data, incidence for 2010 was predicted as being 16.2/100,000 (Gomes et al. 2008).

1.3.2. Type 2 diabetes *mellitus*

In T2DM, autoimmune destruction of islet cells does not occur. This form of the disease is characterized by a combination of resistance to insulin action and an inadequate insulin secretory response (Codario 2010).

Insulin resistance can be defined as the inability of insulin to produce its usual biologic actions in normal individuals. This inability leads to impaired suppression of endogenous glucose production and to reduced glucose uptake. Insulin resistance also signifies that the ability of insulin to suppress the production of very low density lipoprotein cholesterol (VLDL) decreases, leading to an increase in circulating serum triglycerides (Codario 2010).

The pathogenesis of T2DM is still unclear, as patients have a combination of varying degrees of insulin resistance and relative insulin deficiency (Stumvoll et al. 2005). Both these factors contribute to T2DM and can arise through genetic or environmental influences (Pratley and Weyer 2001). It is believed that impaired β-cell function is the primary underlying defect, probably genetic, followed by tissue insulin sensitivity (Schofield and Sutherland 2012). In most individuals who will develop T2DM, the pathogenesis process starts in early life, when glucose homeostasis is normal. Individuals are at risk for T2DM on account of genetic polymorphisms, or on account of an environment that limits the ability of their pancreatic β-cells to adjust for insulin resistance (Pratley and Weyer 2001).

The UK Prospective Diabetes Study (UKPDS) found that β-cell function was reduced by 50% at the time of T2DM diagnosis and that there was subsequent further deterioration, regardless of therapy (UKPDS Study Group 1995a). Impaired β-cell function seems to occur in non-afflicted but genetically predisposed individuals, even when no insulin resistance is apparent (Costes et al. 2013; Pratley and Weyer 2001). As pathogenesis evolves, decreases in insulin sensitivity occur, usually as a result of unhealthy lifestyles, and these are balanced by an increase in β-cell secretion in order to achieve glucose homeostasis. Sometime after, the secretory function of β-cells deteriorates but remains sufficient to maintain normal fasting glycaemia. Further deterioration is due, at least in

part, to toxicity resulting from hyperglycaemia following meals, which can also reduce insulin sensitivity. Fasting plasma glucose concentrations increase on account of an increase in basal endogenous glucose production. Finally, as a result of even further impairment in β-cell function, glycaemia rises to levels consistent with the hyperglycaemia that characterizes diabetes (LeRoith et al. 2004).

T2DM is a complex polygenic disorder, as genetic susceptibility to the disease appears to be determined by many common variants in multiple gene *loci*. Although at least 36 diabetes-associated genes were identified, they explain only 10% of the estimated inheritability of T2DM (Herder and Roden 2011). This suggests a strong role of acquired or environmental factors in impairing β-cell function and in the risk of developing T2DM.

Malnutrition *in utero* and in early childhood, as well as *in utero* exposure to hyperglycaemia, have been linked to an increased risk of T2DM later in life (J. P. Burke et al. 2004; Lawlor et al. 2006; Schellong et al. 2012). A meta-analysis reports that low birth weight (below 2500 g) was associated with increased risk of T2DM, with an odds ratio (OR) of 1.32 (95% CI 1.06-1.64) (Harder et al. 2007). It is proposed that malnutrition *in utero* and during the first few months of life may damage β-cell development and that nutritional deficiency at this stage may limit β-cell ability to adapt to overnutrition (Pratley and Weyer 2001; Stumvoll et al. 2005). Not all individuals with early life malnutrition develop T2DM, even if they become obese; thus these findings must be viewed as one risk factor among many that can influence disease susceptibility.

Taylor, in a literature review, (Taylor 2013), reports that it seems apparent that β-cell defect, not solely hepatic insulin resistance, may be reversible by weight loss at least early in the course of type 2 diabetes. Even if formal recommendations on how to reverse type 2 diabetes in clinical practice must await further studies, the evidence for T2DM reversibility from studies after bariatric surgery (Dixon et al. 2008; Guidone et al. 2006; Holst 2011) or in patients that underwent a calorie restriction diet (Lim et al. 2011), suggests that T2DM can be understood as a potentially reversible metabolic state, precipitated by chronic excess of pancreatic and liver triacylglycerol stores. Taylor (Taylor 2013) suggests that although a cause-and-effect relationship between excess

intraorgan fat and metabolic effect has not yet been proven, data are highly suggestive for a causal link. Furthermore, obesity, linked to overnutrition, seems the most predictive acquired risk factor for development of T2DM (Codario 2010).

Chronic overnutrition with a diet rich in fat and sugars originates an accumulation of body fat which is considered the primary cause of chronic inflammation in obese patients, which may promote the development of systemic insulin resistance. Obesity causes metabolic disturbances associated with insulin secretion and insulin action, particularly in liver, muscle and adipose tissue, that lead to T2DM in susceptible individuals (Codario 2010).

There is evidence that an increased supply of fatty acids from adipose tissue competes with glucose utilization, particularly in muscle, which oxidizes the largest proportion of glucose. The mechanism underlying this process is an inhibition of the glycolytic enzymes pyruvate dehydrogenase, phosphofrutokinase, and hexokinase, which reduce the rate of glucose oxidation. The increased fatty acid turnover is accompanied by an increased release of glycerol from adipose tissue which is then used in hepatic glucose production, further increasing the imbalance of glucose metabolism (Szablewski 2011).

Reports that obese subjects and those with T2DM have a high intramyocellular lipid accumulation suggest that the increased availability of fatty acids, further enhanced by chronic overnutrition with a high dietary fat intake, may be the most important factor in disturbing insulin action in obesity. A chronic exposure of β-cells to excessive fatty acids is also associated with marked impairment of glucose-stimulated insulin secretion and to a decrease in insulin biosynthesis (Bray et al. 2003).

Adipose tissue also acts as a secretory organ, producing and releasing several factors that may contribute to insulin resistance. These factors include resistin, leptin, adipsin, amylin and TNF–α, a multifunctional cytokine which is a mediator role of tumour necrosis factor α, first found to be expressed in adipose tissue and which is related to several catabolic effects (Bray et al. 2003).

The distribution of body fat also seems to be important in the association between obesity and T2DM. Fat distribution was found to be an independent risk factor for T2DM, as subjects with a more abdominal body fat distribution have an increased risk of T2DM and other metabolic and cardiovascular complications due to the metabolic effect of adipose tissue (Wang et al. 2005). Intra-abdominal adipocytes are more active than subcutaneous adipocytes and exhibit greater accumulation of lymphocytes and macrophages, which indicates a more active pro-inflammatory role. Visceral adipocytes also have higher vascularization and nerve density, which signifies greater metabolic activity (Bray et al. 2003; Codario 2010).

Waist circumference (WC) has become a common assessment tool for estimating the risk of T2DM (Klein et al. 2007), because body fat distribution pattern strongly predicts the risk for diabetes (Qiao and Nyamdorj 2009) and the majority of T2DM patients show a visible abdominal accumulation of excess body fat. WC is encouraged to be used as a surrogate marker of abdominal fat mass (Klein et al. 2007; Zhu et al. 2002) since precise measurement of abdominal fat requires the use of radiological imaging techniques (Klein et al. 2007) and correlates with subcutaneous and intra-abdominal fat (Pouliot et al. 1994).

The specific cut-points applicable to WC of European men and women which, according to the WHO (WHO 2011), are associated with increased risk of metabolic disease are presented in table 1.

Table 1. Waist circumference and correspondent classification of metabolic and cardiovascular risk for Europeans, adapted from WHO (2011) Waist Circumference and Waist-hip Ratio: Report of a WHO Expert Consultation, Geneva, 8-11 December 2008, World Health Organization.

Gender	Waist circumference (cm)	
	Increased metabolic and cardiovascular risk	Substantially increased metabolic and cardiovascular risk
Men	›94	›102
Women	›80	›88

Studies in different populations suggest that there are significant differences in adiposity throughout specific ethnic groups and, thus, some researchers have proposed specific cut-off points for WC its association with and metabolic risk. On the overall, when compared to Europeans, Asians have greater visceral adipose tissue, while African populations and, possibly, Pacific Islanders have less visceral adipose tissue or percentage of body fat at any given WC (WHO 2011).

Asian populations, probably due to higher levels of body fat and abdominal adipose tissue, appear to have an increased metabolic risk at lower WC than Europeans, and research indicates a lower WC for Asians, set at 85 cm for men and 80 cm for women (Diaz et al. 2007; Huxley et al. 2008). Oksun et al. (Okosun et al. 2000) recommend setting the waist circumference cut-off points at 75.6 cm and 80.5 cm for men, and 71.5 cm and 81.5 cm for women of Nigerian and Cameroon origin, and suggest that cut-off points based on Europeans provided low sensitivity with respect to metabolic risk factors for the Hispanic population. Sánchez-Castillo et al. (2003) recommend a waist circumference of 90 cm for men and 85 cm for women in Hispanic populations, and Lear et al. (2009), in a sample of participants of South American origin, recommended waist circumference cut-off points of 88–90 cm for men, and 83–84 cm for women.

WC above the proposed cut-off points has been associated with increased risk for T2DM (Djoussé et al. 2013; Guh et al. 2009; Klein et al. 2007), and allow to infer that maintaining a healthy weight can have an important role in T2DM prevention and control.

A review of published analysis shows that waist-to-height (WtH) ratio is an appropriate tool for assessing adult cardiometabolic risk (Ashwell et al. 2012) and there is evidence that WtH ratio is superior to waist circumference as a risk discriminating tool (Browning et al. 2010). Waist-to-height ratio levels above a cut-point of 0.5 are good predictors of cardiometabolic risk (Ashwell et al. 2012).

Besides WC, nutritional status and adiposity can be assessed by the body mass index (BMI), the usual index for obesity diagnosis and classification.

BMI is a simple anthropometric index calculated from body weight and height (a person's weight in kilograms divided by his squared height in meters), independent of body height and correlated with body fat mass, that is considered a fast and non-invasive way to assess short and long term nutritional status (Donini et al. 2013; Prentice and Jebb 2001). High BMI is associated with an increased risk of coronary disease, hypertension and T2DM (T.A. Wadden and Stunkard 2004).

The WHO established categories to classify BMI (WHO 2000), defining obesity with an index of 30 kg/m^2 or above, and subdividing this classification further, as BMI increases with the severity of body fat excess. A BMI in the range of 25–29.9 kg/m^2 represents overweight, associated with an increased risk of comorbidities related to excess fat, albeit a smaller risk than that of obese individuals (table 2).

Table 2. Categories of body mass index classification, adapted from WHO (2000) Obesity: preventing and managing the global epidemic, World Health Organization.

Classification	BMI (kg/m^2)
Underweight	‹18.5
Normal weight	18.5 – 24.9
Overweight	25 – 29.9
Obesity grade I	30 – 34.9
Obesity grade II	35 – 39.9
Obesity grade III	≥ 40

In Europe, the trends in obesity prevalence point out to an increase in adult individuals, with rates between 15–30%. Data from Portugal for 2003-2005, collected in individuals aged 18-64 years, allow to identify 45.2% of overweight men, from which 15% are obese. Overweight prevalence in women was reported as 34.4% and obesity prevalence as 13.4% (Do Carmo et al. 2008). Worldwide, in 2010, it was estimated that approximately 475 million adults were obese, one billion adults were overweight. At the same time, in the 27 member states of the European Union, 60% of all adults were overweight or obese (IOTF 2010). The incidence of obesity has been rising in the last decades to the

extent that is now considered a pandemic and constitutes an important cause of death in industrialized countries (Rippe and Angelopoulos 2012).

Excess weight is an established risk factor for T2DM, with a relative risk (RR) of 2.7 (95% confidence interval (CI) between 2.1 - 3.3) reported in a prospective cohort study in women who gained 8.0 to 10.9 kg. This study concludes that the excess risk for diabetes is substantial, even with modest and typical weight gain in adults (Colditz et al. 1995). Other reports, also from a prospective cohort study, claim that a gain of 1 kg/m^2 between the ages of 25 and 40 years increases the relative risk of T2DM by 25% (Schienkiewitz et al. 2006). Additionally, data from a USA populational follow-up between 2000 and 2004 suggest that the increase in obesity was an important determinant of the increase in diabetes prevalence (Gregg et al. 2007). A meta-analysis of nine prospective cohort studies of the general population of Western countries (Guh et al. 2009) further strengthens this inference, showing that elevated BMI and WC were significantly associated with T2DM in men and women, with reports of pooled relative risks (RR) across BMI categories ranging from 2.40 to 6.74 in men and from 3.92 to 12.41 in women.

Although there is accumulating evidence that even modest weight reduction can improve glycaemic control and reduce diabetes risk (Djoussé et al. 2013), the pathogenesis linking obesity and diabetes needs to be further clarified. Several mechanisms have been proposed to link obesity to T2DM risk, including the increased production of adipokines, resistin, and retinol-binding protein 4, or ectopic fat deposition and mitochondrial dysfunction (Deng and Scherer 2010). Impaired mitochondrial mass and/or function in overweight individuals results in an insulin sensitivity decreased and a compromised β-cell function (Rippe and Angelopoulos 2012). It was also recently suggested that the link between obesity and diabetes can be due to the role of a protein that controls the differentiation and function of immune cells (Stolarczyk et al. 2013), due to endoplasmic reticulum stress, or to complex genetic interactions (McCarthy 2010). Despite these findings, neither the relative importance of the described links is clearly defined nor are the connections between obesity and

T2DM explored in a conclusive way. Nevertheless, both clinical trial and populational studies on obesity and its modifiable lifestyle risk factors identify adiposity as a major determinant of diabetes. The association between obesity and T2DM has also led to the suggestion that a shared pathogenesis underlies both diseases, implying that life styles that give rise to progressive weight gain and metabolic impairment also contribute to β-cell impairment (Eckel et al. 2011). Hotamisligil and Erbay have suggested that long term cell exposure to nutrient concentrations that exceed energy requirements can lead to endoplasmic reticulum stress, excess production of reactive oxygen species, mitochondrial dysfunction, and triglycerides accumulation (Hotamisligil and Erbay 2008). These authors also suggest that obesity-associated cellular injury can activate an immune response that originates tissue inflammation and, concomitantly with cell responses to excess energy, contributes to the pathogenesis of insulin resistance. Obesity-induced metabolic impairment can favour insulin resistance and progressive β-cell dysfunction that, in turn, contribute to enhance the excess nutrient problem. Nutrient excess triggers inflammatory responses, leading to insulin resistance and placing a greater demand on the β-cell. As β-cell function declines, the toll taken by nutrient excess increases. However, since not all obese individuals develop T2DM, an underlying abnormality of the β-cell must coexist with nutrient excess, to promote this pathogenic cycle (Kahn et al. 2006).

It is reported that individuals with obesity or with excessive abdominal fat deposition account for about 80% of all T2DM patients and, although the specific link is still not clear, it is known that a decreased insulin sensitivity is frequent in obese and overweight adults. Decreased insulin sensitivity has been established as an independent risk factor for the development of T2DM and is positively correlated with BMI (Kahn et al. 2006). There is evidence that decreased insulin sensitivity progressively increases with time, constituting a late step in the development of T2DM, after years of normal glycaemia in the presence of insulin resistance (C. Day and Bailey 2011).

Ultimately, obesity arises due to an excessively positive energy balance, created by a complex set of interrelated factors, as its determinants involve sociocultural, genetic,

physiologic, metabolic, behavioural and psychological components. It is believed that there is an underlying genetic susceptibility to the disease, which is heavily modified by environmental circumstances and individual lifestyle choices (McCarthy 2010). The decline in manual occupation, the rise of motorized transport, and increasingly sedentary leisure activities, have reduced overall energy needs. The rise in the proportion of food consumed out of the household, the offer of energy dense foods, and the increased usual portion sizes, also had an effect in the incidence of obesity (Rippe and Angelopoulos 2012). The risk of T2DM further increases with other environmental and lifestyle factors, like physical inactivity, excessive alcohol intake, or smoking, which have an effect in insulin sensitivity (ADA 2013a; Reis et al. 2011).

A meta-analysis of 10 prospective cohort studies reported a lower risk of T2DM associated with regular moderate physical activity (RR=0.69, 95% CI 0.58-0.83). These results are maintained after adjustment for BMI, suggesting an independent effect of exercise on glucose metabolism (Jeon et al. 2007). The Pre-diabetes Risk Education and Physical Activity Recommendation and Encouragement (PREPARE) study, examining 98 overweight or obese individuals with impaired glucose tolerance, suggests that the benefits of moderate physical activity are sustained after 24 months (Yates et al. 2011), with subjects who underwent a 3h structured education session with personalized pedometer use showing a significant reduction in 2h post exercise plasma glucose, when compared with a control group.

Alcohol consumption seems to present an association with the risk of developing T2DM in the form of a U or J curve, implying that a modest alcohol consumption reduces the incidence of T2DM and that an excessive alcohol intake is related to an increase in incidence (Pietraszek et al. 2010). A systematic review and meta-analysis, comparing lifetime abstainers with individuals with different daily alcohol consumption patterns, reports that alcohol intakes above 60 g/day in men and above 50 g/day in women increase the risk for T2DM (Baliunas et al. 2009). There are some conflicting results regarding the daily alcohol intakes that become deleterious, but this may be due to different drinking patterns, beverage preference, or health behaviour (Pietraszek et al.

2010). The association between alcohol and T2DM also seems BMI-dependent, as both moderate and excessive alcohol intake increase T2DM risk in men with low BMI, whereas moderate alcohol consumption appears to have a protective effect in men with a higher BMI (Reis et al. 2011).

Cigarette smoking also increases the risk of T2DM. According to a meta-analysis of prospective cohort studies, smokers have a pooled adjusted RR for T2DM of 1.4 (95% CI 1.3-1.6) compared with non-smokers (Willi et al. 2007). Data from a physicians' health study (Manson et al. 2000) suggest that approximately 10% of the incidence of T2DM may be attributable to smoking.

The risk of developing T2DM increases with age (particularly after 45 years) and the disease is also more common in individuals with a family history of diabetes, in women with history of diabetes during pregnancy, in certain ethnic groups (African American, Hispanic), and in women with polycystic ovarian syndrome (UKPDS Study Group 1995a). Furthermore, most patients with T2DM present a cluster of clinical features of insulin resistance named metabolic syndrome. In non-diabetic individuals, this cluster of clinical features confers substantial additional risk for cardiovascular and metabolic complications. The cluster of features confers a risk of T2DM that is above the risk associated with each individual clinical feature.

According to a study group of IDF researchers (Alberti et al. 2005), a person is diagnosed with metabolic syndrome if central obesity is present (assessed by increased waist circumference with ethnic-specific WC cut-points), together with any two of the following:

- Serum triglycerides above 150 mg/dL (1.7 mmol/L) or treatment for elevated triglycerides;
- Serum HDL cholesterol below 40 mg/dL (1.03 mmol/L) in men or below 50 mg/dL (1.29 mmol/L) in women, or treatment for low HDL;
- Systolic blood pressure above 130, diastolic blood pressure above 85, or treatment for hypertension;

- Fasting plasma glucose above 100 mg/dL (5.6 mmol/L) or previously diagnosed T2DM;
- An oral glucose tolerance test is recommended for patients with an elevated fasting plasma glucose, but not required.

Based on the results from 16 cohort studies, the RR for T2DM in individuals with four or more clinical features from the metabolic syndrome ranged from 10.9 to 24.4 (Ford et al. 2008), suggesting that the metabolic syndrome has a strong association with diabetes incidence.

T2DM prevalence varies substantially from one geographical region to the other, as a result of environmental and lifestyle risk factors. The IDF (2011) estimated that worldwide diabetes prevalence for 2012 would correspond to 371 million people with diabetes between 20-79 years old. Approximately half of those cases were expected to be undiagnosed. As it is believed that T2DM makes up for 85% to 95% of all cases of diabetes in high income countries and that it may account for an even higher percentage in countries with lower incomes (WHO 1994).

Western Pacific, Middle East, and North African countries have the highest prevalence of all types of diabetes. The Federal State of Micronesia, in the Western Pacific region, has the highest reported adjusted prevalence, with 37.7%. Europe shows marked differences in prevalence. The Russian Federation is the country with the highest prevalence (9.7%) and the Republic of Moldova the country with the lowest prevalence (2.7%). Portugal is reported as the country with the second highest prevalence in Europe (9.6%). This rate is above the estimated proportion of diabetics for the USA (9.4%), which is the country with the third greater number of diabetic individuals (preceded only by India and China). The estimated prevalence for Portugal in 2012 is significantly higher than the prevalence of its only neighbour country, Spain (7.15%)(IDF 2011).

Data from a national prevalence study in Portugal (Gardete-Correia et al. 2010) point to an age-adjusted T2DM prevalence of 11.7% in 2009, corresponding to an estimated 900,000 patients. The age-adjusted prevalence reported for the Algarve in 2009 was 11%. In 2011, the global diabetes prevalence for Portugal was estimated as 12.7%, in an

increase that, according to the authors, was also due to population ageing (Gardete Correia et al. 2013). The same study analyses previous data on diabetes, and reports an increase in incidence of 79.6% between 2002 and 2011.

In the United Kingdom, the Quality and Outcomes Framework reports an average prevalence of diabetes of 4%, representing around 2.6 million individuals (Health and Social Care Information Centre 2012). Approximately 85% of those were T2DM cases. IDF data for the United Kingdom shows a 4.5% prevalence of T2DM in 2012 (IDF 2011).

T2DM is also increasingly observed among children, adolescents, and younger adults, accompanying the obesity increase in paediatric age. Evidence suggests that the progression of insulin resistance to T2DM is faster in obese children than in adults (D'Adamo and Caprio 2011).

All the trends in T2DM prevalence indicate that the disease will increase further in the next two decades, and much of the increase will occur in developing countries where the majority of patients are aged between 45 and 64 years (L. Chen et al. 2012).

1.3.3. Gestational diabetes *mellitus* and other specific types of diabetes

Insulin resistance and hyperinsulinemia are common during pregnancy, due to placental secretion of hormones that are considered diabetogenic, including growth hormone, corticotrophin releasing hormone, placental lactogen, and progesterone. The inability to secrete additional insulin to overcome the diabetogenic effect, along with increased adipose deposition, higher caloric intake, and reduced physical activity, predispose some women to develop a form of diabetes during pregnancy that, in most cases, subsides after the delivery (ADA 2013b; Crowther et al. 2005).

This form of diabetes deriving from a glucose intolerance with onset or first recognition during pregnancy is classified as gestational diabetes (ADA 2013b; WHO/IDF 2006) and its prevalence is associated with a higher incidence of preeclampsia, macrosomia, and caesarean delivery (Landon et al. 2009).

In Europe, although practices related to its detection are inconsistent, gestational diabetes is estimated to occur in 2 to 6% of pregnancies, with a trend for lower prevalence in the North of Europe and higher prevalence in the South (Buckley et al. 2012).

In Portugal, estimates for 2011 using a sample of 77 431 deliveries within the National Health Service, report a 4.9% prevalence of gestational diabetes (Gardete Correia et al. 2013).

Other specific types of diabetes include several conditions that can cause some degree of impairment in insulin production or secretion. These conditions include genetic defects of the β-cell, genetic defects in insulin action, genetic syndromes such as Down or Prader-Willi syndromes, diseases of the pancreas (cystic fibrosis or pancreatitis), and endocrinopathies such as acromegaly or hyperthyroidism. Furthermore, diabetes can be caused by the administration of drugs such as glucocorticoids, due to infections like congenital rubella, or due to uncommon conditions that lead to autoimmune forms of the disease (ADA 2013b).

Patients with these specific types of diabetes present a widely variable extent of glucose intolerance, often simulating type 1 diabetes *mellitus* or T2DM (Ewald et al. 2012). Specific types of diabetes represent about 1% to 2% of all cases of diabetes (IDF 2011).

1.4. Diagnosis of diabetes *mellitus*

The diagnosis of diabetes *mellitus* is made through various clinical and biochemical features, mainly by cut points in fasting plasma glucose (FPG) levels, or plasma glucose levels 2h after an oral glucose tolerance test (OGTT), consisting in the ingestion of a glucose solution containing the equivalent to 75g anhydrous glucose dissolved in water (ADA 2013b). Additionally, the diagnosis can be aided by the observation of classic symptoms of hyperglycaemia: thirst, polyuria, weight loss, and blurry vision.

Recently, HbA1c has been considered as a measure of glucose control, as it correlates closely with a complete measure of average glycaemia over a period of 8 to 12 weeks

(Nathan et al. 2007), and both the WHO and the IDF (WHO/IDF 2011) recommend that HbA1c can be used as a diagnostic tool if quality control of the test can be assured.

The current diagnosis criteria for diabetes are based on the revised report of the WHO/IDF Expert Committee on the Diagnosis and Classification of Diabetes *Mellitus* (WHO/IDF 2006), which resulted from the analysis of epidemiological data. The ADA, upon further reviews of the evidence from observational and analytic studies, recommends a set of slightly different diagnosis criteria (ADA 2013b) that are widely used. In Portugal, the *Direção Geral de Saúde* (DGS - National Health Directorate)**,** under its National Program for Prevention and Control of Diabetes, issued normative diagnosis criteria (DGS 2011b) based on the WHO/IDF Expert Committee report, that also integrate the ADA standards for diabetes care (ADA 2013a) and diagnosis criteria.

The current diagnosis criteria adopted in Portugal (DGS 2011b) state that an individual has diabetes *mellitus* if he presents one of the following:

- HbA1c ≥ 6.5%;
- FPG ≥ 126 mg/dl (7.0 mmol/l);
- 2h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during a OGTT;
- Presence of classic hyperglycaemia symptoms and a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).

These criteria consider that the fasting period for FPG analysis must be of at least 8 hours and the *Direção Geral de Saúde* advises that if an individual is asymptomatic for hyperglycaemia, the diagnosis should not be made only through HbA1c.

The detection of gestational diabetes follows a standardized practice of performing a 75g OGTT at 24-28 weeks of gestation on women not previously diagnosed with diabetes. Diagnosis of gestational diabetes is made if one of three plasma values is exceeded:

- Fasting plasma glucose ≥ 92 mg/dl (5.1 mmol/l);
- 1 hour plasma glucose ≥ 180 mg/dl (10.0 mmol/l);
- 2 hours plasma glucose ≥ 153 mg/dl (8.5 mmol/l).

The prevailing clinical guidelines affirm the need to classify the disease according to one of the four types of diabetes (type 1 diabetes *mellitus*, T2DM, gestational diabetes, other specific types of diabetes). The diagnosing physician must decide the type of diabetes according to the circumstances at the time, and the pathogenesis and hyperglycaemia that can be identified for the disease.

Besides the four types of diabetes, the Expert Committee on the Diagnosis and Classification of Diabetes (ADA 2003b) and the position statement from WHO and IDF (WHO/IDF 2006) propose additional classification categories for increased risk for diabetes, identifying a group of individuals whose glycaemia does not meet diagnostic criteria for diabetes but is significantly higher than the usual glycaemia in non-diabetic individuals. These individuals are defined as having impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Both the presence of IFG or IGT are referred as pre-diabetes and these conditions should not be viewed as individual clinical entities but rather as an intermediate stage in the disease process leading to one of the four types of diabetes. The classification categories for pre-diabetes used in Portugal represent the WHO/IDF criteria and are presented in table 3.

Table 3. Pre-diabetes diagnosis criteria, adapted from WHO/IDF (2006) Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. Geneva, World Health Organization.

Pre-diabetes condition	Diagnosis criteria
IFG	Fasting plasma glucose from 110 mg/dl (6.1 mmol/l) to 125 mg/dl (6.9 mmol/l)
IGT	2 hours plasma glucose between 140 mg/dl (7.8 mmol/l) and 199 mg/dl (11.0 mmol/l) during a OGTT

The use of glycated haemoglobin for the diagnosis of diabetes was not formally translated to categories for pre-diabetes diagnosis, but it is know that there is a continuum of risk according to all glycaemic control measures, and that individuals with HbA1c levels slightly below the diagnostic cut point for diabetes are at very high risk of developing the disease (WHO/IDF 2011).

Observational studies show consistent results indicating that a stronger correlation of HbA1c with diabetic retinopathy than with FPG (Sabanayagam et al. 2009; Tapp et al. 2008). A systematic review of 16 cohort studies concludes that, compared with an HbA1c of 5%, individuals with HbA1c between 5.5 and 6.0% have an increased risk of diabetes with the five-year incidence ranging from 9% to 25%. Individuals with HbA1c ranging from 6.0% to 6.5% have a five-year risk of developing diabetes between 25% and 50%, and a RR 20 times higher compared with the HbA1c of 5.0% (X. Zhang et al. 2010b). In a study of non-diabetic adults, HbA1c was found to be have a stronger association with the incidence of diabetes and cardiovascular events than that of fasting glucose (Selvin et al. 2010). Based on this association and also on further evidence from prospective cohort studies supporting these findings, the ADA infers that it is reasonable to consider an HbA1c range of 5.7–6.4% to identify individuals with pre-diabetes (ADA 2013b). Despite this recommendation, HbA1c is not formally used for the diagnosis of pre-diabetes in Portugal.

HbA1c was proposed as a diagnosis tool for diabetes considering that the chronic hyperglycaemia that leads to diabetes complications could be assessed by a laboratory method that reflects long-term glycaemic exposure. It was proposed that this method could provide a better marker for the presence and severity of the disease than single measures of glycaemia (International Expert Committee 2009).

HbA1c is formed through the non-enzymatic binding of circulating glucose to haemoglobin, a process defined as glycation. HbA1c is measured as the ratio of glycosylated to non-glycosylated haemoglobin, and higher levels represent a higher level of glycation due to higher levels of blood glucose. As glycation occurs over the entire 90 to 120 day lifespan of the red blood cell, HbA1c can be interpreted as an indicator of blood glucose during that time (Peterson et al. 1998).

HbA1c can be used as a diagnostic test for diabetes, provided that quality assurance tests are in place, and assays are standardised to criteria from international reference values (WHO/IDF 2011). This marker also presents a lower variability than that of FPG, with day-to-day within-person variation of 2% for HbA1c, and 12–15% for

FPG (Playle et al. 1999). Furthermore, several practical advantages support the use of HbA1c to diagnose diabetes, like the fact that samples for HbA1c testing can be obtained at any time, requiring no patient preparation or fasting. Data also suggest greater pre-analytical stability, and less day-to-day variations during periods of stress and illness (Bonora and Tuomilehto 2011).

1.5. Public health impact of diabetes *mellitus*

There is evidence that diabetes related to mortality is underestimated, due to the fact that death certificates in diabetes patients frequently do not mention the underlying disease as a cause of death. The immediate cause of death in a considerable portion of patients is cardiovascular disease, but this condition would not have developed if diabetes was not present (Roglic et al. 2005). It is believed that cardiovascular disease is responsible for 50% of all deaths in diabetes patients (Zimmet 2003).

According to the IDF, in 2011, 4.6 million deaths were attributed to diabetes in individuals aged 20-79 years old, corresponding to a proportional mortality of approximately 8.2% (IDF 2011). In Portugal, the age-adjusted diabetes mortality rate and the proportional mortality for diabetes have been slowly rising since the year 2000. The proportional mortality for diabetes was reported as 4.2% in 2002 and 4.4%, in 2011, while the age-adjusted mortality rate in 2010 was 24.9/100,000, similar to the rate in 2002 (Gardete Correia et al. 2013). In Portugal, each death attributed to diabetes corresponds to seven years of potential life lost (YPLL) below the age of 70 years old. This represented, in 2010, a rate of 59 years of potential life lost (YPLL) for every 100,000 inhabitants (INE 2011).

The impact of diabetes on hospital care has also been estimated. If hospital stays of less than 24 hours are excluded, in Portugal, for 2010, individuals who were hospitalized due do diabetes symptoms or complications associated with the disease had a mean of 10.5 days of hospitalization. This value is significantly higher than the mean for all-causes hospitalization, estimated at 7.5 days (Gardete Correia et al. 2013).

Health economic analyses in the USA have suggested that a 50 year-old patient who is recently diagnosed with diabetes has an annual medical expenditure that is 4,174 US dollars higher than the expenditure of an identical person without diabetes. Furthermore, each additional year with diabetes increases the annual medical expenditure by 158 US dollars above the increases in medical costs attributable to ageing (Trogdon and Hylands 2008).

In 2011, the morbidity and mortality of diabetes is believed to have represented, in Portugal, 0.8% of the gross domestic product (GDP), and 8% of all health related expense. In 2001, the IDF World Atlas proposed that each diabetes patient had an estimated mean cost of 2,522 US dollars (IDF 2011). If this estimate is applied to Portugal, the direct costs with diabetes will rise to 1% of GDP and to 10% of all of the government expense with health. Zhang and colleagues, analysing the expenditures for 193 countries, reported that, globally, 12% of all health expenditures was expected to be due to diabetes (P. Zhang et al. 2010a). This expenditure estimate does not include indirect costs of diabetes, like the effects of work absenteeism and lack of productivity due to diabetes related complications, which means that the real expenditure with the disease may be higher. It is believed that the complications of diabetes are associated with a substantial number of absent days from work, and that the avoidance of these complications would benefit both patients and society (Sorensen and Ploug 2013).

The major complications of diabetes are cardiovascular disease, nephropathy, neuropathy, retinopathy, and cataracts (Carl Asche et al. 2011b; Pollreisz and Schmidt-Erfurth 2010).

Ischemic heart disease among diabetes patients between 45 and 64 years old is approximately three times more prevalent than in non-diabetics (14.3% versus 4.7%), and diabetes also raises 1.5 to 2 fold the RR of death after myocardial infarction (Engelgau et al. 2004). In a European study involving 7 countries, patients with diabetes were more likely to have limb weakness ($P<0.02$), dysarthria ($P<0.001$), ischemic stroke ($P<0.001$), and lacunar cerebral infarction ($P=0.03$) (Megherbi et al. 2003).

Although cardiovascular and cerebrovascular disease are major complications of diabetes, the diabetic foot, a predominant peripheral neuropathy, is the most common cause of hospitalization in patients with diabetes and responsible for at least 33% of the direct costs with the disease (Driver et al. 2010). This implies a considerable economic burden in healthcare services, as the cost of care for patients with a foot ulcer is 5.4 times higher in the year after the first ulcer episode than that of diabetic patients without foot ulcers. Patients with diabetic foot ulcers require more frequent emergency department visits, are more commonly admitted to hospital, and require longer length of stays. A retrospective cohort study with data from 7,758 patients concludes that the progression of nephropathy was strongly associated with higher subsequent medical care cost (Driver et al. 2010).

Diabetes can also lead to multiple eye pathologies, including retinopathy, which is the leading cause of blindness in people between 20 and 64 years old, accounting also for 12% of all new cases of blindness (Engelgau et al. 2004). A Swedish population-based study with 252 386 individuals found a diabetic retinopathy prevalence of 41.8% (95% CI 38.9–44.6) for patients with type 1 diabetes and of 27.9% (27.1–28.7) for patients with T2DM (Heintz et al. 2010). Retinopathy was sight-threatening in 12.1% and 5.0% of the type 1 and T2DM populations, respectively. This study concluded that the annual cost for diabetic retinopathy was €106,000 per 100,000 inhabitants, with the costs increasing considerably with the severity of this complication.

Overall, it is believed that most of the expenditure with diabetes is associated with the disability and the YPLL resulting from the disease and its complications (L. Chen et al. 2012; P. Zhang et al. 2010a). In fact, it is estimated that about half of the expenditure with diabetes is allocated to the treatment of its complications and, due to the rise in incidence of the disease, the related costs are expected to at least double in the next two decades if no significant changes in public or private strategies for prevention and control are put in place (E. S. Huang et al. 2009).

1.6. Metabolism and postprandial glycaemia in type 2 diabetes *mellitus*

The main role of the pancreatic hormones is to regulate the uptake and release of metabolic fuels from the hormone-sensitive tissues: liver, muscle, and fat. After meals, when nutrient levels in the blood are high, insulin secretion is stimulated, glucagon secretion is inhibited, and the high insulin to glucagon ratio promotes nutrient storage. But the regulation of glucose concentration after a meal is determined by the extent to which glucose entering the systemic circulation exceeds or is exceeded by the rate at which glucose leaves the systemic circulation (Standl et al. 2011). PPHG is primarily caused by a reduced glucose disappearance, due to the fact that the insulin secretion in response to higher glucose concentrations after a meal is impaired in individuals with IFG and T2DM (Bock et al. 2006).

In healthy individuals, PPG is usually below 120mg/dl and rarely exceeds 140mg/dl, prompting PPHG to be defined as a plasma glucose level exceeding 140mg/dl (IDF 2007). This is one of the earliest abnormalities of glucose homeostasis associated with T2DM, and progresses to fasting hyperglycaemia as the condition worsens (Monnier et al. 2007).

The impairment in insulin action and insulin secretion associated with diabetes led to suspect that PPHG is common in most patients, and today it is believed that PPHG contributes significantly to the overall glycaemic control. In fact, the postprandial state is the norm for individuals who consume at least three meals a day at relatively fixed times, and during the postprandial period insulin secretion does not fully compensate for insulin resistance in T2DM (Standl et al. 2011).

According to van Dijk et al. (2011), who conducted a study with 60 male patients with T2DM and 24 age and BMI-matched normal glucose tolerant controls during a three day period of continuous glucose monitoring, hyperglycaemia is highly prevalent throughout the day, even in patients with diabetes presenting a HbA1c level well below 7.0% and receiving adequate medical care. In this study, T2DM patients with a standardized diet experienced hyperglycaemia more than nine hours per day. Even those patients with

apparent good glycaemic control, measured by HbA1c below 7.0%, experienced PPHG for nearly six hours per day.

Data gathered in non-insulin treated patients with T2DM also suggests that at HbA1c levels below 7.3%, postprandial glucose contributes approximately 70% to elevated HbA1c levels, and at HbA1c levels of 7.3% to 8.4%, approximately 50% of the HbA1c contribution comes from postprandial glucose (Monnier et al. 2003).

PPHG also seems most common after breakfast. Data from 200 non–insulin-treated patients with T2DM suggest that high plasma levels over morning periods after breakfast seem to occur independently of BMI, HbA1c, therapy, and residual β-cell function. Monnier et al. (2002) suggest that this can likely be attributable to an elevated hepatic glucose output in the early morning.

According to the evidence of long term prospective cohort studies and clinical trials (DCCT/EDIC Study Research Group 2005; Levitan et al. 2004; UKPDS Study Group 1995b), there is a strong correlation between glycaemic control and the incidence of microvascular and macrovascular complications. The DECODE study, which analysed 13 prospective European cohort studies (DECODE Study Group 1999), suggests that fasting-glucose concentrations alone do not identify individuals at increased risk of death associated with hyperglycaemia. This study reports that during the follow-up period the largest number of excess deaths was observed in subjects who had impaired glucose tolerance but normal fasting blood glucose levels and concludes that the glucose level two hours after the start of a meal is a better predictor of deaths from all causes and cardiovascular disease than is fasting blood glucose.

PPHG seems associated with an increased risk of retinopathy, impaired cognitive function, and with increased carotid intima-media thickness. PPHG is also identified as a causal factor in oxidative stress, inflammation, and endothelial dysfunction (Ceriello et al. 2008).

Diabetes treatment aimed at lowering postprandial blood glucose reduces vascular events, and there is strong evidence that, especially for patients with very poor control

over the disease, targeting both PPHG and FPG is an important strategy for achieving optimal glycaemic control (Standl et al. 2011). These treatment strategies should be initiated at any HbA1c level (Ceriello et al. 2006).

The importance of targeting PPHG is accepted by the leading diabetes organizations, which currently include in their treatment and management guidelines recommendations for the monitoring of blood glucose in the period of two hours following meals, in order to assess glycaemic control (ADA 2013a; IDF 2007).

It is proposed (Ceriello et al. 2008; IDF 2007) that two-hour postprandial plasma glucose should not exceed 7.8 mmol/l (140 mg/dl), as this is considered a reasonable and conservative target, and argue that currently the most practical method to measure postprandial glycaemia is patient self-monitoring. The ADA recommendations are based on the correlation with HbA1c values, and it is proposed that in order to achieve an HbA1c of 7%, the peak postprandial capillary blood glucose that usually occurs one hour to two hours after the start of a meal, should be below 180 mg/dl (10.0 mmol/l). It is believed that these targets may help to lower HbA1c to 7% or below, which has shown to reduce microvascular complications of diabetes, and, if achieved soon after the diagnosis of the disease, is associated with long-term reduction in macrovascular disease (ADA 2013a).

Data on the prevalence of PPHG is limited, and although target values exist for postprandial glycaemia, most practitioners and clinicians rely solely on HbA1c and FPG concentrations to evaluate and adjust therapeutic strategies. (Bonora and Tuomilehto 2011; Ceriello et al. 2008; Hanas and John 2010). FPG and HbA1c are easy to measure, and the latter is especially used in the clinical setting to monitor diabetes, and to establish the degree of metabolic control. Deviation from individualized HbA1C targets prompts physicians to modify treatment strategies (Bonora and Tuomilehto 2011). Nevertheless, the accumulating evidence on PPHG allows to infer that by focusing solely on HbA1C or FPG levels, clinicians may miss opportunities to help patients to meet glycaemic targets, and minimize glucose variations which can have negative effects on long-term outcomes (Standl et al. 2011; van Dijk et al. 2011).

1.7. Treatment and management of type 2 diabetes *mellitus*

The chronic nature of diabetes and its associated complications, as well as their potential for impact on the overall quality of life of those affected, confirm the need for adequate treatment and management of the disease, preferably from a team that may include physicians, nurses, dietitians, pharmacists, and mental health professionals with expertise and a special interest in diabetes. individuals with diabetes should also assume an active role in their care, for the therapeutic plan to succeed (ADA 2013a).

Diabetes care should be achieved by an integrated team approach, and the management of the disease should be a collaborative therapeutic alliance among the healthcare team and the patients and their families (Arterburn and O'Connor 2012). At the same time, the goals and management plan should be individualized in order to take into account the patient's age, school or work schedule and conditions, physical activity, eating patterns, social situation, and cultural factors. Treatment of patients with T2DM includes education, evaluation for microvascular and macrovascular complications, normalization of glycaemia, minimization of cardiovascular and other long-term risk factors and avoidance of drugs that can aggravate abnormalities of insulin or lipid metabolism. In order to achieve the preconized glycaemic goals, most patients require continuous treatment that, according to the severity and characteristics of the disease, is focused on increasing insulin secretion and responsiveness, or decreasing the rate of carbohydrate absorption (ADA 2013a).

Improved glycaemic control lowers the risk of microvascular complications in patients with T2DM and weight reduction, diet, and exercise can all be used to improve glycaemic control. In addition to glycaemic control, vigorous cardiac risk reduction by the mean of smoking cessation, blood pressure control and reduction in serum lipids should be a priority for all patients. However, in spite of evidence that risk factor reduction lowers the risk of both microvascular and macrovascular complications, less than 50% of patients do not achieve recommended goals for HbA1C, blood pressure control, and management of dyslipidaemia. In the twentieth century, about two-thirds of diabetes patients died of premature cardiovascular disease (UKPDS Study Group 1998b).

Adherence to prescribed therapies is an important factor in the management of T2DM that shows a wide range of results. Inadequate adherence to oral anti-diabetic agents, even if it has a greater adherence than lifestyle modifications, is estimated to apply to between 36% and 93% of patients (C. J. Bailey and Kodack 2011).

Several literature reviews suggest that a significant proportion of T2DM patients exhibit poor adherence to treatment and poor management of the disease. Some of the identified factors that compromise adherence include complex pharmacological treatment dosing regimens, clinical inertia, safety concerns, socioeconomic issues, ethnicity, poor patient education, beliefs, and social support (Carl Asche et al. 2011b; Delamater 2006; 2006).

Both pharmacological and non-pharmacological approaches to treatment and care in T2DM should be considered and discussed with the patient. Lifestyle interventions should be the first step in treating recently diagnosed T2DM and, on account of this, nutritional management of the disease must play a pivotal role in patient self-care, as there is strong evidence of its effectiveness (Wheeler et al. 2012). The UK National Institute for Health and Clinical Excellence (NICE) evidence-based guidelines for diabetes care (NICE 2009) recommend that metformin, the first ADOA to be used, should only be started in a person who is overweight or obese and whose blood glucose is inadequately controlled by lifestyle interventions alone, but evidence suggests that the majority of patients will require medication over the course of the disease (Nathan et al. 2009).

Overall, the objective of diabetes treatment and management is to avoid hyperglycaemia without exposing patients to unnecessary risk for hypoglycaemia, in order to prevent or delay the progression of the chronic complications associated with the disease. Other cardiovascular risk factors should be addressed and minimized (Ismail-Beigi 2012), and adequate glycaemic control should be achieved as soon as possible, as it is believed that the first years of the disease's clinical stage have a strong impact in the late-onset complications of diabetes (Holman et al. 2008).

The ADA guidelines for glycaemic control (ADA 2013a) propose that patients should achieve an HbA1c below 7%, while the IDF and the European Association for the Study

of Diabetes (EASD) propose a more strict cut point of 6.5% (Ray and Singhania 2011; Secnik et al. 2007). These HbA1c cut points reflect a level of glycaemic control associated with a reduction in the risk of microvascular and macrovascular complications (UKPDS Study Group 1998b).

The poor adherence to therapy reflects on the prevalence of glycaemic control. Bertoni and collaborators reported a 45% prevalence of HbA1c below 7% in a sample of 5145 T2DM patients (Bertoni et al. 2008), and Shi and colleagues, a prevalence of 56% (Shi et al. 2011). A ten year follow-up of 1772 patients between 1996 and 2006 revealed a prevalence of adequate glycaemic control between 23.4% and 26.9% (Blumenthal et al. 2010).

In Portugal, an assessment of 2673 T2DM patients revealed an HbA1c below 7% in 51.7% of them. The same study found that 6.7% of the patients had an HbA1c above 10% (Cortez-Dias et al. 2010).

Considering the prevailing adherence to treatment, the prevalence of adequate glycaemic control and integrating information on therapy, its outcomes, synergistic effects, costs and potential for adverse events, the ADA and the European Association for the Study of Diabetes issued a consensus treatment algorithm for clinical and therapeutic management of T2DM (Nathan et al. 2009) that is also reflected in the ADA Standards of Medical Care in Diabetes (ADA 2013a). This algorithm serves as a basis for the guidelines for the treatment of diabetes proposed by the Portuguese Society of Diabetology (Duarte et al. 2007). In these guidelines, a pharmacological therapy with metformin is advised at the time of diagnosis, together with the implementation of an adequate diet and physical activity programs. Following the diagnosis, periodical assessments of the therapeutic objectives should guide the need of adjusting pharmacological agents in order to achieve and maintain, for most of the patients, an HbA1c below 7%. The guidelines focus on obtaining metabolic control, without recommending a strict sequence of pharmacologic agents that should be used. In 2011, in Portugal, the DGS issued a code of practice for diabetes pharmacological treatment that guides clinicians in the Portuguese National Health Service (DGS 2011a).

1.7.1. Pharmacological therapy and management

Most of T2DM patients will need medication over the course of the disease as lifestyle interventions often fail to achieve or maintain the metabolic control goals (Nathan et al. 2009). As metabolic control usually worsens with age, early treatment that can maintain proper HbA1c is associated with improved glycaemic control over time and with decreased long-term complications (Stephen Colagiuri et al. 2002), supporting the claim for early pharmacological therapy use.

The majority of treatment guidelines now recommend that oral anti-diabetic agents (OADA), be initiated around the time of diagnosis, accompanying diet and physical activity interventions (Aguilar 2011). Nevertheless, considering the increasingly complex process of pharmacological glycaemic management (due to a widening array of pharmacological agents), a position statement for the management of hyperglycaemia was issued by the ADA and the EASD, recommending a non-prescriptive, patient-centered approach to treatment, encouraging clinicians to integrate the current evidence in the context of patient-specific factors, including patient preferences, needs, and values (Inzucchi et al. 2012). This position statement advises that patients with moderate hyperglycaemia or in whom lifestyle changes are anticipated to be unsuccessful, should promptly start an anti-hyperglycaemic agent, which can be modified or discontinued if lifestyle changes are successful. At the time of diagnosis, highly motivated patients with HbA1c near 7% could be given the opportunity to engage in lifestyle change interventions for a period of 3 to 6 months before the use of any pharmacotherapy.

The results from a trial on T2DM cardiovascular outcomes (Turnbull et al. 2009) suggest that aggressive therapy for glycaemic control can be unbeneficial in some patients, and that long-term, large scale, clinical trials are still needed in order to clarify the benefits and risks of using different treatment approaches, with different pharmacological agents, each with its specific properties and side effects.

OADA are the most common pharmacological therapy in adult patients without ketoacidosis, and are grouped in different pharmacological classes, according to their mechanisms of action. Table 4 presents the OADA available in Portugal, in 2013.

Table 4. Classes and types of antidiabetic oral agents available in Portugal. Adapted from INFARMED (2012) Prontuário Terapêutico 2013. INFARMED, Portugal.

Classes					
Biguanides	Sulfonylureas	α-glucosidase inhibitors	Thiazolidinediones	Meglitinides	DPP-4 inhibitors
Metformin	Glibenclamide Glicazide Glimepiride Glipizide	Acarbose	Pioglitazone	Nateglinide	Sitagliptin Vildagliptin

Metformin is the most well-known biguanide and, in the absence of specific contraindications, is recommended as the initial pharmacotherapy agent for its high level of acceptance, absence of weight gain or hypoglycaemia, generally low level of side effects, and relatively low cost (Nathan et al. 2009). It can reduce HbA1C levels by 1.5%, promote weight loss or weight stabilization, prevent cardiovascular complications, and lower LDL cholesterol and triglyceride levels (Inzucchi et al. 2012; Moghissi et al. 2009). Metformin was also shown to decrease the risk of diabetes-related endpoints and all-cause mortality (UKPDS Study Group 1998a). Metformin decreases hepatic glucose output, and increases insulin-mediated glucose utilization in peripheral tissues, such as muscle and liver, particularly after meals. Its action is dependent on the presence of insulin, and, besides the effects on glucose, has an anti-lipolytic effect that lowers serum free fatty acid concentrations, thereby reducing substrate availability for gluconeogenesis (Clifford J Bailey 1992; Stumvoll et al. 1995).

Metformin is associated with some gastrointestinal side effects, including a metallic taste in the mouth, mild anorexia, nausea, abdominal discomfort, and soft bowel movements or diarrhoea. These side effects are mild, transient, and reversible after a dose reduction or discontinuation of the drug. Due to its effects on glucose utilization,

most current guidelines state that metformin should be initiated concurrently with lifestyle intervention, at diagnosis (Aguilar 2011).

The oldest class of oral hypoglycaemic agents are sulfonylurea insulin secretagogues, which act by stimulating the beta-cells to produce endogen insulin, regardless of glycaemia levels. Sulfonylureas have shown to reduce HbA1C levels by 1-2%, and medications in this class include second-generation sulfonylureas such as glipizide, glimepiride, and gliclazide (Bolen et al. 2007). They are only effective in patients with some pancreatic beta-cell activity, and are contraindicated for type 1 diabetes, advanced liver or kidney disease, sulfa drug allergy, or in situations of ketoacidosis (Moghissi et al. 2009).

Sulfonylureas block ATP-dependent potassium channels in pancreatic beta-cells and reduce the potassium permeability of these cells. This causes a calcium influx and increased insulin secretion, with consequent lowering in plasma glucose (Bolen et al. 2007). In addition, a number of extra-pancreatic effects, such as increased tissue sensitivity to glucose, and reduced hepatic production of glucose, have been described as associated with this class of OADA, but they occur at a minimal level (Schmitz et al. 2002).

The most common side effect of sulfonylureas is hypoglycaemia, especially in older patients, and when using long-acting sulfonylureas. This makes shorter-acting sulfonylureas, such as glipizide, a preferred course of treatment. Risk factors for sulfonylurea use include physical effort, alcohol abuse, stress, poor nutrition, kidney disease, and concurrent therapy with salicylates, allopurinol, sulphonamides, and fibrates. Further adverse effects of this pharmacotherapy include weight gain, hunger, gastrointestinal upset, light sensitivity, and liver abnormalities (Nathan et al. 2009).

Acarbose is an OADA that slows the digestion of complex carbohydrates by inhibiting the upper gastrointestinal enzymes alpha glucosidases, which results in a delayed glucose absorption and decreased postprandial hyperglycaemia. In addition, acarbose reduces the insulinotropic and weight-increasing consequences of sulfonylureas, and is expected to reduce HbA1C levels by 0.5-0.8% (Inzucchi et al. 2012; Rodbard et al. 2009).

Acarbose may be used alone or in combination with other OADA. When used in monotherapy, it has proven to improve the metabolic control of patients (Inzucchi et al. 2012). However, due to its specific mechanism of action, its administration is especially recommended in combination with other agents; for instance, in patients with postprandial hyperglycaemia and increased HbA1C, it may be used as an additive to metformin (Aguilar 2011)

Acarbose administration is contraindicated in patients with diabetic ketoacidosis, cirrhosis, and intestine/bowel problems (e.g., inflammatory bowel disease, intestinal obstruction, colon ulceration, and digestion or absorption disorders). As acarbose slows the digestion of complex carbohydrates, the most common side effects are flatulence, diarrhoea, aerophagia, stomach pain, and bloating. It can also cause higher liver transaminase levels and hypoglycaemia when in combination with sulfonylureas, and increase insulin sensitivity in older patients (ADA 2013a; Rodbard et al. 2009).

Thiazolidinediones are a recent class of OADA, represented currently by pioglitazone for the treatment of T2DM. It acts by reducing insulin resistance and improving glycaemic control, alone or in combination with other OADA, such as sulfonylureas or metformin. Pioglitazone activates a specific nuclear receptor to enhance insulin sensitivity, causing an improved insulin-dependent glucose disposal, and a decreased hepatic gluconeogenesis (Kaku 2009; Schernthaner et al. 2004). As monotherapy, thiazolidinediones are considerably more expensive than generic sulfonylureas and metformin, and seem less effective in lowering glycaemia than metformin: thiazolidinediones lower HbA1C by 0.5 to 1.4%. They are also associated with more weight gain and fluid retention than metformin (Schernthaner et al. 2004). The reported weight gains varies between 3 to 6kg in the first year, and there is also evidence that pioglitazone may lead to peripheral fat mass, fluid retention (which may cause peripheral oedema, particularly in combination with insulin therapy, and induce cardiac failure), muscle pain, sore throat and headaches (Bolen et al. 2007)..

The use of pioglitazone in T2DM must be considered carefully, and it is usually not chosen for initial therapy, being reserved for second-line treatment in combination with other OADA, where synergistic effects can lower HbA1c (Aguilar 2011; Bolen et al. 2007).

Meglitinides are non-sulfonylurea insulin secretagogues that decrease blood glucose levels by stimulating pancreatic insulin secretion. This group includes repaglinide, (not available in Portugal), and nateglinide, which are associated with the same increased risk of weight gain that sulfonylureas. Meglitinides use is more expensive than the use of sulfonylureas, but as the two classes of OADA are pharmacologically distinct, meglitinides may be used in patients who have an allergy to sulfonylureas. Meglitinides use may also imply less risk of hypoglycaemia, making them useful for the treatment of T2DM in elderly individuals when the goal of avoiding hypoglycaemia is very important. Apart from this, there are no further advantages of meglitinides use over sulfonylureas (Nathan et al. 2009).

Nateglinide showed a similar ability to metformin to reduce HbA1c and both OADA can be used simultaneous for and improved effect, especially in postprandial hyperglycaemia. Nateglinide is not recommended for patients with diabetic ketoacidosis and severe hepatic insufficiency. Other side effects of nateglinide include headache, nasal congestion, runny nose, diarrhoea, cough, flu-like symptoms, nausea, back pain, joint pain, and dizziness (Inzucchi et al. 2012; Moghissi et al. 2009).

DDP-4 inhibitors are a class of oral hypoglycaemic agents that block dipeptidyl-peptidase-4, a ubiquitous enzyme that deactivates other bioactive peptides, including glucagon-like peptide-1 and gastric inhibitory peptide, and therefore potentially affect glucose regulation through multiple effects. Sitagliptin and vildagliptin are the only DPP-4 inhibitors available in Portugal (INFARMED 2012).

As DPP-4 inhibitors are more expensive, less effective in lowering glucose levels, and have limited clinical experience, they are mostly administered in combination with other agents, especially in patients who do not react to other monotherapies or when adequate glycaemic control is not provided by combining metformin and sulfonylureas. DPP-4 inhibitors are not associated with weight gain or increased risk of hypoglycaemia, and when used as monotherapy, HbA1C levels decrease by 0.6%-0.9% (Raz et al. 2006).

In sitagliptin-treated patients, reported side effects comprise severe hypersensitivity reactions, pancreatitis, nasopharyngitis, upper respiratory tract infection, and

headache. In patients treated with vildagliptin, clinical trials describe rare cases of hepatic dysfunction, including hepatitis, that is usually asymptomatic (White 2008).

Patients with T2DM can also be treated with insulin, but both patients and providers are often reluctant to initiate insulin therapy, despite its proven efficacy and cost advantage compared with many newer agents; this may be due to concerns about life-restriction, weight gain, hypoglycaemia, and also with the patient's perception that insulin therapy is associated with a worsening of the disease (Peyrot et al. 2005b).

Despite the weight gain and hypoglycaemia risk, data support using insulin earlier and more aggressively in T2DM. After achieving normoglycaemia with intensive insulin therapy, both endogenous insulin secretion and insulin sensitivity improve, and this glycaemic control can be maintained with diet, exercise, and OADA (UKPDS Study Group 1998b).

Most clinicians consider insulin a reasonable choice for initial therapy in patients who present symptomatic or poorly controlled diabetes, and is the preferred second-line medication for patients with HbA1C >8.5% or with symptoms of hyperglycaemia, despite initial therapy with metformin and lifestyle intervention (Inzucchi et al. 2012). In patients with poor glycaemic control on two OADA, switching to insulin is usually preferable than adding a third oral agent. A clinical trial with 188 subjects with T2DM showed that patients on three oral agents (a sulfonylurea, metformin and a thiazolidinedione) had similar glycaemic control, but more side effects, a more atherogenic profile, and substantially higher costs than patients on twice daily insulin along with metformin (Schwartz et al. 2003).

All these multiple approaches to pharmacotherapy will require a thoughtful role for clinicians, who should consider all scientific evidence, all patient-specific factors, and all non-pharmacological treatment options, in order to achieve the therapeutic goals.

1.7.2. Evidence for nutritional therapy in T2DM

The link between nutrition and maintaining adequate blood glucose levels, a lipid profile that reduces the risk for cardiovascular disease, blood pressure in an ideal range, and improved quality of life, has been addressed in several randomized controlled trials and observational studies. Franz et al. (2010), in a comprehensive literature review, expanding on a practice guideline from the Academy of Nutrition and Dietetics (ACD), conclude that there is strong evidence that nutritional therapy provided by registered dietitians is an effective and essential therapy in the management of diabetes (ACD 2008; Marion J. Franz et al. 2010). These authors also report clear improvements in metabolic outcomes, such as glycaemia and HbA1C, in diabetes patients included in nutrition intervention studies, both when interventions have independent nutritional therapy, or when nutrition therapy is provided as part of an overall program for diabetes patient self-management. Other literature reviews of clinical trials and analytical studies concluded that, depending on the duration of the disease, nutritional therapy for T2DM decreases HbA1c between 1% and 2% (Pastors et al. 2002; Pastors et al. 2003).

Data from the UKPDS, with 3044 adults with T2DM, showed that three nutritional interventions in one-month intervals, consisting in the proper adjustment of the macronutrient (carbohydrates, proteins and lipids) and energy contents of the diet, were significantly associated ($p<0.001$) with a reduction of 1.9% in HbA1c, of 4.5kg in weight, of 7.8 mg/dL in LDL cholesterol, and of 28.4 mg/dL in triglycerides (UKPDS Study Group 2000). Ziemer and colleagues, in a randomized controlled trial with 648 T2DM adults, report that four nutrition education counselling sessions, focused on healthy food choices, during a six-month period, were responsible for a reduction of 1.9% in HbA1c and of 35.5 mg/dL in total cholesterol (Ziemer et al. 2003). Different randomized controlled trials recorded mean reductions in HbA1c ranging from 0.3% to 0.7% (M.-C. Huang et al. 2010) and mean weight reductions of 4.8kg (Andrews et al. 2011), and 2.1kg (Coppell et al. 2010a) as a result of six-month nutrition interventions.

The existing evidence supports the claim that lifestyle interventions to improve glucose levels, blood pressure, and lipid levels, and to promote weight loss or at least avoid

weight gain, should be considered throughout the management of T2DM, independently of the use of pharmacological therapy (Nathan et al. 2009). The Standards of Medical Care for Diabetes proposed by the ADA (2013a) further express the importance of nutritional therapy for diabetes, recommending that all individuals with pre-diabetes or diabetes should receive individualized nutritional therapy, preferably provided by a registered dietitian familiar with the process of care and, due to the evidence that nutrition therapy can result in improved outcomes and in treatment cost-savings, that this non-pharmacological treatment should be adequately covered by insurance and other payers.

According to the ADA, the main goals of nutrition therapy for individuals with diabetes are (ADA 2008):

I. To achieve and maintain
    - Blood glucose levels in the normal range or as close to normal as is safely possible
    - A lipid and lipoprotein profile that reduces the risk for vascular disease
    - Blood pressure levels in the normal range or as close to normal as is safely possible

II. To prevent, or at least slow, the rate of development of the chronic complications of diabetes by modifying nutrient intake and lifestyle

III. To address individual nutrition needs, taking into account personal and cultural preferences and willingness to change

IV. To maintain the pleasure of eating by only limiting food choices when indicated by scientific evidence

Nutrition therapy contributes to important and essential outcomes in the management of diabetes, but the relative importance of each nutritional goal varies with individual patient characteristics. Just as several approaches exist for pharmacotherapy, there is no uniform dietary intervention that is appropriate for all diabetes patients. What is essential is that professionals select nutritional therapy interventions that are appropriate to the patient they are counselling and that will lead to positive outcomes.

Randomized controlled trials and observational outcome studies have reported decreases in HbA1C similar to those from OADA, achieved by different types of nutrition interventions, which include reduced energy/fat intake, carbohydrate counting, simplified meal plans, individualized meal-planning strategies, exchange choices, use of insulin-to-carbohydrate ratios, physical activity, and behavioural strategies. The evidence reviews seem consistent in the conclusions that reducing the energy content of usual food intake is paramount to achieve successful outcomes, and that nutritional interventions should have multiple encounters between patient and health professional, in order for education and counselling to be provided on a continued basis (Marion J. Franz et al. 2008).

1.7.3. Nutritional recommendations in T2DM

There is no individual strategy for completely and unequivocally achieving the nutritional goals in T2DM, but there are several evidence-based recommendations for nutritional therapy. The Evidence-Based Practice Committee for the ACD, proposes a set of evidence-based nutrition practice guidelines for adults with type 1 and type 2 diabetes (Franz et al. 2010) that complement previous literature reviews from the ACD. The ADA has also published a set of evidence-based nutrition guidelines (ADA 2008) that have been updated and included in the diabetes standards of medical care and reviewed annually, as new evidence becomes available (ADA 2013a). In the United Kingdom, a group of experts in diet and diabetes in the Diabetes UK Nutrition Working Group proposed evidence-based nutrition guidelines for the prevention and management of diabetes and the implementation of nutrition advice (Dyson et al. 2011), drawn jointly from the ADA recommendations and a literature review of published evidence from 2008 to 2010. These nutrition guidelines were further completed with specific position statements regarding low-carbohydrate diets for people with T2DM (Diabetes UK 2011), and regarding the consumption of carbohydrates in people with diabetes (Diabetes UK 2012). Other widely known evidence-based references include the American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Management

of Diabetes *mellitus* (Rodbard et al. 2007), and the Evidence-based Nutritional Approaches to the Treatment and Prevention of Diabetes *mellitus*, from the European Association for the Study of Diabetes (EASD) Diabetes Nutrition Study Group (Mann et al. 2004). Despite some differences in these reviews and position statements, the general agreement suggests that nutrition therapy must be aimed at weight loss/maintenance interventions, at adequate distribution of macronutrients and eating patterns and, also, to coadunate with other interventional strategies, like promoting physical activity.

Specifically, nutrition intervention should consider the caloric intake, the consistency in day-to-day carbohydrate intake in all meals, as well as the timing for the meals and the nutritional content of foods. Weight loss and management interventions must be combined with increased physical activity, appropriate to the characteristics of the patient (e.g., age, mobility, diabetes complications).

The nutritional treatment and management of T2DM is a complex process that should be started at diagnosis and maintained throughout all activities of patient care. The ACD recommends the process to be started by an initial series of three to four sessions or consultations with a dietitian, each lasting from 45 to 90 minutes, during the first three to six months after diagnosis. After this period, at least one yearly follow-up encounter is recommended, to reinforce lifestyle changes and to evaluate and monitor outcomes. As the patient progresses towards desired outcomes, additional sessions should be held if the health professional considers appropriate (ACD 2008).

The Diabetes UK recommendations propose that every patient and/or their carer should receive diabetes education at the time of diagnosis, with an annual follow-up, and that nutritional advice from a registered dietitian should be constant during patient education (Dyson et al. 2011).

The nutrition intervention during initial patient evaluations must include the assessment of food intake, use of OADA, and levels of metabolic control, as inferred by glycaemia, lipids, and blood pressure. Physical activity habits and anthropometric measurements, such as weight, waist circumference or percent of fat mass, should also be recorded, in

order to serve as the basis for implementation of the nutrition prescription and to establish the goals and type of intervention (ACD 2008; ADA 2008; Dyson et al. 2011; Mann et al. 2004). The goal set for glycaemic control should be the lowering of HbA1c to around 7%. This goal may be set lower than 7%, and as close to normal as possible (below 6%), if this can be achieved without significant hypoglycaemia. Patients who have adequate pre-prandial glycaemia values but have HbA1C values above target, should be monitored regarding PPG, in order to reduce PPG between one to two hours after the start of a meal to levels below 180 mg/dl (ADA 2013a).

1.7.3.1. Weight management

Weight control plays a pivotal role in the treatment and management of T2DM, and, during patient assessment, the relative importance of weight control for the overweight or obese patient should be analysed. Modest weight loss has been shown to improve insulin resistance, but sustained interventions lasting one year or longer reported inconsistent effects on glycaemic control (Wing et al. 2011).

Data from the Look AHEAD (Action for Health in Diabetes) study, a randomized trial in 5145 overweight or obese T2DM patients with the aim of assessing if weight reduction and physical activity can reduce cardiovascular disease morbidity and mortality, suggest that at one-year follow-up, weight reduction was associated with the frequency of education interventions. This study randomized patients in either intensive lifestyle intervention (ILI) or diabetes support and education (DSE). After one year, ILI subjects had a higher reduction in average body weight and improvements in cardiovascular fitness and HbA1c when compared to DSE subjects (Look AHEAD 2007). Patients in the ILI group had weekly individual or group education interventions for the first six months, and three times per month from the seventh month up to the end of the first year of follow-up. Weight reduction at one year was associated with improvements in triglycerides and HDL cholesterol, greater in individuals who lost 10% to 15% of their initial body weight (Look AHEAD 2007). The weight-loss strategies associated with a lower BMI were regular self-weighing, eating breakfast, and infrequent consumption of

fast food (Raynor et al. 2008). Better attendance levels in education sessions, and exercising a mean of 137 minutes/week, were indicators of success after one year. Greater self-reported physical activity presented the strongest correlation with weight loss (Thomas A. Wadden et al. 2009).

In this study, from the second through the fourth year of follow-up, the ILI subjects were accompanied in a monthly, individual or group-based, educational session, while the DSE group patients were invited to three group sessions each year. The results from the follow up show a maximal weight lost by the end of the first year, with slow weight regain in the ensuing years (Thomas A. Wadden et al. 2011). This provides an important insight on the determinants of maintaining weight loss, even when patients are provided with frequent education opportunities and support at no cost.

As weight reduction is effective in improving glycaemic control and cardiovascular risk factors, this should be the primary nutritional strategy in managing glycaemic control for T2DM patients who are overweight or obese. Dietary, physical activity, surgical, and pharmaceutical approaches that are currently recommended for individuals without diabetes can be adopted by diabetes patients with the guidance of a health professional (Dyson et al. 2011).

The main strategy in a dietary approach for weight reduction is to balance energy intake in a way that it becomes less than energy expenditure. This can be achieved by first obtaining the individual estimated energy requirement by predictive equations, like the Harris-Benedict equation, one of the more commonly used predictive equations to estimate basal energy expenditure used in clinical settings (Rippe and Angelopoulos 2012), or by the set of equations from the report on dietary reference intakes from the Institute of Medicine (IOM) in the USA (IOM 2005)

The equation set from the IOM allows the determination of estimated energy expenditure according to factors that that account for energy expenditure, age, sex, weight, height, and physical activity level, based on the energy intake needed to maintain energy balance in individuals with healthy weights, as measured by doubly-labelled-water (IOM 2005).

In order to promote weight loss, a trained health professional can encourage an energy reduction of 500 kcal/day, or obtain the energy requirements for a safe weight goal below the current weight, and prescribe a meal plan accordingly. Weight loss is then monitored and assessed in order to assure a correct decrease in fat body mass (Rippe and Angelopoulos 2012).

1.7.3.2. Macronutrient composition of the diet

Although the focus in nutritional therapy for glycaemic control should be total energy intake, the macronutrient composition is also important, as the total amount of carbohydrate consumed is a strong predictor of glycaemic response (Dyson et al. 2011). Nevertheless, it is unlikely that an ideal macronutrient intake exists for all T2DM adult patients (ACD 2008; ADA 2008; Marion J. Franz et al. 2010; Wheeler et al. 2012).

Different macronutrient distributions have shown different results in weight management, lipid profile and metabolic control in T2DM patients.

Results from a randomized controlled trial show that a high carbohydrate diet, compared with a diet high in monounsaturated fat, is associated with a modest rise in blood pressure. Nevertheless, high total fat intake might increase the risk of atherosclerosis, and excess protein could promote the development of diabetic nephropathy (M. Shah et al. 2005).

Wheeler et al., in a systematic review analysing research on macronutrients, food groups, and eating patterns in the management of diabetes, concluded that several different macronutrient distributions may lead to improvement in glycaemic and/or cardiovascular disease risk factors, but the results were inconclusive regarding an ideal macronutrient balance. This study analysed very-low-carbohydrate diets (with 21 to 70 g/day of carbohydrate), moderately low–carbohydrate diets (30 to 40% of daily energy intake as carbohydrate), moderate-carbohydrate diets (40 to 65% of daily energy intake as carbohydrate), and high-carbohydrate diets (65% of daily energy intake as carbohydrate). The authors reported that when total carbohydrate intake was low,

markers of glycaemic control and insulin sensitivity improved, but the short duration of the low-carbohydrate diet, the lack of randomization, and the high dropout rates in some studies, do not allow to recommend a specific low-carbohydrate distribution. Serum lipoproteins typically improved with reduction of total carbohydrate intake but, with the exception of HDL cholesterol, were not statistically better than those of the comparison diet (Wheeler et al. 2012).

Based on similar results, the ADA suggests that either low-carbohydrate or low-fat calorie-restricted diets may be effective to reduce weight and to improve glycaemic control, up to one year. During the course of the diet, hypoglycaemia should be prevented and also for patients on low-carbohydrate diets, lipid profiles, renal function, and protein intake must be monitored and adjusted as needed, especially if OADA are used (ADA 2013a).

Overall, research does not support an ideal percentage of energy from macronutrients in the daily meal plan for patients with diabetes, and the macronutrient distribution should be adjusted to meet individual metabolic goals (ACD 2008; ADA 2008, 2013a; Dyson et al. 2011; Nield et al. 2007; Wheeler et al. 2012). According to this evidence, it is recommended that the macronutrient intake in T2DM patients should follow the patterns associated with a healthy, balanced diet (ACD 2008; Dyson et al. 2011).

The macronutrient content of a healthy daily diet can be prescribed based on the dietary reference intakes reported by the IOM (2005), presented in table 5.

Table 5. Acceptable distribution ranges for macronutrients. Adapted from Institute of Medicine (2005) Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients), National Academies Press.

Macronutrient	Acceptable distribution ranges of total energy intake (%)
Carbohydrate	45–65
Fat	20–35
Protein	10–35

Regardless of the macronutrient distribution, total energy intake must be appropriate for weight management and there should be an encouragement for food choices that the patient is able and willing to follow in the long term (ADA 2008). A diet that a patient enjoys and finds acceptable is more likely to succeed and to lead to improved outcomes, as it seems that diet outcomes are predicted by the degree of diet adherence rather than by the type of dietary intervention (Nield et al. 2007).

Individualization of the macronutrient composition of the diet can be considered, depending on the metabolic status of the patient, which may present a lipid profile that can benefit from specific interventions. There is evidence that nutritional therapy provided by a dietitian to individuals with dyslipidaemia can reduce patients' daily dietary fat by 5% to 8%, with a decrease in 2% to 4% in saturated fat. This can result in a reduction in serum total cholesterol between 7% and 21%, in LDL cholesterol reduction between 7% and 22%, and in triglycerides reduction between 11% and 31% (ACD 2011).

Patients with diabetes have an increased risk of cardiovascular disease (CVD), estimated to be about the same as in individuals without diabetes but with pre-existing CVD. This is partly due to abnormalities in plasma lipids and lipoprotein concentrations that are common in T2DM (Buse et al. 2007). Due to this similarity in CVD risk, an ACD review of 43 studies related to the prevention and treatment of CVD in diabetes, recommends that the dietary goals for patients with diabetes should be the same as for individuals with pre-existing CVD. It is also suggested that a cardio-protective nutrition intervention should be implemented in the initial series of nutrition therapy sessions (ADA 2008; Marion J. Franz et al. 2010).

A cardio-protective nutrition intervention should provide 20% to 35% of calories from fat, with less than 7% of calories from saturated (SFA) and *trans* fatty-acids (TFA). The association between TFA and elevated levels of total and LDL cholesterol leads to believe that TFA intake should be as low as possible. Furthermore, cholesterol intake should be below 200 mg/day, and the majority of total fat intake should be derived from unsaturated fat sources (ACD 2011). The ADA recommends that HDL cholesterol should be above 40 mg/dL in men and above 50 mg/dL in women, and that the desirable goal

for triglyceride levels is below 150 mg/dL (ADA 2013a). In individuals without overt CVD the goal should be to achieve a LDL cholesterol below 100 mg/dL, and in individuals with overt CVD, a lower LDL cholesterol goal below 70 mg/dL.

Overall, regarding lipid profile in T2DM, the main position papers are in agreement that the goals are to limit SFA below 7% of total energy, a minimal intake of TFA, and cholesterol intake below 200 mg/day, so as to reduce risk for CVD (ACD 2008; ADA 2013a; Dyson et al. 2011). Further recommendations include a daily consumption of foods fortified with plant sterols or stanols (2g to 3 g⁄day), which significantly improve total and LDL cholesterol in diabetes patients, irrespective of statin treatment (Dyson et al. 2011). The consumption of oily fish, rich in ω-3-unsaturated fats, is recommended at least twice per week (ADA 2008; Dyson et al. 2011).

Weight loss can also benefit lipid profile, as it has been shown that it can decrease triglycerides and raise HDL cholesterol (Look AHEAD 2007). Nutrition interventions like the DASH diet (Azadbakht et al. 2011), Mediterranean-style eating patterns, and high-protein diets also seem effective in improving various markers of cardiovascular risk in patients with diabetes, and should be considered in the overall strategy for the management of the disease (Ajala et al. 2013).

Although there is evidence that high-protein diets promote significant decreases in serum total cholesterol, LDL cholesterol, triglyceride levels, and blood pressure, these results are only reported in studies with a short-term follow-up (Ajala et al. 2013; Wheeler et al. 2012). Considering the available evidence from systematic reviews and randomized controlled trials in diabetes patients with normal renal function, neither the ACD (ACD 2008; Marion J. Franz et al. 2010), the ADA (2008) or the Diabetes UK organization (Dyson et al. 2011) support recommending a change in the usual protein intake of 15% to 20% of total daily energy intake. This includes the use of high-protein diets as method for long-time weight loss, as the long-term effects of protein above 20% of total caloric intake are still unclear (ACD 2008). Exceptions for suggesting different changes in protein intake are in individuals with an excessive intake of protein-rich foods that are high in SFA, in people who have a protein intake of less than 0.8g good-quality

protein/kg body weight/day, or in patients with diabetic nephropathy (Wheeler et al. 2012).

The role of carbohydrates in glycaemic control, and in insulin secretion and action led to believe that managing carbohydrate intake is a primary strategy for achieving glycaemic control. But although the total amount of carbohydrate ingested is the main determinant of postprandial blood glucose response, there is little evidence to support specific recommendations for carbohydrate intake in T2DM (Dyson et al. 2011). In type 1 diabetes or in T2DM patients treated with insulin, additional monitoring is needed to achieve an adequate balance between carbohydrate intake and insulin units administered, but, overall, the total amount of recommended carbohydrates is in accordance with the guidelines for carbohydrates in a healthy diet.

The acceptable macronutrient distribution ranges from the IOM predict 40% to 60% of total daily intake in the form of carbohydrates, and set a recommended dietary allowance (RDA) for carbohydrates of at least 130 g/day for adults and children. This RDA is based on the estimated average requirement for carbohydrate ingestion that will provide the brain with adequate glucose, and a coefficient of variation of 15% based on the variation in brain glucose utilization. The RDA is equal to the estimated average requirement plus twice the coefficient of variation, to cover the needs of 97–98% of individuals (IOM 2002).

Evidence suggests that most patients with diabetes do not eat a low- or high-carbohydrate diet, but rather have a moderate intake of this macronutrient. Data from the USA general population suggest that individuals have an intake of carbohydrates corresponding to approximately 50% of the total daily caloric intake (Marriott et al. 2010; Moshfegh et al. 2005), which does not differ significantly from reported intakes in patients with diabetes. A sample of 2757 food frequency questionnaires completed by T2DM patients in the Look AHEAD trial showed an average carbohydrate intake of 44% (Vitolins et al. 2009). Other results included the findings that more than 10% of total calories were from saturated fat, and that 20% of participants met the proposed fibre goal, while less than 50% met the minimum recommendation for servings of fruits,

vegetables, dairy foods, and whole grains. Although the proportion of total carbohydrates is adequate in this study, the qualitative analysis conducted suggests that the reported proportion is achieved with a dietary pattern than can be improved. Other studies reported an intake of carbohydrates of approximately 46% in individuals with type 1 diabetes (Delahanty et al. 2009) and approximately 44% in patients with T2DM (Esposito et al. 2009). Data from the UKPDS also suggest that despite receiving individual education from dietitians that was designed to promote a carbohydrate intake of 50–55%, patients with T2DM report a carbohydrate intake of 43%, similar to the intake of the general population.

When comparing higher-carbohydrate diets to low-carbohydrate diets, data from clinical trials report similar improvements in HbA1c, and it appears likely that the total energy intake of the eating pattern outweighs the distribution of carbohydrates. High-carbohydrate diets are generally low in fat, and tend to have beneficial effects on total cholesterol and LDL cholesterol, whereas low-carbohydrate diets tend to have beneficial effects on triglycerides and HDL cholesterol (Wheeler et al. 2012). On account of the relative similarities in outcomes, it seems prudent to recommend an eating pattern with moderate amounts of carbohydrate, which includes carbohydrates sources like fruits, vegetables, and whole grains, in appropriate amounts and portion sizes (ACD 2008).

As day-to-day consistency in the amount and source of carbohydrate intake is associated with improved glycaemic control in type 1 diabetes (Wolever et al. 1999) and in T2DM (Boden et al. 2005), the ACD recommends, in its practice guidelines, that patients with diabetes receiving either medical nutrition therapy alone, glucose-lowering medications, or fixed insulin doses, should consistently distribute carbohydrate in meals throughout the day, on a daily basis (ACD 2008). The same guidelines add that patients that administer insulin should adjust insulin doses to match carbohydrate intake, which can be adequately achieved by collaboration with the health care team and by comprehensive nutrition education on interpretation of blood glucose patterns and nutrition-related medication adjustment (ACD 2008; Marion J. Franz et al. 2010).

Overall, the different position statements agree that the adequate carbohydrate intake for the treatment and management of T2DM should be similar to the one in the acceptable ranges in the general population. If weight loss is to be encouraged, either low-carbohydrate or low-fat calorie-restricted diets may be effective up to one year (ACD 2008; ADA 2008; Marion J. Franz et al. 2010).

Regarding the type of carbohydrates that should exist in patients' daily meal plan, it is recommended that sucrose-containing foods can be substituted for other carbohydrates, in order to avoid excess intake in energy, and excess intake of simple, fast-absorbing carbohydrates. Intake of dietary fibre, a group of no digestible polysaccharides, is encouraged in the same amount as for the general population. There is not enough evidence to recommend a higher fibre intake for diabetes patients (ADA 2008).

Diets containing a daily fibre intake between 44g to 50 g seem associated to an improved glycaemic control, while more usual intakes (up to 24 g/day) have not shown beneficial effects on glycaemia (Marion J. Franz et al. 2010). Nevertheless, the evidence sustaining high-fibre diets is reported in a controlled, experimental setting, with a short follow-up period. The meal plan needed to achieve a daily intake of 50g of dietary fibre cannot be easily sustained in a free-living environment. The current agreement is that fibre intake for patients with diabetes should be similar to the recommendations for the general population, which state that daily diet should include foods containing 25–30g of fibre, with special emphasis on soluble fibre sources (between 7g and 13 g), on account of their beneficial effect on lipid profile (ADA 2008). A prospective study with a 26-year follow-up of 7822 women with T2DM showed that intakes of whole grain, cereal fibre and bran were inversely associated with all-cause and CVD mortality (He et al. 2010), contributing to the evidence that fibre-containing foods such as legumes, fibre-rich cereals, fruits, vegetables, and whole-grain products should be privileged (ADA 2008). Regarding fibre intake, the ACD notes that it may be difficult to meet dietary fibre recommendations with a low carbohydrate intake, so weight-loss diets with low carbohydrate content must be adequately planned (ACD 2008, 2011).

1.7.3.3. Glycaemic index of carbohydrates

When considering carbohydrate intake in patients with diabetes, some evidence has suggested that the use of glycaemic index (GI) for meal planning can provide a modest additional benefit over the one observed when total carbohydrate is considered alone (ADA 2008).

The glycaemic index measures the relative area under the glucose curve of 50 g digestible carbohydrate, compared with 50 g of a standard food, either glucose or bread (although glucose is the usual reference). This allows to rank foods according to their blood glucose response and to infer that foods with a lower GI are associated with a less pronounced response, producing gradual rises in blood sugar and insulin levels (Wolever 2013).

Research that suggests advantages of the GI is controversial. A one year controlled trial with T2DM patients has shown no evidence of benefit of low glycaemic index over other nutritional strategies (Wolever et al. 2008), but a review of randomised controlled trials with follow-up of four weeks or longer reports a decrease of 0.5% in HbA1c in low GI diets (Thomas and Elliott 2009). Recent evidence considers that the GI has limitations as an indicator of carbohydrate quality compared with other measures such as dietary fibre or whole grains (Wolever 2013), and the practice guidelines of the ACD for nutritional therapy in diabetes suggest that if the GI is proposed as a method of meal planning, the patient should be advised on the conflicting evidence of effectiveness of this strategy (ACD 2008; Wheeler et al. 2012). The ADA notes that most individuals already consume a moderate-GI diet, but states that, however, for individuals consuming a high-GI diet, consuming a low-GI diet may result in a modest benefit in postprandial hyperglycaemia (ADA 2008).

1.7.3.4. Micronutrient contents of usual diet

Other agreements on nutritional therapy for diabetes focus on micronutrients and alcohol consumption.

Micronutrients are vitamins and minerals, which are required in small quantities for specific physiological functions. Micronutrients often function as coenzymes or cofactors for metabolic processes and, as such, are involved in the metabolism of carbohydrates and other nutrients, and with the body's use of glucose and insulin. Healthy adults can receive all the necessary nutrients from foods, but specific populational groups, such as growing and developing children and youths, pregnant and lactating women, individuals with a low energy intake (less than 1,200 kcal/day), elderly individuals, patients in intensive care units or long-term nursing facilities and vegetarians, have an higher risk of micronutrient deficiency (Marion J. Franz et al. 2010).

Patients with diabetes that exhibit poor glycaemic control also seem more likely to have deficiencies in magnesium, zinc, vitamin D, and water-soluble vitamins (Marion J. Franz et al. 2010; Pastors et al. 2002), but the current evidence does not justifies for routine supplementation of vitamins and minerals in patients with diabetes (ACD 2008; ADA 2013a).

Systematic reviews on micronutrient intake and diabetes report that findings from small clinical and animal studies, where diets can be manipulated easily in comparison to the diet of human free-living subjects, are frequently extrapolated to clinical practice, and that human studies with diabetes patients often do not take into account that urinary losses are increased if uncontrolled hyperglycaemia with glycosuria is present. This leads to biases in the recorded effect of the response to micronutrients (Marion J. Franz et al. 2010; Wheeler et al. 2012)

The nutritional therapy guidelines for diabetes state that, presently, there is no evidence of benefit from vitamin or mineral supplementation in diabetes patients without underlying evidence of a deficiency, but it is recommended that meal planning includes

optimization of food choices to meet the daily recommended intake (DRI) for all micronutrients (ACD 2008; ADA 2013a).

1.7.3.4. Alcohol intake

Recommendations on alcohol intake in diabetes follow the same trend as other recommendations, as there is no data to support alcohol use to people with or without diabetes who do not currently drink. Abstinence is recommended for individuals with risks related to alcohol consumption but, for patients who consume alcohol in moderation, alcohol consumption does not need to be discouraged if limited to one drink per day or less for adult women, and two drinks per day or less for adult men (ACD 2008; ADA 2013a). This allowed intake is based on the protective effect of alcohol against coronary heart disease, reported in the general population. Several systematic reviews and meta-analysis (Corrao et al. 2004; Rimm et al. 1999; Xin et al. 2001) document a 10 to 40% reduction in risk associated with one to three drinks per day. This is attributed to the association of alcohol with increased HDL cholesterol, decreased platelet aggregation, decreased clotting factors such as fibrinogen, improvement in markers of inflammation and endothelial dysfunction, and enhanced insulin sensitivity. This association seems consistent, backed by the existence of plausible biological mechanisms, but the true magnitude of the effect of alcohol may be lower than suggested, due to difficulties in removing confounding factors from comparisons, as well as the problems caused by the use of non-drinkers as the reference group (Corrao et al. 2004).

In T2DM, moderate alcohol consumption is associated with decreased CHD and mortality risks, and decreased total mortality. The type of alcoholic beverage does not influence beneficial effects, and the most consistent mechanism reported for the beneficial effects is an increase in insulin sensitivity. Improvements in markers of inflammation and endothelial dysfunction are also reported (Koppes et al. 2006; I. Shai et al. 2004).

Moderate consumption of one to two alcoholic drinks (15g to 30g/day) has minimal effects on the glycaemia of patients with, and a U- or J-shaped association is reported between these variables, supporting the benefits from moderate alcohol consumption (Iris Shai et al. 2007).

A systematic review of the effect of alcohol concludes that moderate consumption does not acutely impair glycaemic control in T2DM patient, and may actually result in a small decrease in glycaemia concentrations. On the other hand, chronic ingestion (above 45 g/day) is associated with deterioration in glucose control (Howard et al. 2004).

1.7.4. Physical activity and nutritional therapy efficacy

The success of nutritional therapy is also determined by other interventions and care strategies, such as physical activity. In T2DM, physical activity paired with nutrition interventions for weight loss has shown to be helpful in achieving weight control, and improve glycaemia, blood pressure, and lipid profile (Marion J. Franz et al. 2010). A joint position statement of the ADA and the American College of Sports Medicine on exercise and T2DM, which also includes an evidence-based literature review, reports that regular exercise improves blood glucose control, reduces cardiovascular risk factors, contributes to weight loss, and improves well-being. Both aerobic and resistance training improve insulin action, glucose control, and fat oxidation in muscle tissue (Colberg et al. 2010).

The Pre-diabetes Risk Education and Physical Activity Recommendation and Encouragement (PREPARE) study suggests that the benefits of moderate physical activity are sustained after 24 months (Yates et al. 2011), with subjects who underwent a 3h structured education session with personalized pedometer use showing a significant reduction in 2h post exercise plasma glucose, when compared with a control group.

Physical activity is also important for maintenance of weight loss, as suggested by the results of the Look AHEAD trial, in which 4-year data indicated that greater physical activity is a factor for success in minimizing weight regain (Wadden et al. 2011).

The evidence on the benefits of physical activity is reflected on the standards for diabetes care, which state that exercise is an important part of the diabetes management, and that adults with diabetes should perform at least 150 minutes every week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least three days, with no more than two consecutive days without exercise. Furthermore, in the absence of contraindications, adults with T2DM should be encouraged to perform resistance training at least twice per week (ADA 2013a).

Individuals who already exercise at moderate intensity may be encouraged to consider increasing the intensity of their exercise to obtain additional benefits in both aerobic fitness and glycaemic control (Franz et al. 2010)

1.7.5. Adherence to treatment and management of T2DM

The pathophysiology of diabetes and its complications entail that the treatment and management of diabetes require a long-term, multifaceted and comprehensive approach that includes nutritional therapy, physical activity combining aerobic and resistance training, and behavioural modification strategies. As the disease progresses, most patients require an increasing care in order to be able to achieve glucose, lipid, and blood pressure targets. This increase in care implies an additional effort from health care providers and also an increased patient commitment to adhere to the behaviours associated with an adequate treatment and management of the disease (ADA 2013a).

The majority of daily care in diabetes is handled by patients or families (Asche et al. 2011a), making evident the importance of patient self-care. Nevertheless, being compliant to self-care activities will not lead to good metabolic control. Metabolic control is a combination of many variables, not just patient compliance (Sabatâe 2003; Schechter and Walker 2002; Seidu and Khunti 2012). A literature review highlights adherence, attitude, beliefs, knowledge about diabetes, culture and language capabilities, health literacy, financial resources, co-morbidities, and social support, as patient-related determinants of glycaemic control (Nam et al. 2011). The same study

identified effective communication, and the attitude, beliefs and knowledge about diabetes, as clinician-related determinants.

According to the American Association of Diabetes Educators (AADE), self-care activities are behaviours undertaken by people with or at risk of diabetes in order to successfully manage the disease on their own. The AADE identified seven essential self-care behaviours for diabetes patients, positively correlated with good glycaemic control, with the reduction of complications, and with improvement in quality of life. These essential behaviours are healthy eating, being physically active, monitoring of blood sugar, compliant with medications, good problem-solving skills, healthy coping skills and risk-reduction behaviours (AADE 2008). A recent literature review states that self-care encompasses not only performing these essential activities, but also the interrelationships between them, as diabetes self-care requires the patient to make dietary and lifestyle modifications with the supportive role of healthcare providers in order to maintain a high level of self-confidence. Adherence to these activities has been found to be low, especially when looking at long-term changes, as diabetes patients are expected to follow a complex set of actions on a daily basis, further complicated by the need to integrate and sequence these actions into daily routine (Shrivastava et al. 2013).

Adherence to treatment is defined as the active, voluntary involvement of the patient in the management of his or her disease, by following a mutually agreed course of treatment and sharing responsibility between the patient and health care providers (Barofsky 1978). In health studies, non-adherence to treatment regimens has been described and measured as complying in less than 80% of the prescribed treatment (Delamater 2006), and it is believed that, as a group, diabetes patients are especially prone to substantial adherence problems (Day 2000; Kurtz 1990; Shrivastava et al. 2013). A 2003 report from the WHO states that non-adherence rates for chronic illness treatment regimens and for lifestyle changes are approximately 50% (Sabatâe 2003) and, in the case of diabetes, literature reviews report general adherence to treatment ranging from 23% to 77% (Cramer 2004; Delamater 2006; Walker and Usher 2003). Adherence to one component of the treatment also seems independent of the

adherence to other components (Walker and Usher 2003), as research suggests that adherence to pharmacotherapy is higher than adherence to nutritional therapy or lifestyle change behaviours (Asche et al. 2011a; Cramer 2004; Sabatâe 2003). A Portuguese study on adherence to therapy in T2DM patients also reflects these results, recording an adherence to pharmacotherapy that is higher than to nutritional therapy and physical activity (do Ó and Loureiro 2007). However, it is believed that the methods for measuring adherence can be biased, and that there are serious methodological problems in the treatment of diabetes adherence estimates (Schechter and Walker 2002). This can account, in part, for the wide range of results in the published estimates of adherence.

Adherence to pharmacotherapy seems to be the behaviour with the highest prevalence, with reports of adherence to therapeutic regimens of OADA ranging from 70% to 80% (Ahmad et al. 2013; Asche et al. 2011a; Cramer 2004). Glucose monitoring, even with the availability of technologies that allow patients to conveniently measure glycaemia at home, is infrequent in T2DM patients, with several studies reporting approximately one third of participants as non-adherent to regular glycaemia monitoring (Adams et al. 2003; Karter et al. 2000; Vincze et al. 2004). Regular physical activity also presents a low prevalence in diabetes patients, with a literature review reporting an adherence to a physical activity plan of 26%, and stating individuals with diabetes are considered among the least likely to engage in regular physical activity (Qiu et al. 2012). This review also suggests that only 25% of older adults with diabetes meet the recommendations for physical activity proposed by the ADA (2013a).

Adherence to proper dietary habits can also be improved. An USA cross-sectional study suggests that approximately half of diabetes patients follow a meal plan (Jill Armstrong Shultz 2001). An Italian sample of 540 patients with T2DM showed that 43% of patients had an intake of more than 10% of saturated fat, and only 6% of patients had an adequate intake of fibre. Caloric intake exceeded the individual estimated daily requirements in about 300 kcal in men and in about 200 kcal in women (Rivellese et al. 2008). A cross-sectional study in 1895 patients with T2DM from six countries in the

Mediterranean Basin (Greece, Italy, Algeria, Bulgaria, Egypt and Yugoslavia) reports that dietary habits vary greatly among countries, showing a clear trend for low carbohydrate intake and high fat and protein intakes, resulting in a poor compliance with nutritional recommendation (Mann et al. 2004). In this study, dietary habits were compared with the nutritional recommendations of the Diabetes Nutrition Study Group of the EASD, and compliance after age-standardisation ranged from 3.5% in Bulgaria to 56.4% in Egypt for carbohydrates, and from 5.7% in Bulgaria to 67.3% in Yugoslavia for fat.

It is suggested that low adherence to dietary recommendations can be improved by nutritional education by a trained professional. Norris et al. (2002), in a meta-analysis of 31 studies, report that contact time with a diabetes educator was the best predictor of improvements in glycaemic control. A cohort study with 18404 diabetes patients followed between 1993 and 2001 revealed that educational consultations, especially by a trained nutrition professional, were associated with fewer hospitalizations and reductions in total hospital charges (Robbins et al. 2008). Despite these data, the literature suggests that not all patients receive nutrition education. Results from the Diabetes Prevention and Control Programs in the USA from 2000 to 2010 indicate an yearly mean of 45.1% of patients with diabetes who report that they did not attend any type of diabetes self-management class (CDC 2011). Robins and colleagues (Robbins et al. 2008) also report that only 9.1% of patients had at least one nutrition consultation with a dietitian within a 9-year period.

A report from the Portuguese Health Regulation Authority (*Entidade Reguladora da Saúde* – ERS), the independent public body responsible for regulating the activity of health care providers in Portugal, states that the National Health System coverage for dietitian consultations for diabetes patient is far from adequate. There are several Health Centres without a dietitian and the report concludes that, considering the impact that nutrition has on diabetes patients, the lack of appropriate response is reason for great concern. The ERS recommends that a multidisciplinary consultation is needed, with support by a dietitian, in order to implement Nutrition Therapy and Education Programs for diabetes patients (Entidade Reguladora da Saúde 2011).

The literature on the determinants of food choice has reported the complexity of the process of selecting food, indicating that what we choose to eat is not only determined by physiological factors, but also by major biological, economic, physical, social and psychological factors (Nestle et al. 1998; Sobal and Bisogni 2009). The predominance of the different determinants of food choice varies according to the stage of life and health status, thus implying that an intervention to modify food behaviour will not suit all population groups. This constitutes a challenge for health and nutrition professionals, who need to adequately tailor their health promotion messages to their specific target population. As food intake is of paramount importance in the control of T2DM and in the prevention of its associated comorbidities, the identification of factors influencing patients' decisions on food choice can prove to be extremely useful in the quality of care that is to be provided.

Health psychology research has helped to enlighten the understanding of the way people make decisions about their health and has been the source of health behaviour models which have been used to predict the likelihood that dietary behaviour change will occur (Spahn et al. 2010).

It is known that changing food behaviour is not an easy task because it requires alterations in habits that have been built up over the course of an extended period of time, but targeted interventions that include behaviour and nutrition counselling have proven to be successful in primary care and community settings, including in T2DM patients (Spahn et al. 2010).

As previously stated, a proper food intake in patients with T2DM is associated with improvements in metabolic outcomes and with the delay of health complications, contributing to the conclusion that nutritional therapy is an effective and essential therapy in the management of diabetes (ACD 2008). Nevertheless, adherence to the behaviours needed to achieve and maintain a healthy diet has been reported as being low, especially in diabetes patients (Shrivastava et al. 2013).

Reports from focus group studies state that the diagnosis of T2DM seems to inflict an emotional toll on the patients, who identify stress, frustration, depression, and denial,

as factors inhibiting adherence to a healthy mode of living. Patients also frequently mention the failure to recognize the risks and consequences of diabetes as a promoter of low adherence to therapy, while suggesting that they feel the need for additional counselling, like follow-up consultations and refresher courses, support group discussions, nutrition and medication education, availability of different education modalities, and expanded clinic hours (Gazmararian et al. 2009; Jerant et al. 2005; Toobert et al. 2000; UKPDS Study Group 1995b; Vijan et al. 2005).

Besides the lack of awareness of the disease and of educational programs for its control, patients also report dissatisfaction with the nutritional advice given, namely the perceived low applicability of the nutritional advice to patients' daily routine (Jerant et al., 2005).

Other factors for low adherence to nutrition and lifestyle changes include social and family pressures for maintaining eating habits, due to the social gathering nature of meals, comorbidities like osteoarthritis, which make patients feel that they cannot participate in regular exercise, and financial issues, with patients stating that they believe that a healthy diet is more expensive (Gazmararian et al. 2009; Jerant et al. 2005; Toobert et al. 2000; UKPDS Study Group 1995b; Vijan et al. 2005). Some patients also consider a burden to change their diet, comparing the troubles of a diet aimed at weight loss to the burden they associate with daily insulin injections, and perceiving the food portion sizes in a recommended diet as small for their nutritional needs (Gazmararian et al. 2009; Jerant et al. 2005; Toobert et al. 2000; UKPDS Study Group 1995b; Vijan et al. 2005).

The determinants of food choice are influenced by health status, thus making an analysis on the role of glycaemic control in the adherence to a proper diet and in the perception of barriers to adequate food behaviour in T2DM, a direction in research that can contribute to improve the care provided to diabetes patients.

1.7.6. Novel therapies and monitoring systems

The burden that diabetes and its complications pose for patients and for health systems, together with the still unclear pathogenesis of this disease and the high worldwide prevalence, have established the importance for continuous research and development of diabetes preventions strategies, therapies, and disease monitoring systems. Improvements in technology and care efficiency have played a role in controlling both type 1 diabetes and T2DM, and there are, currently, several branches of research that may lead to promising results in this field.

Recently, a novel class of pharmacological agents called sodium- glucose cotransporter 2 (SGLT2) inhibitors has been studied and suggests good results in T2DM control (Kim and Chung 2014; Riser Taylor and Harris 2013). SGLT2 inhibitors contribute to reduce the reabsorption of filtered glucose in the kidney and lowering the blood glucose concentration at which glucose is no longer reabsorbed from the proximal tubule but is instead excreted (L. H. Chen and Leung 2013).

The current approved drugs in this class are dapagliflozin, canagliflozin and empagliflozin, with others undergoing phase II or phase III clinical trials (Kim and Chung 2014; Riser Taylor and Harris 2013). SGLT2 inhibitors could be a promising therapeutic agent that acts independent of insulin secretion, and can also provide useful to treat co-morbidities of diabetes such as hypertension, obesity, and dyslipidaemia. Epidemiological surveillance will ultimately assess the safety and efficacy of SGLT2 and further studies are needed for assessing their long-term benefits and risks in larger populations, but the inhibition of SGLT2 represents a highly promising therapeutic approach for T2DM treatment (Haas et al. 2014; Kim and Chung 2014).

Improvements in glucose monitoring also have been important for diabetes managing, hoping to address one of the most inconvenient components of insulin therapy, which is the need for patients being treated with multi-dose insulin to monitor their glycaemia, usually by puncturing the fingertips, several times in a single day. These glucose measurements are painful to the patients and the strips used in the glucometers are expensive, which means that replacing this method would represent a significant

improvement in patients' quality of life and reduction in the disease's economic burden (Ratheau et al. 2011).

Research suggests that patients with diabetes, especially those with T2DM, avoid self-monitoring of blood glucose due to their unwillingness to think about blood glucose values and, more broadly, diabetes itself, to the belief that self-monitoring is unlikely to be of value, and to the sense of self-monitoring as an unpleasant, costly task (Polonsky et al. 2014). Although healthcare professionals need to assess and improve the way they present, make use of and discuss self-monitoring of blood glucose with patients with diabetes (Polonsky et al. 2011), technology improvements during the last few decades have allowed for the glucose measurements to be performed in a more patient-friendly way. For example, there has been an increasingly reduced requirement for blood in the sample tested and additional approaches using subcutaneous sensors to determine glucose concentration in interstitial fluid have also been developed. Several manufacturers have produced accurate, reliable, and portable continuous glucose sensors that can be used for up to seven consecutive days, and which appear to be associated with HbA1c reduction (Langendam et al. 2012; Vashist et al. 2011). Despite their accuracy, they still imply discomfort to patients and require continuous calibration (Vashist et al. 2011).

The development of non-invasive glucose measuring systems using thermal, raman impedence, and infrared spectroscopy, optical coherence tomography, temperature-modulated localized reflectance, ultrasound, and electromagnetic sensing have all shown promising accuracy and reliability (Ciudin et al. 2012; Langendam et al. 2012; Vashist et al. 2011), and encouraging evidence exists for the development and use of methods using infrared laser light applied on top of the skin, (Pleitez et al. 2013) or exhaled breath analysers (Prathibha et al. 2013; Schivo et al. 2013). Nevertheless, the manufacturing costs and portability of these devices have yet to be improved to the point where they can be widespread.

Subcutaneous glucose sensors gave rise to continuous subcutaneous insulin infusion systems, which appear to be linked to a lower incidence of severe hypoglycaemia and

provide patients with a flexible and convenient way of controlling glycaemia (Hanaire-Broutin et al. 2000; Joubert and Reznik 2012). Yet, although these insulin delivery systems offer a way of fine-tuning metabolic control and thus allowing for a better glucose control in everyday planned and unplanned activities, patients who are candidates for these devices should be carefully selected, educated and motivated, as it is desirable that patients be aware of the intricacies of insulin therapy to adequately self-monitor and to know the relationship between the insulin dosage needed for the meals they consume (Didangelos and Iliadis 2011). Despite this link in monitoring and infusion systems, a truly automated closed loop device has yet to be achieved, partly due to the fact that the systems do not work directly in the blood stream. Monitoring is made interstitially and the delivery is subcutaneous, which makes inevitable for a lag both in sensing glycaemia changes and in the insulin response. Research efforts sponsored by industry are underway, and it is to be believed that advances in the next few years are very likely (Vashist et al. 2011).

The ultimate goal of continuous insulin infusion is to create an artificial pancreas, where glucose levels trigger appropriate insulin release from an insulin reservoir. Although the lag between insulin sensing and releasing is, until now, impossible to avoid, predictive algorithms for determining insulin need are in development, together with techniques and devices that can mean that future insulin pumps may be internally implanted. Current challenges with these devices include insulin precipitation, short battery life, pocket infections, and catheter obstructions (Joubert and Reznik 2012; Siegmund et al. 2013). Nevertheless, emerging technology on electronics and biomedicine, seems to make the realization of a continuous insulin infusion system that can be used to prevent hypoglycaemia and maintain stable glycaemic control with less variability of blood glucose concentration, a possibility in the near future (Bakhtiani et al. 2013; Gifford 2013; Hanazaki et al. 2013).

Other methods for insulin administration have also been proposed, like inhalation, which has by now largely ceased development due to reports of increased risk for pulmonary function complications (Hegewald et al. 2007). Nasal, oral and buccal insulin

administrations continue to show some promise, although with mixed results (Guevara-Aguirre et al. 2007; Heinemann 2014).

On par with novel administration methods, insulin pen devices have become more convenient, discrete, attractive, and portable. Insulin pens for long-term use now have software memory functions and insulin dose calculators, and their combination with microfine needles makes insulin delivery almost painless. This is still the most used insulin delivery method and it is important to note the role that doctors and other diabetes educators play in providing appropriate training in their use, as the outcomes of this treatment and correct use are closely related (Heinemann 2014).

Surgical treatments for diabetes, with whole or segmental pancreas transplantation which aims to restore endogenous insulin secretion, have also been evolving. Patient survival seems better with simultaneous pancreas-kidney grafts than with a pancreas transplant alone, but even so, the procedure is associated with significant mortality and morbidity in the early period following transplant, with survival being around 80% at 3 years and less than 25% at 10 years (Tavakoli and Liong 2012). Ongoing research will continue to refine the surgical techniques and immunosuppressive regimens to further improve outcomes, but it is unlikely that this diabetes treatment will significantly evolve, due to the limitations on the supply organs for transplant and the specific indications for the procedure (de Kort et al. 2013; Tavakoli and Liong 2012).

Surgical procedures can benefit from advances in other forms of treatment, like gene therapy, which is still much in its infancy, or stem cell therapy, which aims to provide a source of cells nearly identical to the pancreatic β cell for treatment of diabetes by transplantation. Both embryonic and adult stem cells have been studied and manipulated to produce insulin and some trials have shown positive results in reducing blood glucose in animals, but although tremendous progress has been made in recent years, the challenge of reconstructing an in vitro β-cell, whether through stem cell differentiation or reprogramming, remains open (Pagliuca and Melton 2013). Serious side effects in stem cell therapy, mostly related to immunosuppression, need to be

resolved in future trials in order to establish the long-term safety and cost benefit of this treatment (Ashcroft and Rorsman 2012).

Despite the novel therapies involving advanced medical procedures, and also the new knowledge and products resulting from a vast body of research in pharmacology and OADA therapy (Grunberger 2013b, 2013a; Ludvigsson 2012; Munro and Levy 2007), the future of diabetes therapy must also be supported on studies aimed at improving the diabetes care process (Burke et al. 2014; Leroy 2011; Paschou and Leslie 2013).

Diabetes patients show low adherence to therapy, and complex strategies, which may include combinations of more thorough counselling, close follow-up, supervised self-monitoring, and family therapy, have been demonstrated to improve adherence and treatment outcomes and improvements in diabetes control are associated with a more frequent interaction between health professionals and patients, which seems an important determinant in adherence (Tahmasebi et al. 2013). Nevertheless, frequent contacts with patients require a substantial amount of effort and Health Service's resources. This has been a reason for the development of simple and technological strategies for improving patient monitoring and treatment adherence. These strategies range from electronic monitoring devices to increase medication adherence, like electronic caps for insulin injection systems or other pharmacological therapies which use visual and acoustic reminder signals (De Bleser et al. 2010), to recent smartphone software that doctors may find useful to recommend (Demidowich et al. 2012).

At the time of the writing of this document, an internet search using "diabetes" as a keyword in the two main application stores for smartphones and tablet personal computers with iOS and Android operating systems, results in more than 800 applications ready to download. Approximately half of these applications are provided at no cost, while others have prices ranging between €0.89 and €12.50. The applications have different natures, offering food pyramid guides, calorie and carbohydrates counters, physical activity trackers, recipes repositories, recipes ingredients converters, access to specific diabetes forum, glycaemia, blood pressure and other health variables

tracker, medication reminders, information booklets and various types of multimedia educational material on the disease.

Research on the usability, features and characteristics of diabetes applications for Android smartphones has proposed that few provide a comprehensive method of diabetes management, and attributed a mean usability score of 3.0 out of a possible 5.0 to the applications reviewed (Demidowich et al. 2012). Despite the recent proliferation in this type of software, it seems that the potential to deliver real-time feedback, dynamic diabetes education, and secure data sharing remains largely underexplored (Goyal and Cafazzo 2013). Nevertheless, as patients become more technologically aware, an increasing demand for applications that provide a response to consumer needs may contribute to the improvement of the applications that are currently offered, and this form of disease monitoring and prevention can be a significant determinant of care in the future (Goyal and Cafazzo 2013) and contribute to reduce health disparities (Silow-Carroll and Smith 2013).

In order to fulfil their potential for contributing to patient care, mobile health applications for diabetes control should focus on automatic data transfer between patients and health professionals, motivational and visual user interfaces, and on including context sensitivity. This can empower patients to take a more active role in managing their own health (Arsand et al. 2012). Overall, the widespread access to wireless communication indicates that future care models incorporating home monitoring and tailored feedback have the potential for a broad adoption by T2DM patients, if the systems and software can be intuitive and clear enough for patient use.

Self-monitoring of blood glucose in patients with T2DM that are not using insulin seems to present advantages for the overall care process mainly in patients that are included in a programmatic, structured intervention (Polonsky et al. 2011) with a structured feedback management (Garg and Hirsch 2014; Heller 2014; Welschen et al. 2005). For patients with T2DM, engaging in routinely scheduled appointments with healthcare professionals who make appropriate use of data from blood glucose monitoring at home can be clinically meaningful and contributes to significant improvement in glycaemic

control (Polonsky et al. 2011). This provides insight on the importance and potential of information technologies aimed at improving home glucose monitoring. As the use of electronic medical records advances, it is likely that it may be possible to provide patients with the ability to upload home glucometer readings, which can then be interpreted by a clinician.

Apart from research into technological advances for diabetes care, studies aimed at improving the system of patient care and the approaches for therapy and prevention interventions have also led to promising results. Strategies for tailoring care to specific patients or groups of patients, combining patient education with arrangements for follow-up by multiple professionals, have resulted in positive improvements in HbA1c, glycaemic control, and other health outcomes (Loewenberg 2011; Mudd-Martin et al. 2013; Tricco et al. 2012; Umar-Kamara and Adams Tufts 2013; Weymann et al. 2013).

As strategies to improve the care for diabetes patients, it is recommended that care systems support team-based care, community involvement, patient registries, and embedded decision support tools to meet patient needs, while also being tailored to individual patient preferences, prognoses, and comorbidities (ADA 2013a).

1.8. Diabetes complications risk perception

Beliefs and perceptions are considered determinants of health behaviours, but research has poorly addressed, so far, patients' perception and emotional responses to the risk of developing diabetes complications. A thorough understanding of perceived risk of diabetes complications can provide insight on the actions taken by patients to achieve adequate self-care and good glycaemic control, as well as contribute to the study of adherence to diabetes therapy and management. Although health educators are generally aware that knowledge of risk is important to adopt and sustain behaviour change, the degree of perceived risk and the type of risk perceptions are not fully understood (Fisher et al. 2002), and the nature of the relationship between risk

perceptions for chronic disease and health behaviours to reduce risk of disease is unclear (Weinstein 2003).

Risk perception can be defined as the subjective assessment of the probability of a specified type of event happening and how concerned we are with the consequences. Risk perception includes evaluations of the probability as well as the consequences of a negative outcome (Weinstein 1980).

Risk perception is related to risk knowledge. Individuals may have, or believe they have, sufficient information for adequate decision making, but knowledge does not always translates into desirable behaviour. An example of this is the reported knowledge and perceptions regarding food and nutrition, and their assessment considering indicators of adequate intake. Buttriss (1997), in a representative sample of adult UK residents, concludes that although most respondents believe that they are informed about nutrition and can correctly identify proper nutrition-related health behaviours, they do not choose nutritionally adequate foods in their usual daily meals. Bowen and Beresford (2002) have concluded that individuals choose and adequate food intake and incur in health promotion behaviours if they believe and perceive that those behaviours will be useful to them.

It is believed that the perception of the consequences associated with certain health behaviours is an important factor for the decision to act, at an individual and populational level, and that health promotion policies should be created taking this into account (Krewski et al. 2012). The WHO, in its 2002 World Health Report, states that in order to identify proper strategies and interventions for health promotion, it is necessary to assess health risks, considering the social, cultural and economic contexts (WHO 2002). This report describes that, overall, individuals perceive new or unknown risks with a higher degree of fear. A risk factor is also considered more important if it affects us personally, instead of affecting the general population. Furthermore, we assess in a more negative way risk factors that are imposed on us, while we fear less a risk factor in which we believe we can exert some degree of control. Slovic, in a pioneer work in risk perception (Slovic 1987), proposed that the assessment of probabilities

associated with risk factors are not independent from the possible losses or damages they incur. We tend to assess in a more optimistically way risks that have desirable consequences while overestimating the risk associated with particularly damaging consequences. Slovic also identifies anchoring behaviours, in regard to risk assessment and perception, as it is believed that initial assessments and perceptions are resistant to change, and that additional information will only be correctly considered if it is consistent with initial beliefs.

Weinstein and colleagues (Weinstein et al. 2007) suggest that there is a discrepancy between perceived and desired risks, as some individuals tolerate higher risks to gain greater benefits. These authors also agree that perceived risk predict health behaviour better than a purely cognitive probability judgment.

The discrepancy in risk perception is also evident when comparing perceptions between the general population and experts, and this has supported the existence of an unrealistic optimism, translated in a general optimism about the outcome of an event (Weinstein 1980). Individuals seem to have a strong but unjustified sense of subjective immunity, and the tendency to believe that one's own risk is less than that of others may reduce interest in health-protective behaviours. According to Weinstein, this optimistic perception can partly explain why health education messages often fail, as there is evidence that health education can even exacerbate unrealistic optimism (Weinstein and Klein 1995).

Unrealistic optimism, or optimistic bias, is determined by several factors, but it is still unclear how it is triggered. A literature review on optimistic bias and food (Miles and Scaife 2003), concludes that unrealistic optimism is not found in all risk factors nor in the same degree, making it hard to predict its existence. Nevertheless, optimistic bias is lower in risks that are perceived as less probable, and in risks which individuals have some previous experience. Risk factors believed as more controllable are associated with a higher degree of optimistic bias.

The existence of an optimistic bias, and the relationship between risk perception for diabetes complications and diabetes self-management behaviours, has not been

thoroughly studied, even if risk perception for developing diabetes complications is believed to raise patients' awareness of diabetes care. Searle and collaborators (Searle et al. 2008) reported that diabetes patients were concerned and aware of their risk of developing diabetic foot ulceration and retinopathy, but their perceived risk was biased, as patients with foot ulcers held a greater belief in personal control of diabetes, compared to that of diabetic controls without serious complications. A prospective study with 139 diabetic patients (Meltzer and Egleston 2000) with the objective of comparing patients' risk perceptions for major complications of diabetes (blindness, end-stage renal disease, and lower-leg amputation) with the actual risk for these complications, showed that patients significantly underestimate their risk for diabetes-related complications. These results are consistent with the reports that suggest that individuals have a poor ability to predict their risk for developing disease (Weinstein 1980; 2003), but are not consistent with the nature of the prediction. In this case, there was no evidence of an optimistic bias.

Walker et al. (2007b) conducted the first report of comparative risk perceptions and risk knowledge in a mainly low-income, urban, minority sample of persons with diabetes. Results suggest that knowledge about the factors that increase or decrease the risk of diabetes complications was fairly high, and there were no significant differences in risk perceptions between different demographic characteristics, except age and household income. Lower income was associated with less risk knowledge and older subjects (aged 64-85 years) had less risk knowledge than younger subjects (aged 20-52 years). Risk knowledge did not differ between genders or with ethnicity.

Calvin et al. (2011), in an African-American sample of diabetes patients diagnosed for an average of approximately two years, found a low perception of risk for complications, which was incongruent with risk estimates according to HbA1c and blood pressure. Less than 33% of participants saw themselves as being at high risk for developing any complications of diabetes but the mean HbA1c in the sample was 8.7%, and 61.3% of the patients were hypertensive. These results suggest that this population's perception of risk for diabetes complications needs to be addressed, especially if we take into

account the implication that disease perception shapes the procedures for coping with or controlling the disease (Leventhal et al. 1992). Moreover, a patient's perception of a health problem is frequently not in agreement with the clinical assessment, and it is usually the patient's illness perception that influences adherence to treatment regimens (Harrison et al. 2003).

It is proposed that perhaps the perception of being at low risk for diabetes complications may be attributed to the lack of visible symptoms, and to the fact that most patients are engaged in a treatment regimen, even if it may not definitively reduce the risk of complications (Frijling et al. 2004). Symptoms are considered motivators of protective behaviour, and the way people view their symptoms is an important factor in how health is perceived, and whether health care should be sought (Stover et al. 2001).

Risk perception may play an important role in the adherence to diabetes treatment and management, on account that, theoretically, one is more likely to participate in self-care if the perceived risk of developing complications is high (van der Pligt 1998; Walker et al. 2007b). Unrealistic optimism for developing diabetes complications might be a major barrier to behaviour change, particularly in patients who have uncontrolled blood glucose and low education (Hevey et al. 2009).

On the other hand, patients with T2DM have also shown over-pessimistic views about their risk of developing coronary heart disease and stroke, which the researchers suggest to be associated with the reinforcement of the relationship between diabetes cardiovascular complications and mortality by doctors, in regular diabetes consultations, or to the fact that cardiovascular disease may well be a very dreaded and particularly feared outcome of diabetes (Asimakopoulou et al. 2008).

Nevertheless, these authors also mention previous evidence suggesting that perceptions of a threat as likely and severe can result in low motivation to deal with that same threat (Weinstein 2000), which can have an important impact in diabetes self-care, as unduly pessimistic patients may be reluctant to self-care, seeing little point in managing an illness seen as overly risky (Asimakopoulou et al. 2008).

Further studies are needed to clarify the unrealistic risk perceptions for diabetes outcomes but the conclusions from the research on risk perception in T2DM agree that the study of risk perception in diabetes can have implications for clinicians, researchers and diabetes educators, as communication with the patient can be achieved in a more holistic way if a comparative risk perception indicator is available. Health education interventions can be integrated in the context of other health risks the patient is experiencing, like environmental safety concerns or health behaviours like smoking, for example. Overall, risk perception research can provide further insight on why a patient acts or does not act on risk perceptions related to diabetes

1.9. Aims, research questions and hypotheses

The complexity of diabetes determinants, and of its therapeutic regimens and outcomes, denotes that the management and control of the disease cannot obey to a universal approach. In order to provide patient-centred care, and to effectively target interventions, adherence to treatment and its barriers should be assessed.

Scientific research has proven the efficacy of nutritional therapy in the management of T2DM and its role in controlling and preventing complications associated with the disease. On account of the available evidence, nutritional therapy must be adequately implemented in all patients. Available data also suggests that individuals believe nutrition is important in daily life and that they can identify behaviours related with desirable nutritional health; nonetheless, adherence to proper eating patterns is reported as low, even when nutrition education and consultations are provided.

Among the determinants of adherence to a proper diet, the perceived risk of diabetes complications has not been thoroughly studied, and its assessment can contribute to the development of future nutrition education interventions. Furthermore, patient-centred approaches to treatment can benefit from the knowledge of how optimistic bias and patients' expectations shape self-care behaviours.

In a clinical setting, management of T2DM is evaluated by metabolic control, as inferred by HbA1c. Patients who achieve a low value of HbA1c believe that their treatment is successful, and place higher value on pharmacotherapy, in detriment of nutrition and lifestyle interventions. Recently, the association of PPHG with CVD has brought into attention that postprandial glucose imbalance is common in patients with T2DM, even in those with adequate HbA1c. These findings can imply that additional evaluations should be undertaken in patients with T2DM, so as to fully evaluate metabolic control. As PPG is a state that is highly prevalent throughout the day in most patients, self-monitoring of blood glucose can be a very important behaviour in diabetes self-care.

The main predictor of PPG is the nutritional content of the meal, especially in carbohydrates, which signifies that the best option for regulating PPHG can be nutritional therapy, as it can bring several added benefits to the management of diabetes and its complications (e.g., weight reduction, improvement in lipid profile), without the side effects and costs of pharmacotherapy. This poses a challenge for dietetic and nutrition professionals, as meal plans for patients with diabetes should take into account the need to regulate PPG and, at the same time, the daily routine, preferences, and beliefs of each patient. The construction of effective nutritional guidelines can only be achieved if research addresses the adherence to a proper diet, and the influences of HbA1c on glycaemic response. The comparative analysis of the glucose curve in response to a common meal in patients with different metabolic control may be a useful study design to clarify this issue.

Most study designs on adherence to diet in patients with T2DM are cross-sectional, or based in samples from prospective studies, which are generally undertaken to study the role of a particular set of risk factors and its association with designated health outcomes. The study constructed for the present work starts with patients at the endpoint (adequate or inadequate glycaemic control), and comparatively assesses adherence with nutritional recommendations, while further exploring the perceived risk of diabetes complications, and analysing the similarities between glycaemic responses by exposing patients to a nutritionally controlled meal.

The aim of the present study was to use a case-control design to undertake a comparative analysis regarding PPG, nutritional therapy adherence, and risk perceptions of diabetes complications. Subjects are patients with T2DM which differ in their glycaemic control, based on HbA1c results. This study can contribute to the identification of differences and similarities between patients with different glycaemic control, and provide information for the development of treatment and monitoring guidelines.

The specific research questions in this research are:

- Does adherence to nutrition recommendations differ between patients with adequate glycaemic control and those with poor glycaemic control?
- What barriers patients identify in the adherence to nutrition recommendations?
- What is the association between PPG levels and HbA1c?
- How do patients with T2DM with different glycaemic control perceive their risk of diabetes complications?

Based on the research questions and on the literature review, the hypotheses of this study are:

1. There is no significant difference in PPG between patients with adequate glycaemic control and those with poor glycaemic control;
2. Patients with adequate glycaemic control have a better compliance of nutrition recommendations;
3. Patients with poor glycaemic control identify barriers to nutrition recommendation compliance different from those identified by patients with adequate glycaemic control;
4. Patients underestimate their risk for health complications of diabetes associated with food behaviour;
5. There is a significant difference in risk perception for diabetes complications between patients with adequate glycaemic control and those with poor glycaemic control.

Chapter 2: Methods

2.1. Study design

This study followed an analytic, case-control design. Analytic studies allow to examine associations and causal relations as they concern with identifying, measuring and interpreting the effects of risk factors or of specific exposures. In an analytical study, individuals may be classified according to the absence or presence of a known attribute (Ahrens and Pigeot 2007).

The research questions for the current study can be defined as having an analytic nature, due to the intention to measure and describe possible causal relationships between the presence of glycaemic control and several outcome variables. Additionally, the analytic nature is also reflected in the assessment of past exposures and their association with current glycaemic control.

Each subject was classified as "case" if he/she had been recorded as having an HbA1c of 7.0% or above in the 60 days prior to data collection. Alternatively, subjects with a recorded HbA1c below 7.0% were considered "controls".

Additional information pertaining to the inclusion of subjects in an analytic, case-control study are considered and detailed in sections 2.2.

I used a mixture of prospectively and retrospectively measured variables, which could account on the present study being described as either prospective or retrospective. Several definitions have been used for the terms "prospective" and "retrospective" and a central feature of case-control studies has been the assessment of exposure by recall, after the disease or outcome being analysed has occurred, which has led to case-control studies being generally classified as retrospective (Porta 2008). Nevertheless, not all case-control studies involve recall, as there are case-control studies that evaluate exposures by having the information on the exposures and risk factors taken from records or registries that predate development of the outcomes. These case-control studies may described as prospective, at least with respect to the measurement of exposure (Rothman et al. 2008).

The study design for the present work was, thus, a case-control that included a retrospective measurement of exposures and risk factors, and also a prospective measurement that allowed group comparisons of outcomes associated with the characteristic that defines the study groups.

The retrospective assessment was aimed at addressing the hypotheses regarding better compliance of nutrition recommendations, identification of barriers to nutrition recommendation compliance, optimistic bias in the risk perceptions for diabetes complications, and the existence of group differences in the risk perception for diabetes complications.

The prospective measurement was conducted to address the hypothesis regarding the smilaritues in PPG between patients with adequate glycaemic control (HbA1c of 7% or below) and those with poor glycaemic control (HbA1c above 7%). The prospective assessment involved the exposure of both cases and controls to a nutritionally controlled meal, in order to assess glucose responses and its similarities between patients. This feature of the research design allows this branch of the study to be classified, according to some authors, as quasi-experimental, due to the fact that conditions during the period of study were changed (Ahrens and Pigeot 2007). As the exposure (controlled meal) was not different for cases or controls and there was no random allocation of subjects for each group, this cannot be classified as an epidemiological or clinical trial (Porta 2008).

2.2. Population and sample

2.2.1. Population

The study population was composed by patients with T2DM receiving health care in a Diabetes Clinic in the municipality of Faro, in the Portuguese region of the Algarve. The clinic is integrated in a regional association of diabetes patients (AEDMADA). The AEDMADA Diabetes Clinic is an outpatient clinic based in Faro which offers consultations with highly experienced and qualified diabetologists, and other consultations aimed at

increasing the quality of life in patients with diabetes and at providing care across all of the complications and impairments associated with diabetes (e.g., foot care, psychology, dietetics and nutrition, pharmacotherapy adjustments, orthotics and prosthetics) (AEDMADA 2013).

2.2.2. Sampling and sample size

The sampling procedure was non-randomized. Patients were invited to be a part of this study during their Diabetology consultations in the AEDMADA Diabetes Clinic and afterwards were contacted by the researcher to proceed with the data collection. Recruitment for the study started on June 3rd 2012 and lasted up to the end of November 2012. All patients who met the inclusion criteria were invited to be a part of the research and the final sample was composed of 32 controls and 34 cases.

A minimum sample size was estimated through the formula proposed by Fleiss and collaborators (Fleiss et al. 2004) for testing differences between two proportions, solved for *n*, the number of subjects.

In order to estimate a proportion for use in the sample size formula, I used the results from the Guideline Adherence to Enhance Care (GUIDANCE) study, suggesting more than two thirds of patients with elevated HbA1c do not satisfactorily comply with T2DM treatment while patients with a good glycaemic control appear more compliant, even if at least one third of them also show poor treatment adherence (Stone et al. 2013). Thus, I assumed a hypothetical proportion of non-adherence of 35% in patients with HbA1c below 7% (controls) and a hypothetical proportion of non-adherence of 75% in patients with HbA1c of 7% or above (cases). According to the calculations, a minimum of 25 case subjects would be required in order to detect a real odds ratio with 80% power and two sided type I error probability of 5%. This sample size was then continuity-corrected for use with corrected chi-square and Fisher's exact tests, resulting in a minimum sample size of 28 cases.

For a fixed number of subjects, statistical power for testing the null hypothesis is optimized by having equal numbers of cases and controls (Ahrens and Pigeot 2007), so the minimum sample size was set at 56 patients with T2DM, half of them cases and half of them controls.

2.2.3. Inclusion and exclusion criteria

The inclusion criterion for this study were:

- Male or female patients with medical diagnosis of T2DM for at least 12 complete weeks, obtained by previous assessment and identification of one or more of the following: HbA1c ≥ 6.5%, FPG ≥ 126 mg/dl (7.0 mmol/l), 2h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during a OGTT, or presence of classic hyperglycaemia symptoms and a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l);
- Age below 85 years

The exclusion criteria were:

- Undergoing a pharmacotherapy regimen with insulin or any ADOA other than metformin;
- Diagnosis of degenerative disorder of the central nervous system;
- Following a lactose-free or gluten-free diet;

2.2.4. Sample construction procedures and final sampled subjects

The subjects in the study population were invited to be a part of this study in the Diabetology consultations in the AEDMADA Diabetes Clinic. Patients who conformed to the inclusion criteria were approached with a brief explanation of the study by the clinician responsible for the consultations and were asked permission for a later contact by the researcher. Up to five days after the consultation the researcher contacted the patients by telephone, explained the study, and set up an individual appointment with each patient. In this initial contact, the patients were informed that they should attend

the appointment before any intake of food and that a breakfast would be provided, free of charge, as a part of the study. If patients choose to decline participation in the study, they still would be offered breakfast. Furthermore, it was clearly stated at this time that participants would not be compensated monetarily for their collaboration or reimbursed for their expenses with any trips to attend the appointment.

The individual appointments were held in the School of Health of the University of Algarve. At the start of each appointment, the study's protocol was thoroughly explained to the patients and the researcher discussed the important role patients can play in the scientific advances on diabetes research. Patients' comfort and anonymity were assured at all times and all ethical considerations were followed, as detailed in section 2.4.

Two of the patients that were contacted by telephone refused to participate in the study citing their unwillingness to carry out the data collection procedures and a third patient was excluded in his individual appointment. This patient did not comply with the preparatory procedures for data collection, which required the assessment to take place before any intake of food. In order to preserve patient's comfort, the interview was not conducted and was replaced by a nutrition education session.

The final sample was composed of 66 patients with T2DM, divided into 32 cases and 34 controls. As previously stated, the classification of the study's subjects as "case" was done based on an HbA1c value of 7.0% or above in the 60 days prior to data collection.

The HbA1c assay for classification of each patient was conducted at the time of the last consultation which took place up to four weeks before data collection.

2.3. Variables, data collection tools and procedures

The data for this study were collected during an individual interview with each of the patients and by recording information present in the patients' clinical records. After their agreement in be a part of the research, patients were scheduled for a single data collection interview which included all the tools needed for the inquiry. The interview lasted between 150 minutes and 180 minutes and was held in the morning. According to patients' availability and convenience, data collection started between 8:00h A.M. and 9:00h A.M. Subjects were asked to skip their breakfast at home in the day of data collection, in order for some procedures to be performed in the fasting state.

The inquiry was divided into five sections, corresponding to:

I. Clinical data
II. Anthropometric assessment;
III. Glucose response to a meal;
IV. Lifestyle and care assessment;
V. Risk perception of diabetes complications.

2.3.1. Clinical data

Important patient information was collected from the clinical file, as well as data for HbA1c levels which were obtained from a blood sample collected in the AEDMADA Diabetes Clinic in the day the physician informed the patients about this research.

Demographic information was also obtained from the patient file. This information was confirmed and completed during the course of the interview.

Table 6 presents the variables for this study that were constructed with the first stage of the interview and with data from the patients' files.

Table 6. Variables and operational definition for the information obtained from the patients' clinical files.

Variable	Definition
Age	Age stated by the patient in complete years at the time of the data collection
Gender	Gender, as recorded in the patients' files, classified as "male" or "female"
Marital status	Marital status stated by the patient, classified into "married", "widower", "never married" or "divorced/separated"
Persons in the household	Number of persons living in the patient household at the time of data collection
Occupation	Patient occupation, classified as "employed" and "unemployed/ retired"
Years of schooling	Number of years of formal schooling completed
Age at diabetes onset	Age of the patient when diabetes was diagnosed
Previous diagnosis of diabetes related illness	Previous diagnosis of excess weight, renal disease, cardiovascular disease, retinopathy, and hypertension, mentioned in the patient clinical file
HbA1c	HbA1c value as reported in a laboratory analysis by a certified method based on the blood sample collected during eight weeks previous to data collection
Lipid profile	Latest values of total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides, reported in the patient clinical file

2.3.2. Anthropometry and blood pressure assessment

The second section of data collection consisted of measuring height to the nearest centimetre and weight to the nearest 0.1kg, using a stadiometer (Seca, Model 217, Seca, United Kingdom) and a scale (Seca, Model 899, Seca, United Kingdom), appropriated for medical use and calibrated according to the manufacturer's instructions. Waist circumference was measured with an extensible measuring tape (Seca, Model 218, Seca, United Kingdom).

All the measurements followed the International Standards for Anthropometric Assessment procedures (Marfell-Jones and Stewart 2006) and were collected in a consultation office, respecting patients' intimacy and comfort.

Blood pressure was also collected during this stage, using a sphygmomanometer (OMRON, M6 Confort, OMRON Healthcare Co., Ltd., Japan) for upper-arm measurements, validated for clinical use in adults through the European Society of Hypertension International Protocol (Altunkan et al. 2007). Patients were seated and the left arm was used for blood pressure measurement. Three blood pressure measurements were conducted and the data used in this study corresponds to the mean value of the three measurements.

Table 7 shows the variables resulting from this section of data collection:

Table 7. Variables and operational definition for the anthropometric and blood pressure assessment.

Variable	Definition
Height	Patient standing height without shoes measured to the nearest 0.1 cm, with his head, shoulder blades, buttocks, and heels touching the back of a stadiometer, and with his head aligned in the Frankfort horizontal plane.
Weight	Patient weight while wearing only light clothing, measured to the nearest 0.1 kg by standing in the centre of a scale platform with his hands at his sides, and looking straight ahead.
Waist circumference	Patient's waist girth measured to the nearest 0.1 cm at the level of the narrowest point between the lower costal border and the iliac crest, while he is standing erect and has relaxed the abdominal muscles.
Blood pressure	Systolic and diastolic blood pressure measured with a certified oscillatory sphygmomanometer on the patient's left arm, bared and unrestricted by clothing, and positioned so that the midpoint of the upper arm is at the level of the heart.

The anthropometric variables were used to assess metabolic and cardiovascular risk associated with excess body fat. Using the cut-off points for Europeans proposed by the WHO (2000, 2011), men with a WC above 94 cm are considered as having an increased metabolic and cardiovascular risk. If WC is above 102 cm men are considered as having a substantially increased metabolic and cardiovascular risk. In women, the cut-off points in WC for increased risk and substantially increased risk are, respectively, 80 cm and 88 cm.

The BMI was computed by the ratio between weight and squared height, rounded to the nearest 0.1 kg, and participants were categorized according to the cut-off points proposed by the WHO (2000), which state that a BMI in the range of 25–29.9 kg/m^2 represents overweight and is associated with an increased risk of comorbidities related to excess fat. A BMI of 30 kg/m^2 or above represents a high risk of comorbidities related to excess fat and participants in this category are classified as obese.

2.3.3. Glucose response

In order to assess glucose response, all patients were offered a controlled breakfast, constructed according to the dietetic recommendations for patients with T2DM (ADA 2008; M.J. Franz and Bantle 2012), and composed of foods traditionally consumed in a Mediterranean culture and obeying to usual eating habits in the region.

The experimental meal had the following composition (table 8):

Table 8. Foods and nutritional values for the experimental breakfast

Food	Amount (g)	Energy (Kcal)	Protein (g)	Fat (g)	Carbohydrates (g)	Sugars (g)
Wheat bread	80	231.13	6.72	1.76	45.84	1.68
Ham	30	90.98	5.40	7.65	0.15	0.15
Milk	200	93.68	6.60	3.20	9.80	9.80
Apple	135	76.78	0.27	0.68	18.09	18.09
	Total	492.6	19.0	13.3	73.9	29.7

The experimental breakfast corresponded to 24.6% of a daily caloric intake of 2000Kcal. Additionally, this meal was designed to provide 75g of carbohydrate which allowed to establish comparisons with reference values in the literature, due to this being the same amount of carbohydrate ingested in an OGTT.

In the day scheduled for data collection, patients were asked to follow their usual pharmacologic therapy and were offered the experimental breakfast between 8:00h A.M. and 9:00h A.M., according to individual preferences and usual breakfast intake hour. Subjects were asked to completely eat the all food items it contained, while seated, and without significant interruptions.

Glucose response to the experimental breakfast was assessed by the measurement of capillary blood glucose while the patients were in fasting, and in 30 minute intervals after the start of breakfast, up to 120 minutes after the meal. Five glucose measurements were collected for all patients with a portable blood glucose monitoring system (Freestyle Lite, MK-23, Abbot, USA). This particular handheld device has showed good analytical performance and clinical accuracy, with a precision standard deviation (SD) of 2.8–3.9 mg/dl (0.16–0.22 mmol/liter) at glucose concentrations below 100 mg/dl (<5.56 mmol/liter) and a variation coefficient of 3.9–5.0% at glucose concentrations above 99 mg/dl (≥5.56 mmol/liter) (Alva 2008). Approximately 97% of the measurements in the validity study for the device were within the International Organization for Standardization accuracy limits, which specifies an accuracy interval limit of 95% (Alva 2008).

The same device was used for all patients to minimize variability and test strips came from the same batch. Before the data collection with each patient, a test measurement with the Freestyle Control Solution was conducted, in order to guarantee compatibility and precision with the discardable test strips. The blood samples for testing were obtained by puncture in the fingers of the left hand. During all of the measurements, the strictest safety and hygiene procedures were obeyed.

Patients were asked to remain seated during the course of the measurements in order to minimize physical activity, which could influence glucose response during the postprandial period.

2.3.4. Lifestyle and care assessment

The lifestyle and diabetes care assessment variables were obtained by direct interview with the researcher. The interview was conducted between patients' glucose measurements, following a semi-structured interview script (Annex 1). The interview was previously practiced by the researcher with two healthy volunteers, in order to evaluate any shortcomings or interviewer biases. Precautions with language, posture, tone of voice and interviewer appearance were taken, according to specific recommendations for clinical interviews and patient counselling (Gable 2008; Holli et al. 2003; Pope and Mays 2008; Sommers-Flanagan and Sommers-Flanagan 2012).

The interview included dietary and physical activity habits, and assessment of tobacco and alcohol use.

Physical activity was assessed with the short-form version of the International Physical Activity Questionnaire (IPAQ). This tool can be used to obtain comparable estimates of moderate-intensity activities, vigorous-intensity activities, and walking, based on metabolic equivalents (MET) of energy expenditure associated with these specific type of activities (Hagströmer et al. 2007). The metabolic equivalents attributed to each activity are based on their estimated energy expenditure as compared with energy expenditure while resting. Vigorous activities were estimated as requiring eight times the energy expenditure while resting, moderate activities as requiring four times the energy expenditure while resting, and walking as requiring approximately 3.3 times the energy expenditure while resting.

The IPAQ scoring protocol allows for the results to be expressed in MET-min per week (MET level x minutes of activity x events per week) or by classifying individuals into three physical activity categories. Individuals with a high level of physical activity engage in vigorous-intensity activities on at least three days a week, accumulating at least 1500 MET-minutes/week, or, alternatively, engage in a daily combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 3000 MET-minutes/week. Individuals with a moderate level of physical activity engage, weekly, in at least 20 minutes of vigorous activity during three days, or moderate-

intensity activity or walking of at least 30 minutes during five days, or any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 600 MET-min/week, during five days. Individuals who do not meet criteria for the high or moderate physical activity categories are considered as having low physical activity.

The IPAQ is considered internationally valid and reliable in adolescents and adults in diverse settings (Craig et al. 2003). A Portuguese translation of the IPAQ has shown to be valid in men above 60 years old (Benedetti et al. 2007) and the short-form was successfully used in a Portuguese nationally representative sample for assessment of physical activity prevalence (Bauman et al. 2009).

This assessment of food intake was achieved by the recall of all the food items ingested by the patient in the previous day, plus questions regarding usual eating habits, both aided by the use of images representing usual food items and different portions (Cheyette 2011), which were presented to the patients for clarification of their description.

During the course of the interview, the language and communication strategies used allowed to put patients at ease and facilitated their ability to recall food intake. A short history of the previous day's activities was also put together during the interview, in order to help establishing the different meals and snacks of the day. Information like the time of waking up, the time of leaving the house, and any trips to shops or other venues was recorded.

This study intended to estimate usual intake and it is considered that a single recall is insufficient to achieve this goal, as within-individual variability in daily intake is considerable, due to variation in the diet and other random sources of measurement error (Willett 1998).

Several statistical modelling methods have been developed for estimating the distribution of usual intake of nutrients using data from at least two 24h recalls (Dodd et al. 2006). The National Cancer Institute (NCI) method has shown to provide reliable

estimates (Tooze et al. 2006) and is considered an improvement over existing methods (Tooze et al. 2006). One of the advantages of the NCI method is its ability to provide estimates through the incorporation of covariates into the model (Tooze et al. 2010). The characteristics of this method and the fact that it is a non-commercial product used in nutritional epidemiology research prompted its use in this study. Thus, in order to use the NCI method, a second 24h recall was recorded between eight to ten weeks after the data collection interview. This second recall was held by phone interview, as this mode of administration is considered equally valid than a direct face-to-face interview (Willett 1998). The second 24h recall was obtained from a random subset of 10 cases and 10 controls from the initial sample, as statistical significance can be achieved with a subset of the initial group (Tooze et al. 2010).

The nutritional composition of the food items in all 24h recalls was estimated using a food composition table for Portuguese food items (INSA 2010). Some food items reported by the subjects were not present in the Portuguese food composition table and, in other instances, nutrient information was not provided. In these cases, information from the “McCance and Widdowson's The Composition of Foods” food composition reference was used to complete the data set (McCance et al. 2002).

The variables resulting from the data collected in this section were are presented and defined in table 9.

Table 9. Variables and operational definition from the data collected on lifestyle and diabetes care

Variable	Operational definition
Visits to health professional	Number of times patient visited a doctor, dietitian, or nurse, on account of his diabetes, during the last 12 months.
Time of last visit	Time since the patient's last visit to a doctor, dietitian, or nurse, on account of his diabetes
Referencing for consultation	Classification of patient's last visit to a doctor, dietitian, or nurse as being "self-initiated" or "referred" by other health professional.
Measurement of glycaemia	Number of times patient states self-measuring glycaemia each day, week, month, or year.
Smoking habits	Patient statement on whether or not he currently smokes or has smoked in the past.
Number of cigarettes	Number of cigarettes patient states smoking each day, week, or month.
Food shopping	Patient self-classification of his role in food shopping for the household, choosing between "don't engage in food shopping", "share food shopping duty", and "are the main food shopper" categories.
Meal preparing	Patient self-classification of his role in planning and preparing meals for the household, choosing between "don't engage in meal planning/ preparing", "share meal planning/ preparing duty", and "are the main meal planner/ preparer" categories.
Perception of diet advice	Patient perception on whether he was previously told by a health care provider to follow an exercise program, follow a diet or meal plan, weigh or measure food, keep a record of his meals, and use food list to plan meals
Perception of food behaviour	Patient self-rating, in a five point Likert scale ranging from 1 ("never") to 5 ("always"), of the frequency he follows a regular schedule for meals and snacks, weighs or measures food, keeps a record of his meals, and use food lists to plan meals.
Physical activity	Time spent doing vigorous physical activities, moderate physical activities, and walking, as defined in the IPAQ (Hagströmer et al. 2007), in each of the last seven days.
Time sitting down	Mean time spent seated on weekdays, during the last seven days
Special diet	Patient statement on whether he/she currently follows a special diet
Nutritional intake	Intake of macronutrients and micronutrients in the last 24h

The interview also included a section with an open-ended nature, which provided evidence on the views of this specific population on the barriers to a proper diet and on the reasons behind the adherence to nutrition therapy.

In addition to the aforementioned variables, I also calculated the individual estimated energy requirements, using the formulas proposed by the IOM (2005) and taking into account subjects' age, height, sex, and physical activity levels. The physical activity levels used for the calculation were the ones contained in the IPAQ, which was also a part of the data collection tools, as stated before.

The Devine formula was used to calculate the ideal body weight in men:

$$Ideal\ body\ weight\ (kg) = 50 + 2.3\ kg\ per\ inch\ over\ 5\ feet$$

Figure 1. Devine formula for ideal body weight in men (B. Shah et al. 2006).

The Robinson formula was used to calculate the Ideal Body Weight in women:

$$Ideal\ body\ weight\ (kg) = 53.07 + 1.36\ kg\ per\ inch\ over\ 5\ feet$$

Figure 2. Robinson formula for ideal body weight in women (Robinson et al. 1983)

2.3.5. Risk perception of diabetes complication and optimistic bias

In order to study risk perception and optimistic bias, the last stage of the interview included items adapted from the Risk Perception Survey for Diabetes Mellitus (RPS-DM) questionnaire (Walker et al. 2007a). This tool was developed by the Albert Einstein College of Medicine of Yeshiva University to assess comparative risk perceptions related to diabetes and its complications. The RPS-DM is composed by seven subscales totalling 31 items and was constructed based on factors identified in risk perception research that were specifically applied to diabetes. It is available in English and Spanish, for data collection by telephone interview, in-person completion, or by self-administration as a self-fulfilment questionnaire.

For the purpose of the present study, I created specific items, adapted and translated into Portuguese from the interview form of the RPS-DM. The items were translated by the researcher and, independently, by a qualified translator without knowledge of the purpose of the study or the questionnaire. All the items had a straightforward translation, due to the fact that literal equivalents exist in Portuguese. Both translations were reviewed and used to construct the final version of the risk perception items.

This adaptation and translation resulted in 20 items, grouped into an Optimistic Bias subscale, a Personal Disease Risk subscale, and an Environmental Risk subscale. In both the items from the Personal Disease (PD) and the Environmental Risk (ER) subscales, patients were asked to rate their risk of selected diabetes complications and their risk of hazards or dangerous conditions. In the Optimistic Bias (OB) subscale, patients were asked to compare their likelihood of diabetes complications and serious health problems, with the likelihood for the same complications and health problems of other individuals with diabetes.

The subscales and items used are presented in table 10.

Table 10. Subscales and items of the data collection section regarding the risk perception of diabetes complications

Subscale	Items
Optimistic Bias	Rating, in an agreement scale ranging from 1 ("strongly agree") to 4 ("strongly disagree") of two sentences: "Compared to other people with diabetes of the same age and sex, I am less likely than they are to get diabetes complications" and "Compared to other people with diabetes of the same age and sex, I am less likely to have serious health problems".
Personal Disease Risk	Selection between "almost no risk", "slight risk", "moderate risk", and "high risk" for heart attack, foot amputation, cancer, vision problems, high blood pressure, numb feet, stroke, blindness, and kidney failure
Nutritional intake	Selection between "almost no risk", "slight risk", "moderate risk", and "high risk" for experiencing health problems from medical tests, violent crime, extreme weather, driving or riding an automobile, illegal drugs, air pollution, pesticides, household chemicals, and cigarette smoke from other people

Face validity of the subscales was ensured by translating the original English version into European Portuguese according to recommendations for cross-cultural research (Grigorenko 2009). The scales were translated and then back-translated by two independent translators, without access to the original version. These versions were evaluated by a Psychology and Linguistics expert with English skills, in order to ensure the accuracy of the final version.

A pre-test interview was held for the final item list in a convenience sample of eight patients with diabetes, four males and four females, all with age above 50 years old. This pre-test intended to assess if the items and the classification scale were easily understood. After the pre-test interview, patients were debriefed and questioned on their opinion on the items, and asked to repeat them in their own words. All the subjects in this sample stated that the items were understood and showed no difficulty with the classification scale.

A week after the pre-test, the original subjects were retested with the same version of the scales to assess test-retest reliability.

2.3.6. Perceived barriers to adequate food intake

Determinants of food intake have been studied in healthy and diabetic populations and several barriers for following an adequate diet are identified in the literature (Gazmararian et al. 2009; Jerant et al. 2005; Toobert et al. 2000; UKPDS Study Group 1995b; Vijan et al. 2005). In order to analyse this topic, I created a set of sentences reflecting the barriers previously identified in the literature and asked the subjects to rate their agreement with these sentences in a five point Likert scale, ranging from “strongly disagree” to “strongly agree”.

The sentences used in the interview are presented in table 11.

Table 11. Sentences related to barriers to nutrition therapy adherence

Sentences
1. My diet is balanced and adequate to my needs.
2. In general, population in my age group has a balanced diet.
3. A balanced and proper diet takes too much effort.
4. Whatever I eat, my diabetes doesn't seems to be affected by my diet.
5. The amount of food in a balanced diet is less than enough for me.
6. The type of food items in a balanced diet is not to my liking.
7. I do not have enough time to prepare meals.
8. I do not have enough time to eat all the meals in a proper diet.
9. A proper diet implies different meals from the rest of the family.
10. I often eat out or attend to social gatherings and there are no adequate meal options.
11. A proper diet is more expensive.
12. I feel I don't know enough about nutrition in diabetes.
13. I am confused with the nutrition information I received.
14. I feel I need more advice on what is a proper diet.

Both the scale for classification of agreement and the sentences were read to the patients during the course of the interview, with the scale being repeated often between sentences, as to facilitate proper response. For a thorough assessment of the barriers for a proper diet, an additional open-ended question was placed in the end of the interview which encouraged patients to express their opinions on this topic and to identify any barriers not previously referred.

2.4. Ethics considerations

All stages of this study obeyed the ethical rules for health sciences research as stated in the sixth revision of the Declaration of Helsinki, including an informed consent form which was signed by every patient during the briefing and recruitment (Annex 2).

A Cranfield University Health Research Ethics Committee approval was sought (Annex 3), as well as approval from the Ethics Committee of the Algarve Regional Health Directorate, the *Administração Regional de Saúde Algarve* (Annex 4).

Approval was based on this study's protocol (Annex 5).

All questions regarding the participation were answered before written consent was given and subjects did not incur in any costs.

The data resulting from the inquiry were only accessed by the researcher. The information was directly inputted into a password protected electronic spreadsheet, and all patient identification was numerically coded in order to protect the identity of the subjects.

2.5. Data analysis

Data were analysed with IBM-SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). Patient description and characterization were presented as mean values, median values (Mdn), and standard deviations. The prevalence of several variables and characteristics was calculated as the percent of the total number of valid observations in each calculation.

The Kolmogorov-Smirnov test was used to assess adherence to the Normal distribution and, accordingly, parametric or non-parametric statistical procedures were used to compare groups. For comparisons between two groups, Student's t-test or Mann-Whitney test were computed, while a one-way analysis of variance (ANOVA) with Bonferroni *post-hoc* correction was used for multiple group comparisons.

The main statistical procedure for analysing the differences between cases and controls in qualitative variables was the chi-square test, or Fisher's exact test, were applicable. OR estimates and their 95% CI were also computed.

To analyse the predictive effect of age, education, BMI, nutritional intake, and psycho-behavioural characteristics, on glycaemic control, a binary logistic regression model was

constructed, using a backward stepwise covariate selection, based on the probability of the likelihood-ratio statistic, as proposed by Hosmer et al. (2013).

Statistical significance in all procedures was determined by two-tailed analysis and set at 0.05.

Chapter 3: Results

3.1. Clinical, anthropometric and demographic analysis

The distribution of gender, schooling, and occupation is presented in table 11.

Table 12. Demographic characteristics of the sample.

Variable	Cases (N=32) N (%)	Controls (N=34) N (%)
Gender		
Male	20 (62.5%)	17 (50%)
Female	12 (37.5%)	17 (50%)
Schooling*		
Primary school (1 – 4 years)	9 (28.1%)	21 (61.8%)
Middle school (5 – 6 years)	6 (18.8%)	3 (8.8%)
Upper school (7 – 9 years)	7 (21.9%)	4 (11.8%)
Secondary school (10 – 12 years)	5 (15.6%)	5 (14.7%)
Tertiary education (above 12 years)	5 (15.6%)	1 (2.9%)
Occupation**		
Employed	24 (75%)	13 (38.2%)
Retired	8 (25%)	21 (61.8%)

* Statistical significant differences at the 0.05 probability level, according to χ^2 test; P=0.048.

** Statistical significant differences at the 0.01 probability level, according to χ^2 test; P=0.003.

Cases and controls had a statistically similar distribution in gender ($\chi^2(1)=1.046$, P=0.307) but controls have less formal schooling than cases ($X^2(4)= 9.1$, $P=0.048$), with 62% of controls having completed only primary education. In regard to occupation, controls have a higher prevalence of retired participants ($\chi^2(1)=9.046$, P=0.003).

These results suggest that, in this study, low education seems associated with better glucose control. Nevertheless, I found no association between education and occupation ($X^2(1)=1.9$, $P=0.215$).

Apart from the expected differences in HbA1c, there are also significant differences between cases and controls regarding age, age at diagnosis, BMI, total cholesterol, and LDL cholesterol, as shown on table 12.

Table 13. Mean differences between cases and controls in selected clinical, anthropometric, and demographic variables

Variable	Cases (N=32)		Controls (N=34)		P-value of Student's t-test
	Median	Mean (SD)	Median	Mean (SD)	
HbA1c (%)	7.9	8.6 (1.40)	6.1	6.1 (0.51)	< 0.001*
Age (years)	58	57.8 (7.08)	67	63.7 (7.79)	0.002*
Age when diagnosed (years)	52	51.8 (6.45)	58	57.0 (7.87)	0.005*
Disease duration	5	6.0 (3.65)	5	6.4 (5.18)	0.730
BMI (kg/m^2)	31.7	31.3 (4.44)	29.4	28.9 (3.85)	0.024**
Waist circumference (cm)	106.4	105.7 (10.16)	102.8	103.4 (10.36)	0.366
Waist-to-height ratio	0.64	0.64 (0.07)	0.65	0.65 (0.06)	0.668
Systolic blood pressure	127	127.7 (16.10)	128	127.7 (17.14)	0.986
Diastolic blood pressure	71	71.8 (11.10)	68	68.4 (9.71)	0.202
HDL cholesterol (mg/dl)	43	48 (16.84)	47	49.3 (13.76)	0.735
Total cholesterol (mg/dl)	183	182.9 (33.17)	162	163.4 (35.01)	0.026**
LDL cholesterol (mg/dl)	103	113.2 (30.47)	78.5	88.2 (27.75)	0.014**
Triglycerides (mg/dl)	121	151.3 (85.74)	106	113.9 (45.94)	0.108

SD – Standard deviation
* Significant differences between groups at the 0.01 probability level
** Significant differences between groups at the 0.05 probability level

Cases seem to have been diagnosed at an earlier age than controls (P=0.005) and were significantly younger than controls at the time of data collection (P=0.002), although I did not find significant association between HbA1c and years of T2DM duration (P=0.730).

The associations between glucose control, age, and age at diagnosis, are also apparent in the significant correlations found between HbA1c and age at the time of diagnosis

(*r*(66)= -0.367, *P*=0.002) and at the time of data collection (*r*(66)= -0.368, *P*=0.002), and also by the non-significant correlation between HbA1c and years of disease duration (*r*(66)= -0.022, *P*=0.863). The significant negative correlations suggests that glycaemic control is poorer in younger patients, but age seems a better predictor of glycaemic control, as evidenced by the fact that when controlling for years of disease progression, the correlation between HbA1c and age at the time of diagnosis is still significant (*r*(63)= -0.384, *P*=0.002). I also found a significant negative correlation between BMI at the time of data collection and age at diagnosis (*r*(66)= -0.312, *P*=0.011), but not between BMI and years of diabetes duration (*r*(66)= -0.071, *P*=0.570), as shown on table 13.

Table 14. Correlations between waist circumference, waist-to-height ratio, age at diagnosis, and disease duration

Variable	Pearson's correlation coefficient (P-value)	
	Age at diagnosis	Disease duration
Waist circumference	-0.111 (0.376)	-0.085 (0.498)
Waist-to-height ratio	-0.078 (0.534)	-0.030 (0.810)
BMI	-0.312 (0.011)*	-0.071 (0.570)

* Significant correlation at the 0.05 probability level

The correlation between BMI and age at diagnosis is also present when adjusting for years of diabetes duration (*r*(63)= -0.341, *P*=0.005). Although non-significant, the adjusted correlation is also visible when analysing only cases (*r*(29)= -0.231, *P*=0.211) or controls (*r*(31)= -0.305, *P*=0.084).

I did not found significant differences in mean waist circumference between cases and controls (t(64)=-0.91, P=0.366), as shown on table 12, but both groups of T2DM patients have a high prevalence of cardiometabolic risk, according to the classification of waist circumference. Only 3% of cases and 6% of controls (figure 3) show a waist circumference below the WHO proposed cut-point for increased cardiometabolic risk (WHO 2000, 2011).

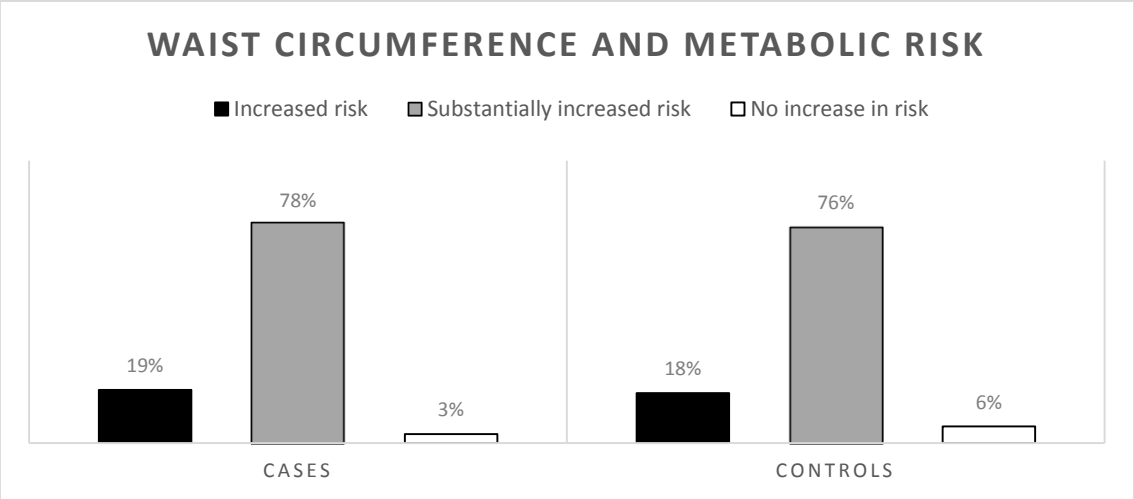

Figure 3. Increase in metabolic risk according to waist circumference (WC), interpreted according to WHO (2011) Waist Circumference and Waist-hip Ratio: Report of a WHO Expert Consultation, Geneva, 8-11 December 2008, World Health Organization. No increase in risk corresponds to WC ≤94cm (men) or WC ≤80cm (women), increased risk corresponds to WC>94cm (men) or WC>80cm (women), and substantially increased risk corresponds to WC>102cm (men) or WC>88cm (women). Differences between cases and controls are statistically non-significant (χ^2 (2)=0.293, P=0.864).

The results of WtH ratio also suggest abdominal obesity and a high cardiometabolic risk, for both cases and controls (figure 4). According to Ashwell et al. (2012), a WtH ratio above 0.5 is an indicator of cardiometabolic risk.

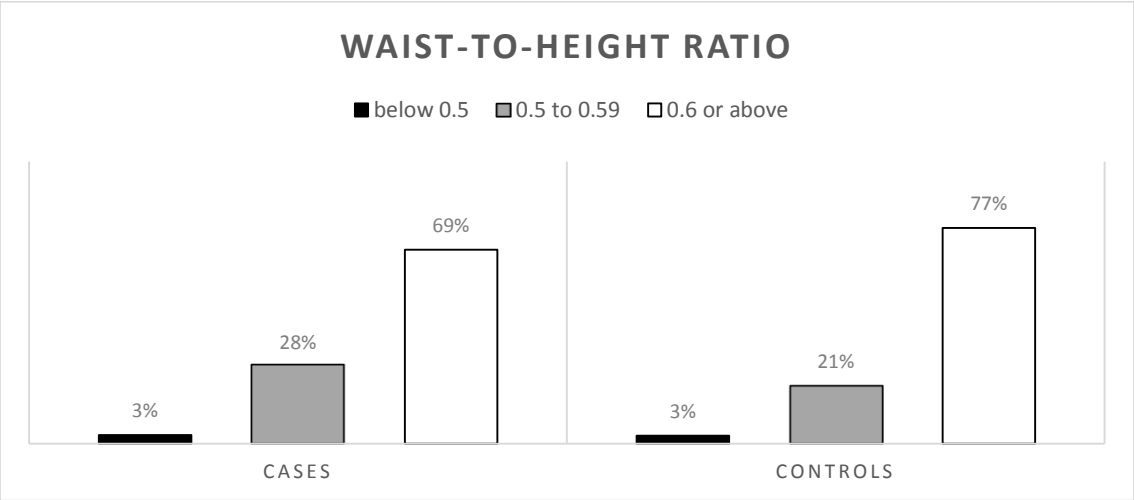

Figure 4. Waist-to-height (WtH)ratio classification, interpreted according to Ashwell et al. (2012; Obesity Reviews 13(3): 275-286). Ratio above 0.5 is considered a good predictor of cardiometabolic risk. Differences between cases and controls are statistically non-significant (χ^2 (2)=0.523, P=0.770).

The BMI for cases and controls also reflects poor nutritional status and high cardiometabolic risk for both groups of patients. Although cases have a higher mean BMI (*M*= 31.2 kg/m^2, *SD*= 4.44 kg/m^2) than controls (*M* = 28.9 kg/m^2, *SD*= 3.85 kg/m^2) in a statistically significant way (*t*(64)=2.308, *P*=0.024), the prevalence of overweight and obesity is statistically similar (χ^2 (42)=9.34, P=0.063). The distribution of BMI categories is presented in figure 5.

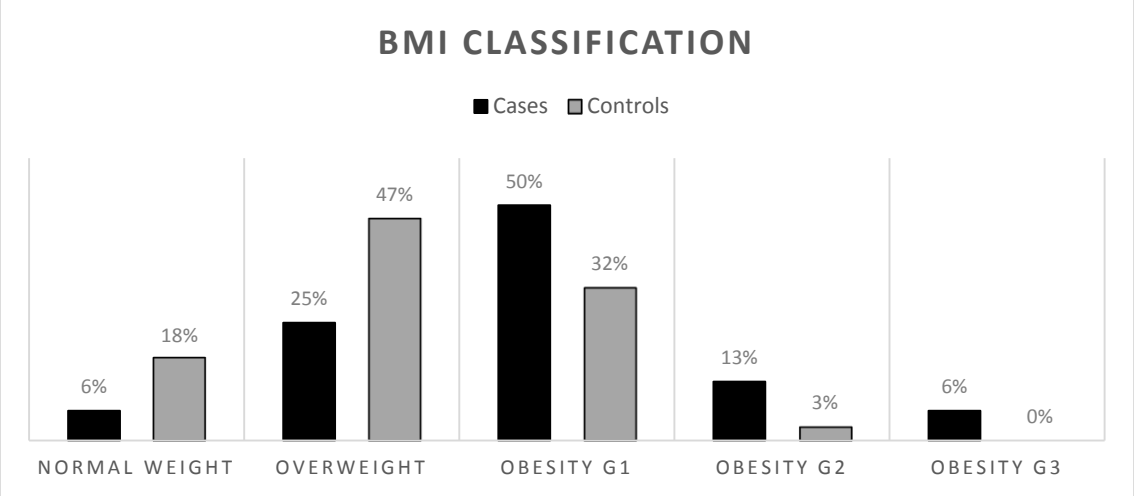

Figure 5. BMI classification, according to WHO (2000) Obesity: preventing and managing the global epidemic, World Health Organization. No underweight participants were present in the study. Differences between cases and controls are statistically non-significant (χ^2 42)=9.34, P=0.063).

In the present study, as reported in table 12, cases have significantly higher mean values for total cholesterol and LDL cholesterol. When comparing the mean values for different components of lipid profile in cases and in controls with the recommended values proposed by the ADA (2013), LDL cholesterol was the only component which presented significant differences. Both cases (*t*(18)=6.2, *P*<0.001) and controls (*t*(17)=2.8, *P*=0.013) have significantly higher LDL cholesterol than the ADA recommended level, set as LDL cholesterol below 70 mg/dl. The recommendations for lipid profiles and recorded mean values in this study are presented in table 14.

Table 15. Lipid profile results in cases and controls, compared with American Diabetes Association recommendations (2013, Diabetes Care 36(Supplement 1): S11-S66).

Lipid profile	Cases (N=32) Mean (SD)	Controls (N=34) Mean (SD)	American Diabetes Association recommendations
Total cholesterol (mg/dl)	182.9 (33.17)	163.4 (35.01)	‹200
LDL cholesterol (mg/dl)	113.2 (30.47)*	88.2 (27.75)**	‹70
HDL cholesterol (mg/dl)	48 (16.84)	49.3 (13.76)	›40 (men)/ ›50 (women)
Triglycerides (mg/dl)	151.3 (85.74)	113.9 (45.94)	‹150

SD – Standard deviation
* Significant differences between recorded values and recommendations at the 0.01 probability level
** Significant differences between recorded values and recommendations at the 0.05 probability level

When analysing the proportion of patients with a recorded value of lipid profile component above the ADA recommendations, it is possible to report that 95% of cases and 72% of controls have a LDL cholesterol level of 70 mg/dl or above. The proportions of patients with lipid profile components above the ADA recommendations are presented in figure 6.

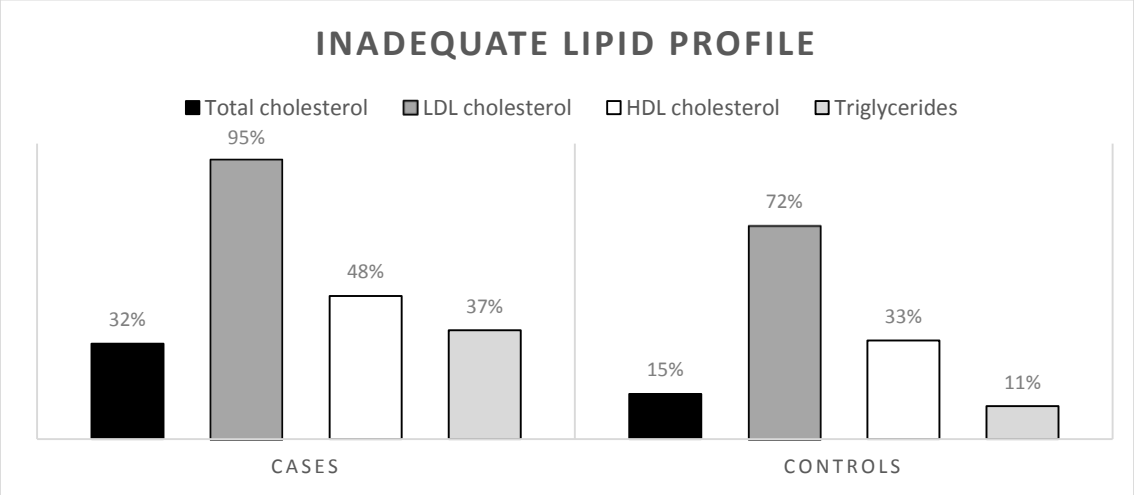

Figure 6. Proportion of patients with lipid profile components above the recommended level proposed by the American Diabetes Association (2013, Diabetes Care 36(Supplement 1): S11-S66). Differences in lipid profile between groups are statistically non-significant in all types of lipids (P›0.05)

According to Pearson's chi-square, none of the differences recorded in the prevalence of lipid levels above ADA recommendations are statistically significant (*P*>0.05).

The prevalence of pharmacological therapy for hyperlipidaemia ($\mathcal{X}^2(1)=2.4$, *P*=0.122) and hypertension ($\mathcal{X}^2(1)=0.655$, *P*=0.418) are also similar in cases and controls. Data regarding hyperlipidaemia and hypertension pharmacotherapy are presented in table 15.

Table 16. Pharmacotherapy for hypertension and hyperlipidaemia in cases and controls.

Lipid profile	Cases (N=32)	Controls (N=34)	P-value for group differences
Hyperlipidaemia pharmacotherapy (%)	31%	51%	0.122*
Years on hyperlipidaemia pharmacotherapy (Mean, SD)	3.5 years SD= 3.45 years	4.6 years SD= 3.50 years	0.433**
Hypertension pharmacotherapy (%)	34%	44%	0.418*
Years on hypertension pharmacotherapy (Mean, SD)	5.1 years SD=5.43 years	5.5 years SD=5.57 years	0.815**

SD – Standard deviation
* P-value computed with the X^2 test
** P-value computed with Mann-Whitney's test

In both forms of pharmacotherapy, the duration of the treatment is also similar between groups (hyperlipidaemia, *U*=69.5, *P*=0.433; hypertension, *U*=78, *P*=0.815).

The present study also analysed some self-care behaviours, among them the number of doctor visits during the last year on account of diabetes, physical activity habits and frequency of glucose measurement.

The number of doctor visits is similar (*U*=503.5, *P*=0.597) between cases (*Mdn*=3) and controls (*Mdn*=3), as is the frequency of glucose measurement ($\mathcal{X}^2(3)=2.81$, *P*=0.454), shown on table 16.

Table 17. Frequency of glucose measurement in cases and controls.

Measurement frequency	Cases (N=32) N (%)	Controls (N=34) N (%)	P-value for the X^2 test
Daily	8 (30.8%)	15 (50%)	0.454
Weekly	15 (57.7%)	11 (36.75%)	
Monthly	2 (7.7%)	2 (6.7%)	
Yearly	1 (3.8%)	2 (6.7%)	

When analysing physical activity levels, classified according with the IPAQ recommendations (Hagströmer et al. 2007) into "low", "moderate" and "high" levels of physical activity, we did not find any participant in the "high" physical activity category. Most participants (81% in cases and 94% of controls) are classified as having low physical activity and the differences between groups are non-significant (*P*=0.143, Fisher's exact test). The distribution of physical activity categories is presented in figure 7.

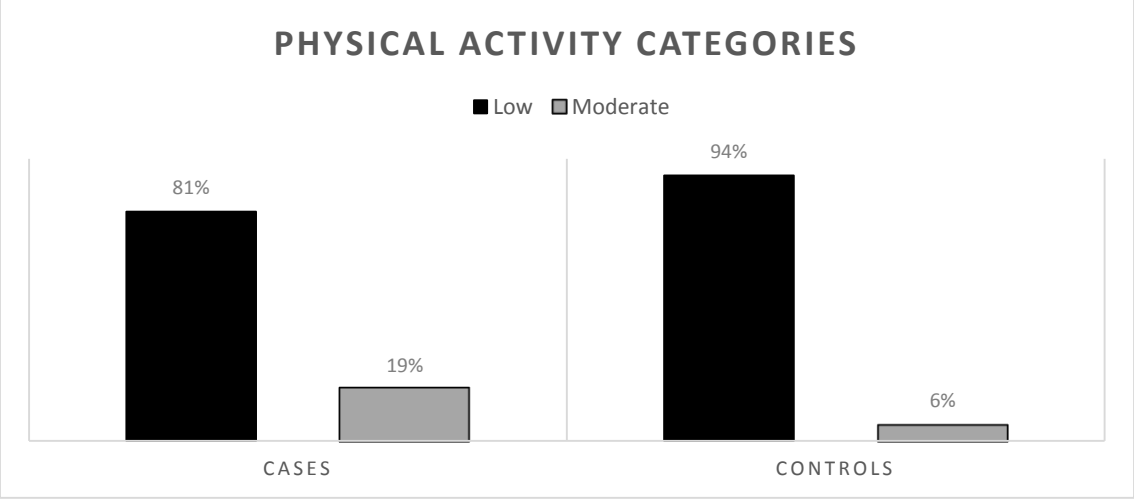

Figure 7. Classification of physical activity according to the International Physical Activity Questionnaire, by Hagströmer et al. (2007; Public Health Nutrition 9(06)). No participants presented high activity level. Differences between cases and controls are statistically non-significant (Fisher's exact test, P=0.143).

I found no statistical association between education and physical activity (χ^2(4)=0.08, *P*=0.078), number of doctor visits during the previous year (*r*(66)=0.02, *P*=0.851), or frequency of glucose measurement (*r*(66)=0.10, *P*=0.483).

Education showed negative correlations with age (*r*(66)=-0.44, *P*<0.001) and with years of diabetes duration (*r*(66)=0-.29, *P*=0.019) but it must be noted that only 6 subjects were younger than 50 years old, with the youngest being 47 years old. In fact, when the comparisons between HbA1c and education are age-adjusted, both show a non-significant correlation (*r*(63)=0.07, *P*=0.572).

3.2. Diet and adherence to nutrition recommendations

The dietary assessment showed significant differences between cases and controls. Cases report a significantly lower (*U*=239.5, *P*<0.001, r= 0.52) number of meals (*Mdn*=3) than controls (*Mdn*=4), and the number of daily meals also has a significant negative correlation with HbA1c (*r*(66)=-0.401, *P*=0.001).

Subjects with inadequate glycaemic control showed significantly higher intakes of energy (P=0.030) and sugars (P=0.012). I also found a significant correlation between energy intake and HbA1c (*r*(66)=0.282, *P*=0.022).

The results of the dietary assessment are presented in table 17.

Table 18. Dietary assessment in cases and controls

Variable	Cases (N=32) Mean (SD)	Controls (N=34) Mean (SD)	P-value of Student's t-test
Energy (kcal)	2449 (781)	2079 (536)	0.030*
Protein (g)	91.2 (29.81)	85.6 (25.78)	0.419
Total carbohydrates (g)	292.5 (124.12)	243.9 (75.62)	0.062
Sugars (g)	128.9 (77.92)	87.2 (51.14)	0.012*
Fibre (g)	18.3 (8.73)	17.7 (8.13)	0.783
Lipids (g)	94.4 (36.95)	84.9 (31.03)	0.263
Total saturated fatty acids (g)	31.0 (14.61)	27.9 (14.53)	0.389
Total monounsaturated fatty acids (g)	35.4 (16.95)	29.5 (12.32)	0.110
Total polyunsaturated fatty acids (g)	19.6 (10.22)	19.7 (7.49)	0.989
Cholesterol (mg)	365 (231)	378 (251)	0.828
Sodium (mg)	4277.7 (2057.04)	3921 (1530.06)	0.425
Potassium (mg)	3083.8 (1375.35)	2601.9 (806.19)	0.085
Water (g)	1247 (1042.31)	943.9 (1205.85)	0.280

SD – Standard deviation
* Significant differences between groups at the 0.05 probability level

When considering individual estimated energy requirements, calculated for each subject's estimated ideal body weight using the IOM equations (2002), a Mann-Whitney test indicated a statistically significant (U= 198, P= 0.034) excess energy intake that is higher in cases (*Mdn*=299 Kcal) than in controls (*Mdn*=172 Kcal). This suggests that patients with T2DM, independently of their level of glucose control, show an excess energy intake when compared to their individual estimated energy requirements. In fact, more than two thirds of both cases and controls present an energy intake above their estimated energy requirements, as shown in figure 8.

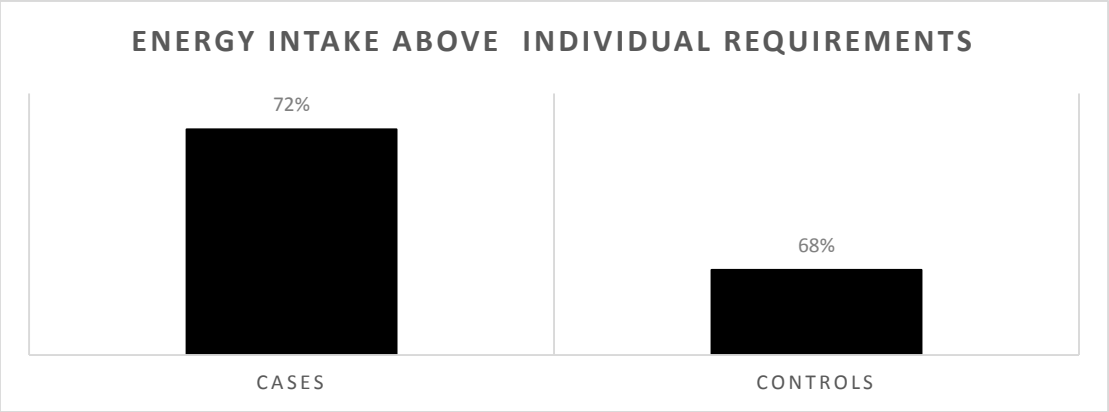

Figure 8. Percentage of cases and controls with an energy intake exceeding estimated individual requirements, computed through the Institute of Medicine energy requirements equations (2005; Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients), National Academies Press)

The distribution of the percentage of daily total caloric intake (TCI) for each macronutrient suggests that all subjects follow a diet with adequate protein intake, high lipid intake, and a moderate carbohydrate intake. When comparing the participants' percentages of TCI for each macronutrient with the IOM recommendations proposing acceptable macronutrient distribution ranges for carbohydrate, fat, and protein of 45–65%, 20–35%, and 10–35% of total energy, respectively (IOM 2005), I found significant differences in carbohydrates and fat, as shown on table 18.

Table 19. Macronutrient distribution of the total caloric intake and comparison with the Institute of Medicine macronutrient distribution range (2005; Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients), National Academies Press)

Percentage of TCI	Mean (SD)			IOM Acceptable macronutrient distribution range	P-value for the comparison of all subjects with IOM nutrient recommendation
	All (N=66)	Cases (N=32)	Controls (N=34)		
Carbohydrates (%)	47 (11)	47 (11)	47 (10)	45%-65%	0.039*
Protein (%)	16 (4)	15 (4)	17 (4)	10%-35%	0.069
Lipid (%)	36 (10)	35 (10)	36 (9)	20%-35%	0.015*

SD – Standard deviation
IOM – Institute of Medicine
* Significant differences between groups at the 0.05 probability level

Cases in this study present a mean of 20.9% (*SD*=9.56%) for the sugars distribution in TCI, whereas controls show a mean of 16.7% (*SD*=9.08%), with the statistically significant differences in the amount of sugars in the usual diet ($t(64)=2.59$, $P=0.012$) evidencing and association with glycaemic control, further supported by the positive correlation between sugars and HbA1c ($r(66)=0.345$, $P=0.005$). The correlation between sugars and HbA1c is also stronger and more significant than the correlation between HbA1c and total carbohydrates ($r(66)=0.245$, $P=0.047$). In fact, when controlling for the sugars content in the diet, the association between total carbohydrates and HbA1c is non-significant ($r(63)=-0.059$, $P=0.641$).

Approximately 35% (n=23) of the patients in this study reported following a specific diet (n=10 in cases and n=13 in controls), but no statistical difference was found between groups ($\chi^2(1)=0.354$, P=0.552). The specific diets mentioned by the subjects are presented in figure 9.

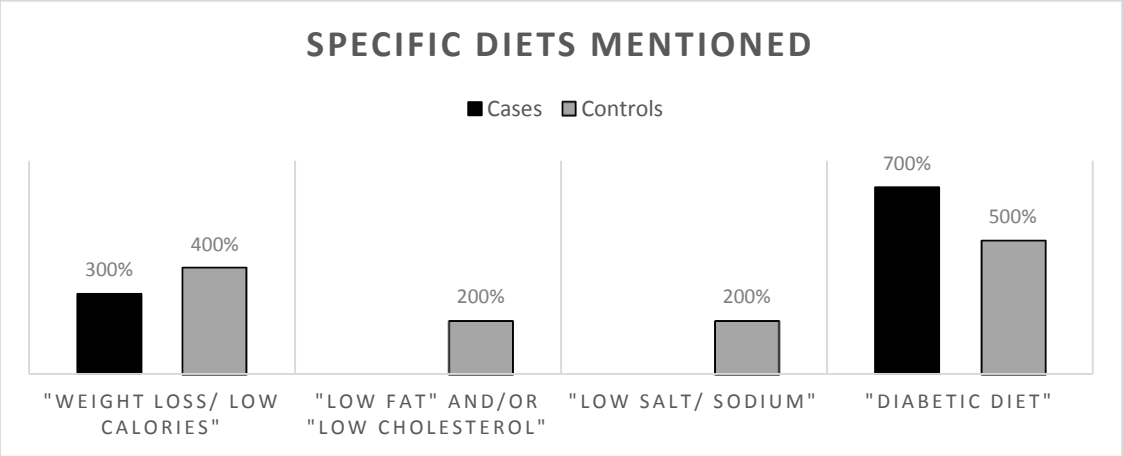

Figure 9. Distribution (n) of specific diets mentioned by the subjects. No statistical differences were found in cases and control for any of the specific diets mentioned (P>0.05).

The diet most frequently mentioned by the patients was a "diabetic diet". All participants that mentioned this diet described it as having low "bread, potatoes, pasta and rice" and two of the cases also stated that it excluded fruit. All 12 patients that mentioned the "diabetic diet" denoted that it was recommended by a doctor and in 8

of them this recommendation was made over 2 years before data collection. None of the 12 patients had ever been in a consultation with a dietitian or other nutrition health professional. All other specific diets mentioned by the patients were recommended by a registered dietitian and the 11 patients were still being monitored by that same dietitian.

When considering different health professionals (table 19), subjects did not differ in any aspect of their consultations with a nurse (*P*>0.05), during the last year. The difference in number of doctor consultations is non-significant (*t*(64)=0.37, *P*=0.71), contrarily to the time since the last consultation with this health professional, which is longer in cases (*t*(64)=3.3, *P*=0.002). Cases also report a lower prevalence of dietitian consultations ($\chi^2(1)= 4.67$, *P*= 0.031), a lower mean number of consultations with a dietitian in the last year (*t*(64)=-1.9, *P*=0.029), and a longer period of time since the last consultation with a dietitian (*t*(28)=2.3, *P*=0.028).

Table 20. Consultations with doctor, nurse, or dietitian on account of diabetes

	Cases			Controls		
Health professional	Consulted during the last year (%)	Consultations during the last year M (SD)	Months since last consultation M (SD)	Consulted during the last year (%)	Consultations during the last year M (SD)	Months since last consultation M (SD)
Doctor	100%	4.3 (2.06)	4.3 (2.06)*	97,1%	3.3 (2.69)	2.4 (0.53)
Nurse	37.5%	1.3 (0.5)	4 (2.45)	58.8%	1.3 (0.5)	4 (2.83)
Dietitian	12.5%**	0.3 (0.5)⁺	22.5 (12.37)⁺⁺	35.3%	1.2 (0.97)	6 (5.79)

SD – Standard deviation

* Higher mean value for cases, when compared with controls using Student's t-test; P=0.002

** Lower prevalence in cases, when compared with controls using χ^2 test; P=0.031

⁺ Lower mean value in cases, when compared with controls using Student's t-test; P=0.029

⁺⁺ Higher mean value in cases, when compared with controls using Student's t-test; P= 0.028

The total number of patients in this study with at least one dietitian consultation in the last year is low (4 cases and 12 controls), which can compromise statistical significance, but, nevertheless, I recorded higher mean values in HbA1c (*t*(64)=2.1, *P*=0.038), total

carbohydrates ($t(64)=2.2$, $P=0.031$), and sugars intake ($t(64)=2.4$, $P=0.021$) in subjects without dietitian consultations.

Only 30 subjects (12 cases and 18 controls) stated ever having a consultation with a dietitian. Among these, none of the cases and only 3 of the controls had a consultation by their own initiative. All other subjects were referred to the consultation by a doctor. These differences are non-significant ($P=0.255$, Fisher's exact test), but reflect a very low prevalence of dietitian consultations by own initiative in both cases and controls.

Previous recommendations from health professionals for engaging in physical activity and proper nutrition were reported by both cases and controls. All subjects were previously recommended by a professional to follow an exercise plan and a meal plan, as shown in table 20.

Table 21. Previous physical activity and nutrition recommendations

	Cases (N=32)	Controls (N=34)	P-value for χ^2 test
Follow a physical activity program	100%	100%	-
Follow a diet or meal plan	100%	100%	-
Weigh or measure your food	28.1%	44.1%	0.177
Keep a record of your meals	9.4%	11.8%	0.753
Use food lists to plan your meals	6.3%	11.8%	0.207

Regarding the barriers to nutrition therapy adherence analysed in this study, cases and controls show significant differences in their reported agreement. Table 21 shows the median and mean agreement for the barriers to adherence to nutrition therapy, ordered by statistical significance of the difference between cases and controls. The only statements that did not differed between cases and controls were the ones regarding the type of foods in a balanced diet not being to the respondents' liking, the need for more advice on what is a proper diet, and the lack of time to prepare meals.

Although the cost of consultations was not mentioned as a deterrent for seeking therapeutic and educational guidance, the perceived expenses with nutrition were considered a limitation to nutrition therapy adherence. When analysing the barriers to adherence that were identified by the literature research and included in patient interviews, cases reported a higher mean and median agreement with the statement indicating a proper diet as more expensive (P=0.013).

Table 22. Mean and median agreement scores with nutrition therapy adherence sentences, assessed in a 5-point Likert scale, ranging from 1 ("Strongly disagree") to 5 ("Strongly agree")

Statement	Cases (N=32)		Controls (N=34)		Mann Whitney's test *P*-value
	Mdn	M (SD)	Mdn	M (SD)	
A balanced and proper diet takes too much effort.	4.00	4.16 (0.51)	3.00	3.56 (0.70)	‹0.001*
A proper diet implies different meals from the rest of the family.	3.00	2.66 (1.04)	1.00	1.41 (0 .50)	‹0.001*
The amount of food in a balanced diet is less than enough for me.	4.00	3.41 (0.98)	2.00	2.38 (1.21)	‹0.001*
Whatever I eat, my diabetes doesn't seems to be affected by my diet.	3.00	2.75 (1.16)	2.00	1.74 (0.71)	‹0.001*
I am confused with the nutrition information I received.	2.00	2.44 (0.98)	2.00	1.65	0.001*
I do not have enough time to eat all the meals in a proper diet.	1.00	1.25 (0.44)	1.00	1.00 (0.00)	0.002*
I often eat out or attend to social gatherings and there are no adequate meal options.	3.00	2.69 (0.97)	2.00	2.03 (0.90)	0.005*
A proper diet is more expensive.	3.00	3.09 (0.73)	2.00	2.50	0.013**
I feel I don't know enough about nutrition in diabetes.	3.00	2.53 (0.72)	3.00	3.00	0.013**
The type of food items in a balanced diet is not to my liking.	3.00	3.25 (0.88)	3.00	3.59 (0.92)	0.180
I feel I need more advice on what is a proper diet.	3.00	2.84 (0.77)	3.00	3.00	0.627
I do not have enough time to prepare meals.	2.00	1.94 (0.67)	2.00	1.97 (0.94)	0.790

Mdn – Median; M – Mean; SD – Standard deviation

* Statistical difference between cases and controls, at the 0.01 probability level

** Statistical difference between cases and controls, at the 0.05 probability level

On the overall, subjects with poor glycaemic control believe that a balanced and proper diet takes too much effort (*P*<0.001), is more expensive than other diets (*P*=0.013), implies different meals from the rest of the family (*P*<0.001), and is composed by less than enough food (*P*<0.001). Additionally, cases also had an increased agreement with the statements indicating that diet doesn't seems to affect glucose control (*P*<0.001), confusion with nutrition information (*P*=0.001), and insufficient knowledge about nutrition in diabetes (*P*=0.013). Furthermore, the number of daily meals recommended in a proper diet also seems to be a barrier to adherence to nutrition recommendation (*P*=0.002), together with the attendance of social gatherings (*P*=0.005), were subjects believe that there aren't adequate meal options.

When asked to identify additional barriers to the ones described in the interview, all but one of the subjects referred any such barrier, considering that the interview focused on the beliefs, behaviours, and situations that they already associate with adherence to nutritional recommendations and with a proper diet. The only additional barrier mentioned by a single subject was "lack of willpower", who further denoted that this was the reflex of a proper diet being composed by food items that were not completely to his liking and of his preference for high energy, sugars-rich foods.

The agreement with the proposed barriers shows no association (P>0.05) with previous consultation with a dietitian, except in the statement regarding the belief of not knowing enough about nutrition in diabetes. Subjects which attended at least a dietitian consultation agree less with this statement (*U*=430, *P*=0.019).

Regarding the perceptions on diet adequacy, cases and controls rated in a statistically similar way the agreement with the adequacy of their own diet (P=0.099) and the adequacy of the diet of the general population their age (P=0.682), as shown in table 22.

Table 23. Classifications of agreement with statements related to diet perception, assessed in a 5-point Likert scale, ranging from 1 ("Strongly disagree") to 5 ("Strongly agree")

Statement	Cases		Controls		Mann Whitney's test *P*-value
	Mdn	M (SD)	Mdn	M (SD)	
My diet is balanced and adequate to my needs.	4.0	4.0 (0.69)	3.0	3.7 (0.86)	0.099
In general, population in my age group has a balanced diet.	2.50	2.44 (0.72)	3.00	2.53 (0.93)	0.682

Mdn – Median; M – Mean; SD – Standard deviation

These results on diet adequacy reflect the existence of an optimistic bias. Only one subject scored their diet as more inadequate than the diet of the general population, and according statistical procedures for paired-samples, both cases (W=-5.0, P<0.001) and controls (W=-4.3, P<0.001) score their own diet as significantly more adequate than the diet of the general population.

The mean difference in the classification of diet adequacy on the Likert response scale is not correlated with previous consultations with a dietitian ($r_{Spearman}$=0.023, P=0.854), HbA1c ($r_{Spearman}$=0.162, P=0.193), BMI ($r_{Spearman}$=0.166, P=0.184), WC ($r_{Spearman}$=0.05, P=0.690), energy intake ($r_{Spearman}$=0.172, P=0.072), carbohydrate intake ($r_{Spearman}$=0.112, P=0.369), duration of diabetes ($r_{Spearman}$=0.190, P=0.127), and age at the time of diagnosis ($r_{Spearman}$=-0.107, P=0.391).

Regarding usual food behaviour, subjects report that they usually follow a regular schedule for their meals (table 23).

Table 24. Patient classification of selected components of diabetes nutrition counselling

How often do you...	Cases		Controls		Mann Whitney's test *P*-value
	Mdn	M (SD)	Mdn	M (SD)	
Follow a regular schedule for meals and snacks?	4.0	3.7 (0.97)	4.0	4.2 (0.64)	0.016*
Weight or measure the food for your meals?	1.0	1.0 (0.0)	1.0	1.0 (0.0)	-
Keep a record of your meals?	1.0	1.0 (0.0)	1.0	1.0 (0.0)	-
Use food list to plan your meals?	1.0	1.0 (0.0)	1.0	1.0 (0.0)	-

* Statistical difference between cases and controls, at the 0.05 probability level

These results are not associated with the number of consultations with a doctor ($r_{Spearman}$=0.188, *P*=0.194), nurse ($r_{Spearman}$=0.106, *P*=0.144), or dietitian ($r_{Spearman}$=0.201, *P*=0.055), age ($r_{Spearman}$=-0.06, *P*=0.863), disease duration ($r_{Spearman}$=0.262, *P*=0.062), BMI ($r_{Spearman}$=-0.089, *P*=0.479), energy intake ($r_{Spearman}$=-0.241, *P*=0.055), or carbohydrate intake ($r_{Spearman}$=-0.257, *P*=0.061). Nevertheless, cases score significantly lower (*U*=368, *P*=0.016), which indicates that better glycaemic control seems statistically associated with a regular meals schedule. Both cases and controls reported that they never weigh or measure foods, keep a record of meals, and use food lists to plan meals.

Food shopping appears to be different for cases and controls but not meal planning and preparing, as shown in table 24. A significantly higher number of controls shares food shopping duty or is the main food shopper ($\chi^2(2)$=6.8, *P*=0.033).

Table 25. Subject's engagement in food shopping and meal planning and preparation

	Cases (N=32)	Controls (N=34)	P-value of X^2 test
Doesn't engage in food shopping	43.8%	14.7%	
Shares food shopping duty	50%	73.5%	0.033*
Is the main food shopper	6.3%	11.8%	
Doesn't engage in meal planning/ preparing	53.1%	73.5%	
Shares meal planning/ preparing	40.6%	20.6%	0.195
Is the main meal planner/ preparer	6.3%	5.9%	

* Statistical difference between cases and controls, at the 0.05 probability level

3.3. Diabetes complications perception and glycaemic control

As previously stated, the perceptions on the risk of diabetes complications was assessed by a scale develop for this study, based on the items of the RPS-DM questionnaire (E. A. Walker et al. 2007a). The items, similarly to the original RPS-DM questionnaire, are grouped in three subscales – Optimistic bias, personal disease risk, and environmental risk. Before the data collection phase, the scale underwent a test-retest procedure using 8 patients with T2DM that were not a part of the final sample. Table 25 shows the mean, standard deviation, and Cronbach's alpha for the scale's internal consistency in first phase of the test-retest procedure.

Table 26. Descriptive statistics and internal consistency of the risk perception subscales in 8 patients

Scale	Number of items	Cronbach's alpha	Test-retest difference M (SD)	Wilcoxon's test P-value
Optimistic bias	2	0.797	0.3 (0.70)	0.823
Personal disease risk	9	0.729	0.2(0.34)	0.900
Environmental risk	9	0.707	0.3(0.57)	0.716

M – Mean; SD – Standard deviation

A week after the pre-test, the original subjects were retested with the same version of the scales and, according to the Wilcoxon signed ranks test for paired samples, the scores in each subscale did not significantly differ between test and retest moments (P>0.05), allowing for the use of the scale in its current version.

The optimistic bias subscale included two statements regarding the likelihood of diabetes complications and serious health problems. When subjects were asked to rate their agreement with the statement "*Compared to people with diabetes of the same age and gender than mine, I am less likely to get diabetes complications"*, the results showed that both cases and controls seem to have a biased diabetes complication perception, favouring less individual likelihood of diabetes complications. The results are statistically significant ($\chi^2(2)= 5.4$, $P=0.04$), with cases having an overall higher agreement with less likelihood of complications (figure 10).

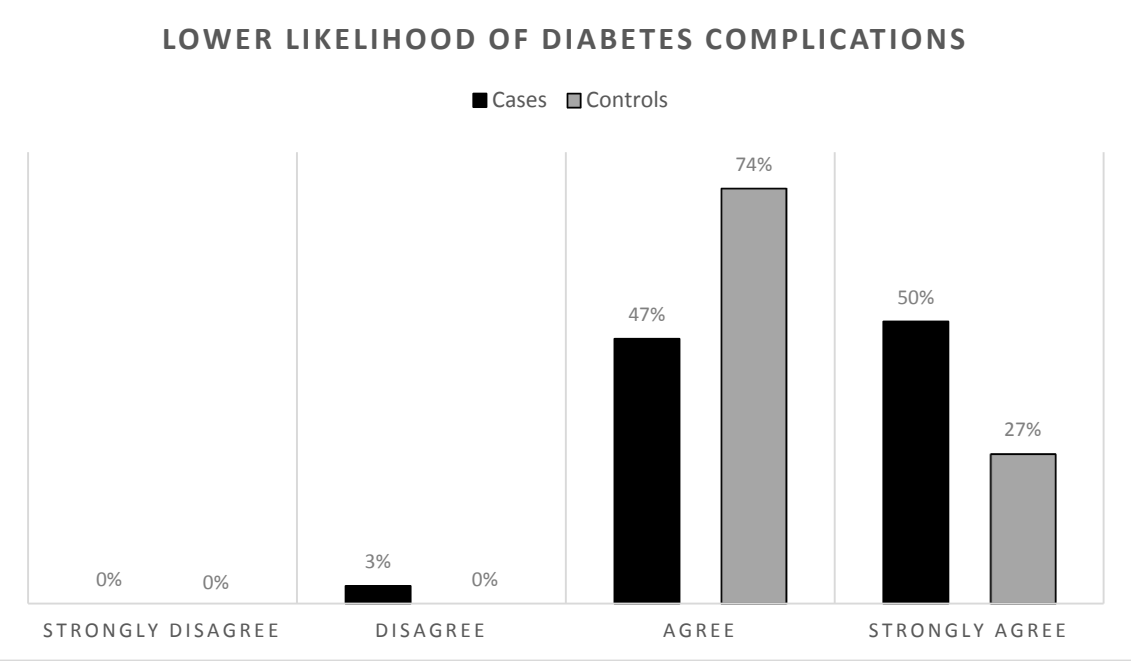

Figure 10. Agreement with a lower likelihood of diabetes complications than the one of other individuals with diabetes

When analysing the agreement with a lower likelihood of serious health problems, and not only diabetes complications, cases show a significantly higher prevalence in the "*strongly agree*" category ($\chi^2(2)=7.6$, $P=0.014$), even if controls show a higher prevalence of answering "*agree*", as presented in figure 11.

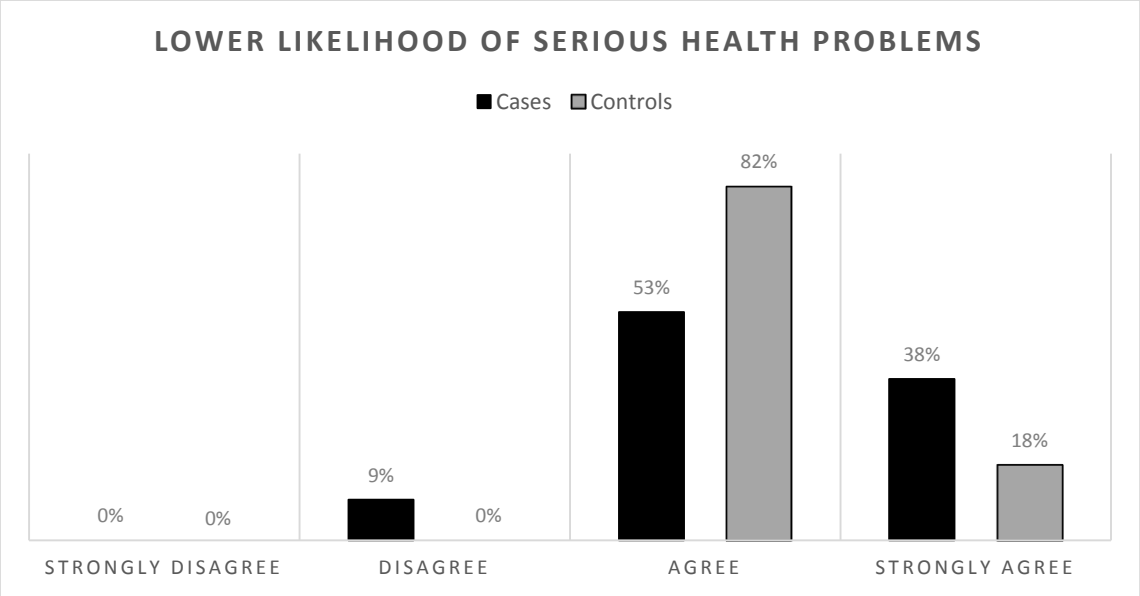

Figure 11. Agreement with a lower likelihood of serious health problems than the one of other individuals with diabetes

The subscale of personal disease risk included nine items for which participants had to rate their risk of experiencing them. Both cases and controls predominantly answered that they have "almost no risk" or "slight risk" for the different health outcomes, as shown in table 26.

Table 27. Individual health risks perception

Item	Almost no risk (%)		Slight risk (%)		Moderate risk (%)		High risk (%)		P-value of X^2 test
	CAS	CTRL	CAS	CTRL	CA	CTRL	CA	CTRL	
Heart attack	31.3	38.2	50.0	44.1	15.6	11.8	3.1	5.9	0.855
Foot amputation	53.1	38.2	46.9	47.1	-	14.7	-	-	0.076
Cancer	18.8	2.9	46.9	55.9	31.3	38.2	3.1	2.9	0.224
Vision problems	28.1	8.8	46.9	73.5	25.0	14.7	-	2.9	0.068
High blood pressure	28.1	20.6	53.1	58.8	18.8	20.6	-	-	0.775
Numb feet	25.0	26.5	62.5	52.9	9.4	17.6	3.1	2.9	0.776
Stroke	28.1	5.9	34.4	55.9	34.4	38.2	3.1	-	0.037*
Blindness	37.5	14.7	28.1	50.0	34.4	29.4	-	5.9	0.062
Kidney failure	43.8	32.4	50.0	58,8	6.3	8.8	-	-	0.624

CAS – cases; CTRL – controls

* Statistical difference between cases and controls, at the 0.05 probability level

The perception of the risk of stroke was the only item that showed significant differences between cases and controls, with the latter group assessing their risk lower than cases (P=0.037), even though, as previously reported, their lipid profile, lipid intake, and physical activity levels all are less than adequate.

The replies in the environmental risk subscale, for perceived risk from items representing different events or situations, is shown in table 27.

Table 28. Environmental risks perception classification in cases (N=32) and controls (N=34).

Item	Almost no risk (%)		Slight risk (%)		Moderate risk (%)		High risk (%)		P-value of χ^2 test
	CAS	CTRL	CAS	CTRL	CA	CTRL	CA	CTRL	
Medical tests	37.5	55.9	25.0	17.6	25.0	17.6	12.5	8.8	0.525
Violent crime	21.9	23.5	40.6	41.2	25.0	20.6	12.5	14.7	0.974
Extreme weather	12.5	20.6	25.0	29.4	46.9	38.2	15.6	11.8	0.745
Driving/ riding in an automobile	3.1.	8.8	15.6	26.5	46.9	50.0	34.4	14.7	0.216
Illegal drugs	96.9	88.2	3.1	11.8	-	-	-	-	0.185
Air pollution	50.0	35.3	25.0	20.6	15.6	35.3	9.4	8.8	0.326
Pesticides	21.9	20.6	37.5	29.4	31.3	29.4	9.4	20.6	0.632
Household chemicals	18.8	14.7	46.9	29.4	31.3	52.9	3.1	2.9	0.345
Cigarette smoke from people around you	25.0	17.6	40.6	32.4	25.0	38.2	9.4	11.8	0.631

CAS – cases; CTRL - controls

When analysing the individual disease risks and environmental risks using the numerical score attributed to each category, which ranged from 1 ("*almost no risk*") to 4 ("*high risk*") the perceived risk of cancer and stroke are the ones that subjects score with a higher mean, or greater likelihood of happening, even if both mean values are only slightly above the scale's mean point (table 28). Heart attack, kidney failure, and foot amputation were the disease outcomes that were considered less likely and mean values for perceived risk are, on the overall, higher in environmental risk. Subjects seem to believe that their risk for health problems is higher from environmental risk factors, like riding an automobile, extreme weather, or pesticides.

Table 29. Mean values for individual disease risk and environmental risk in the sample (N=66).

Individual disease risk item	Mdn	M (SD)	Environmental risk item	Mdn	M (SD)
Cancer	2.0	2.3 (0.70)	Driving/ riding in an automobile	3.0	2.9 (0.84)
Stroke	2.0	2.2 (0.74)	Extreme weather	3.0	2.5 (0.93)
Vision problems	2.0	2.1 (0.67)	Pesticides	2.0	2.4 (0.99)
Blindness	2.0	2.1 (0.83)	Household chemicals	2.0	2.3 (0.79)
High blood pressure	2.0	2.0 (0.67)	Cigarette smoke from people around you	2.0	2.3 (0.93)
Numb feet	2.0	1.9 (0.72)	Violent crime	2.0	2.3 (0.97)
Heart attack	2.0	1.9 (0.81)	Air pollution	2.0	2.0 (1.03)
Kidney failure	2.0	1.7 (0.61)	Medical tests	2.0	2.0 (1.06)
Foot amputation	2.0	1.6 (0.63)	Illegal drugs	1.0	1.1 (0.27)

Mdn – Median; M - Mean; SD – Standard deviation

The interpretation of the risk perception results according with the subscales derived from the RPS-DM questionnaire is shown in table 29.

Table 30. Results in the classification scales for optimistic bias and perceived risk

Scale	Score range	Cases (N=32)		Controls (N=34)		Mann-Whitney's test P-value
		Mdn	M (SD)	Mdn	M (SD)	
Optimistic bias	1 - 4	3.0	3.4 (0.54)	3.0	3.3 (0.39)	0.158
Personal disease risk	1 – 4	1.9	1.9 (0.30)	2.0	2.1 (0.29)	0.030*
Environmental disease risk	1 – 4	2.2	2.2 (0.47)	2.1	2.2 (0.51)	0.918

Mdn – Median; M - Mean; SD – Standard deviation

* Statistical difference between cases and controls, at the 0.05 probability level

Cases and controls score their personal disease risk and their environmental risk around the scale's midpoint and cases present a significantly lower (P=0.03) risk perception for personal disease. When analysing the association between risk perception subscales and previous counselling by a health professional, I did not find any significant correlation, as shown in table 30.

Table 31. Correlation between previous counselling and risk perception

Variable	Pearson's or Spearman's correlations r or ρ (P-value)					
	Cases (N=32)			Controls (N=34)		
	OB	PDR	EDR	OB	PDR	EDR
Doctor consultations in the last year	0.03 (0.873)	0.12 (0.502)	0.21 (0.247)	-0.31 (0.072)	-0.28 (0.115)	0.003 (0.985)
Time since last doctor consultation	-.13 (0.483)	0.26 (0.154)	0.2 (0.272)	0.08 (0.674)	0.03 (0.851)	-0.08 (0.648)
Nurse consultations in the last year	0.20 (0.524)	0.33 (0.063)	0.32 (0.070)	0.32 (0.064)	-0.09 (0.612)	-0.251 (0.368)
Time since last nurse consultation	-0.11 (0.734)	-0.04 (0.899)	-0.11 (0.743)	-0.31 (0.185)	-0.03 (0.893)	-0.22 (0.348)
Dietitian consultations in the last year	-0.04 (0.839)	-0.21 (0.240)	-0.35 (0.063)	-0.21 (0.243)	0.007 (0.969)	0.23 (0.195)
Time since last dietitian consultation	-0.39 (0.216)	0.03 (0.922)	0.57 (0.064)	-0.11 (0.658)	-0.10 (0.698)	0.09 (0.735)

OB – Optimistic bias; PDR – Personal disease risk; EDR – Environmental disease risk

Additionally, I did not find correlations between risk perception and the prevalence of previously diagnosed diabetes complications, as shown in table 31.

Table 32. Previously diagnosed complications in cases and controls

Previously diagnosed complication	Cases (N=32) N (%)	Controls (N=34) N (%)	P-value of X^2 test
Retinopathy	6 (18.8)	7 (20.6)	0.851
Overweight	19 (59.4)	16 (47.1)	0.316
Coronary disease	3 (9.4)	6 (17.6)	0.328
Stroke	1 (3.1)	2 (5.9)	0.512

3.4. Odds ratio for inadequate glucose control

Overall, when considering the similarities and dissimilarities between cases and controls, and by computing the odds ratio for inadequate glucose control from clinical, socio-demographic, and nutritional characteristics, together with the risk perception results, it is possible to infer that being employed, having completed only primary education, having a BMI of 30 kg/m^2 or above, engaging in meal planning or preparation, the lack of a consultation with a dietitian in the last year, and a poor personal disease risk perception are statistically associated with glucose control (table 32). These results suggest that BMI (*OR*=4), being employed (OR=4.8), not having had a dietitian consultation in the last year (OR=3.8), engaging in meal planning or preparation (OR=3.1), and having a low personal disease perception (OR=1.6) increase the odds for inadequate glucose control. Low schooling, in this case expressed as having only completed primary education, appear to act as protective factor for poor glucose control (*OR*=0.24).

Table 33. Odds ratio for inadequate glucose control due to demographic and clinical characteristics (N=66)

Characteristics	OR (95% CI)	P-value of X^2 test
Being employed	4.8 (1.68-13.95)	0.003*
Having only completed primary education	0.24 (0.09-0.60)	0.006*
BMI of 30 kg/m^2 or above	4.0 (1.44-11.26)	0.007*
High blood pressure	1.3 (0.39-4.00)	0.711
HDL cholesterol of 40 mg/dl or above (men) or 50 mg/dl or above (women)	0.53 (0.19-1.46)	0.220
LDL cholesterol of 70 mg/dl or above	6.9 (0.72 – 66.51)	0.063
Total cholesterol of 200 mg/dl or above	2.7 (0.79 – 8.97)	0.106
Triglycerides above 150 mg/dl	4.7 (0.82 – 26.60)	0.068
No consultation with dietitian in the last year	3.8 (1.08-13.49)	0.031*
Engaging in meal planning/ preparing	3.1 (1.12-8.83)	0.027*
Low personal disease risk perception	1.6 (1.03-3.24)	.040*
Low environmental risk perception	1.0 (.38-2.63)	.998

OR – Odds ratio
CI – Confidence interval
* Significant differences between groups at the 0.05 probability level

Nevertheless, these results must be interpreted considering the potential confounding effect of age. In this sample, schooling is negatively correlated with age $r(66)=-0.444$, $P<0.001$), indicating that older participants have significantly less schooling. Age can also be confounding the influence of employment status on glucose control, as employed/ active participants have significantly lower mean age than retired participants, as presented in table 33.

Table 34. Age on data collection and when diagnosed, in active and retired subjects

Age	Active (N=37) Mean (SD)	Retired (N=29) Mean (SD)	P-value of Student's t-test
Age on data collection	55.2 (5.37)	68.1 (3.8)	<0.001*
Age when diagnosed	50.2 (6.13)	60.0 (5.51)	<0.001*

SD – Standard deviation
* Significant differences between groups at the 0.01 probability level

3.5. Postprandial glycaemia

The analysis of the differences in glucose response to a mixed-meal containing 75 of carbohydrates shows that cases and controls do not significantly differ up to 120 minutes post-meal. According to the Student's t-test (*df*=64), statistical significance for group differences is achieved in fasting glycaemia. Mean values up to 120 minutes after the experimental breakfast were similar in cases and controls (table 34).

Table 35. Fasting glycaemia and glycaemia at 30 minute intervals after breakfast.

Time (minutes)	Glycaemia (mg/dl)		Student's t-test	
	Cases (N=32)	Controls (N=34)		
	M (SD)	M (SD)	t	P-value
0 (fasting)	122.3 (7.25)	116.1 (8.00)	3.32	0.001*
30	181.1 (25.70)	178.9 (28.80)	0.34	0.737
60	173.1 (26.54)	171.1 (27.22)	0.294	0.770
90	167.9 (23.21)	166.8 (26.41)	0.186	0.853
120	179.4 (12.34)	179.1 (20.49)	0.076	0.939

M – Mean; SD – Standard deviation
* Significant differences between groups at the 0.01 probability level

All mean values throughout the glucose monitoring were below 200 mg/dl, even at 120 minutes, which corresponds to the diagnosis cut-off point for T2DM when using an OGTT (ADA 2013b).

No significant differences were found in the proportion of subjects above the 200 mg/dl threshold for glycaemia at 120 minutes after breakfast, and all of the subjects presented a PPG level above 140 mg/dl (table 35).

Table 36. Proportion of cases and controls above selected glycaemia thresholds

Glycaemia	Cases (N=32)	Controls (N=34)	X^2 test P-value
Fasting levels ≥ 126 mg/dl	34.4%	11.8%	0.028*
Levels ≥ 140 mg/dl 120 minutes after breakfast	100%	100%	-
Levels ≥ 200 mg/dl 120 minutes after breakfast	6.3%	11.8%	0.436

* Significant differences between groups at the 0.05 probability level

All but 4 of the subjects (2 cases and 2 controls) showed a mean difference between pre-prandial and postprandial glucose above 40 mg/dl. The mean difference was 57.1 mg/dl in cases (*SD*=13.29 mg/dl) and 63.0 mg/dl in controls (*SD*=19.73 mg/dl), with the differences being non-significant (*t*(64)=-1.4, *P*=0.159).

Mean differences between pre-prandial and postprandial glucose were not correlated with age at diagnosis ($r_{Spearman}$=-0.006, *P*=0.963) or at data collection ($r_{Spearman}$=0.024, *P*=0.827), diabetes duration ($r_{Spearman}$=0.108, *P*=0.387), HbA1c ($r_{Spearman}$=-0.215, *P*=0.084), energy ($r_{Spearman}$=0.013, *P*=0.916) or carbohydrate intake ($r_{Spearman}$=-0.129, *P*=0.302), BMI($r_{Spearman}$=0.017, *P*=0.892), or frequency of glycaemia self-measurement ($r_{Spearman}$=0.282, *P*=0.068).

Chapter 4: Discussion

4.1. Study population and sample

The classification of the study's subjects as "case" was done based on an HbA1c value of 7.0% or above in the 60 days prior to data collection. This cut-point was decided after the revision of the ADA guidelines for glycaemic control (ADA 2013a) and the EASD guidelines (Ray and Singhania 2011; Secnik et al. 2007) that reflect a HbA1c cut-point associated with a reduction in the risk of microvascular and macrovascular complications. Although the EASD proposed cut-point of 6.5% is associated with a lower vascular risk, the ADA therapeutic guidelines state that levels below 7.0% can be too strict and requiring a very intensive pharmacological protocol in some patients (ADA 2013a). It is proposed that 7.0% is a more sensible and feasible goal for glycaemic control, which is a recommendation also reflected in the Portuguese Society of Diabetology treatment guidelines (Duarte et al. 2007). Thus, according to this rationale, although a cut-off point of 6.5% could have been selected as it represents the desired goal for glycaemic control, I chose a cut-off point for HbA1c of 7% due to the fact that it may represent a more reasonable and achievable target for most patients.

The data for HbA1c can be biased due to the different procedures that can be used in its collection. In this study, blood samples were collected in the AEDMADA Diabetes Clinic on the day the physician informed the patients about this research, and were submitted to assays completed under the guidelines proposed by the Portuguese Ministry of Health for all assays in the National Health System and for all Clinical Laboratories (DGS 2011c). This guideline indicates that blood samples must be processed by the same laboratory, with a method certified by the National Glycohemoglobin Standardization Program and calibrated according to the standards of the International Federation of Clinical Chemistry and Laboratory Medicine. The international standards are aimed at allowing proper diagnosis and data comparisons between populations (Hoelzel et al. 2004; D. B. Sacks et al. 2011).

Apart from the validity and reliability of HbA1c measurements, the setting were participants were recruited was thoroughly considered in order to predict and detect biases. The Diabetes Clinic were participants were recruited offers consultations and

care services to all patients with diabetes and/or other conditions that are members of the AEDMADA association. Patients must pay for the care received and the cost of care is higher than the fees in the National Health System, but significantly lower than the cost for care in private health care institutions. This selection criterion contributes to the specificity of the sample but, nevertheless, as this study intended to examine only patients undergoing metformin pharmacotherapy or patients that do not yet receive any OADA, I propose that this limitation on the number of possible participants has not resulted in a significant selection bias. Furthermore, analysing a single clinical setting allowed to remove biases related to the subjectivity of the treatment, due to the clinical decisions of each attending physician. The patients that were a part of this study attended consultations from a single clinician, who has his interpretation of the pharmacotherapy and treatment guidelines that are recommended for each individual case. If the study population had been from a different setting (e.g., a Health Centre), there could have been differences in the treatment regimens prescribed by different clinicians, due to heterogeneity in patients and in attending physicians. This would have been against the guidelines for an adequate case-control study, which requires that controls should have an opportunity of exposure similar to the population that is the source of the cases (Rothman et al. 2008). A population were there are different approaches to diabetes treatment and management would not have thoroughly allowed to study the nutritional related outcomes and glycaemia control.

The need to avoid selection biases and confounding in the results is the rationale behind the decision for the study population to be composed by patients in a specific treatment approach. As shown by the literature review, diabetes can be treated with several pharmacological agents, each with its own mechanisms for action and side-effects, and it was considered that the pharmacotherapy regimen could constitute an extraneous factor in the comparison of cases and controls.

Insulin therapy in T2DM is usually one of the last pharmacotherapy options to be considered, when β-cell function is severely impaired. The mode of administration of this pharmacotherapy and its effects on glycaemia imply that patients administering

insulin are fundamentally different than other patients with T2DM. Other pharmacologic agents are associated with weight gain or changes in fat mass, and that would make the anthropometric and nutritional comparison between cases and controls prone to confounding. Additionally, pharmacotherapy is also an indicator of disease progress (e.g., in patients under insulin therapy, T2DM has generally progressed significantly) furthering the eventual confounding effect in the data, as determinants of glycaemic control and diabetes self-care are associated with the duration of the disease (ADA 2013a).

On account of the possible confounding effects of the pharmacotherapy regimens on case-control comparisons, I concluded that patients with T2DM in this study should be recruited from the population who is only treated with metformin or does not receive any OADA. Metformin is the most common OADA and other substances that are used as a second-line pharmacotherapy are more commonly associated with hypoglycaemia and weight gain (Nathan et al. 2009; Schernthaner et al. 2004).

The data available for demographic characterization on the study population suggested that the sample would be composed by elder participants, mainly with low schooling. According to the last population census in Portugal, held in 2011 (INE 2012), the Algarve has 451,005 inhabitants, 64,560 of which in the Faro municipality. The age distribution of the inhabitants in the Faro municipality is presented in table 36.

Table 37. Population in the Faro municipality, by gender and age group (INE 2012).

Age	Population (n)		
	Total	Men	Women
0 - 14 years old	9 400	4 834	4 566
15 - 24 years old	6 400	3 190	3 210
25 - 64 years old	37 106	17 847	19 259
65 years old or above	11 654	5 059	6 595
Total	64 560	30 930	33 630

The Faro municipality has 18.1% inhabitants with 65 years or older, which is slightly higher than the national average (16.7%), and approximately the same than the proportion for all of the Algarve region (17.9%). Between the previous population census held in 2001 and the latest, the proportion of inhabitants in the Algarve with 65 years or older increased by 19.2%, with the increase in the Faro municipality being 26.2%.

The population census of 2011 also suggested an illiteracy rate of 5.4% in individuals 15 years or older, in all of the Algarve. The illiteracy rate represents individuals who state that they cannot, with understanding, read and write a short, simple statement on their everyday life.

According to data available from the World Development Indicators of the World Bank and the United Nations Educational, Scientific and Cultural Organization (UNESCO) Institute for Statistics (World Bank/UNESCO 2012), the illiteracy rate for the Algarve is considerably higher than the mean rates for the European Union (0.97%), countries in the Euro area (1.1%), and Organisation for Economic Co-operation and Development (OECD) members (2.2%). Considering only individuals above 44 years old living in the Faro municipality, 7.9% report not having completed any sort of formal education and 40.4% reports completing only the first stage of formal education, consisting of four years of schooling (INE 2012).

The final sample in this study was composed by 45.5% of participants that completed only up to 4 years of schooling, suggesting a low educational level in this group of patients, as was to be expected.

4.2. Clinical, anthropometric and demographic analysis

The results in this study support the evidence that younger adult patients often have poorer glycaemic control (Naranjo et al. 2013) and that inadequate control seems independent of HbA1c cut points, when comparing younger and older patients (Fox et al. 2006). A cross-sectional analysis of the data from the American 2005-2010 National Health and Nutrition Examination Survey (NHANES), shows that diagnosis of T2DM between the ages of 30 and 65 is significantly associated with worse subsequent glycaemic control (Berkowitz et al. 2013). Nevertheless, the literature also suggests that glycaemic control worsens with the increase of diabetes duration, in part due to the incidence of disease complications (Quah et al. 2013). In longitudinal studies, besides age at onset, disease duration is identified as a significant predictor for diabetes complications (Juarez et al. 2012), as mean HbA1c values progressively increase with disease duration (Benoit et al. 2005) and with early onset subjects appearing more likely to have poorer glucose control (Song and Hardisty 2009). Although the literature reports that patients with early diabetes onset may have a more severe form of the disease, associated with a higher degree of insulin resistance and glycaemic control that is more resistant to some pharmacological treatment (D'Adamo and Caprio 2011), the role of lifestyle habits before and after the diagnosis should also be considered.

The literature supports that the association between weight gain and diabetes duration is still unclear, and that weight gain, and consequently BMI increase, is a common concern in T2DM. Higher BMI, blood pressure, and triglycerides predict diabetes development and are associated with a steeper rate of fasting glucose increase (Fonseca 2009; UKPDS Study Group 1998a). I found a significant negative correlation between BMI at the time of data collection and age at diagnosis ($r(66)= -0.312$, $P=0.011$), supporting the evidence in the literature and suggesting that patients diagnosed at an earlier age present a higher increase in their BMI.

The nutritional status of the participants was also studied through their waist circumference and, according to the WHO criteria for interpreting this parameter (WHO, 2011), only 3% of cases and 6% of controls show a waist circumference indicating normal

metabolic risk. All other participants show an increased or substantially increased metabolic risk. According to the literature, abdominal obesity is common in T2DM and is also increasing in non-diabetic individuals, accompanying the trends in obesity prevalence (Hossain et al. 2007). Data from a Portuguese sample of 16,856 adults (Fiuza et al. 2008) showed a prevalence of abdominal obesity of 46.4%, similar to the results from other studies, like the NHANES, which up to 2010 shows a prevalence of abdominal obesity ranging from 42.4% to 61.3% in adults (Li et al. 2007; Ostchega et al. 2012). Several studies with T2DM patients (Bari et al. 2006; Davari and Khoshnood 2010) show a wide prevalence range for abdominal obesity, from 27.1% to 67%, which is suggested as being the result of the role of lifestyle and food behaviour (Fonseca 2009).

My data reflect the general overweight and obesity trends in T2DM patients. A systematic review of observational studies (Colosia et al. 2013) reports that obesity rates exceeded 30% in 38 of the 44 studies analysed for this variable and 50% in 14 of the 44 studies. Additional data from 3637 UK patients in secondary care (Daousi et al. 2006) showed that 86% of patients with T2DM were overweight or obese and, in Spain, a nationwide population-based cross-sectional survey with 12,077 individuals, reports that only 11.4% had BMI below 25 kg/m^2 or a recommended waist circumference (Navarro-Vidal et al. 2013).

As obesity is considered an important cardiovascular risk factor by itself, successful interventions to control weight gain and to reduce weight would be desirable in T2DM, especially when obesity is considered concomitantly with other diabetes complications associated with cardiometabolic risk. The present data seem to suggest that all T2DM patients could benefit from these interventions. Nevertheless, as poorer glycaemic control is associated with higher BMI, patients with either one of these features should be prioritized in health promotion interventions.

Besides BMI, lipid profile also constitutes an important cardiometabolic risk factor in T2DM, as patients often exhibit an atherogenic lipid profile, which greatly increases the risk of cardiovascular disease when compared with people without diabetes (Chehade et al. 2013). One particular lipid profile seems attributable to insulin deficiency and

insulin resistance, which apparently lead to a high plasma triglyceride concentration, low HDL cholesterol concentration and increased concentration LDL cholesterol (Mooradian 2009).

The literature suggests that dyslipidaemia affects around 50% of T2DM patients (Chehade et al. 2013) and that there is evidence from prospective studies that there is a low prevalence of recommended levels of total cholesterol, HDL cholesterol, and triglycerides in T2DM patients (Jacobs et al. 2005; Study 1997). Reports from the NHANES in 1999-2000 state that among T2DM, control of LDL cholesterol was only achieved in 29.7% of patients, and optimal levels of LDL cholesterol, HDL cholesterol, and triglycerides were only achieved in 3.4% of patients (Jacobs et al. 2005). The ADA recommends that cholesterol levels in T2DM should be below 200 mg/dl, HDL cholesterol should be above 40 mg/dl in men and above 50 mg/dl in women, LDL cholesterol should be below 70 mg/dl, and that the desirable goal for triglyceride levels is below 150 mg/dl (ADA 2013a). My data show that the participants are in need of interventions to decrease lipid levels, as 95% of cases and 72% of controls have a LDL cholesterol level of 70 mg/dl or above.

Regarding education, cases and controls were dissimilar in a way that is contrary to the reported in the literature. In this study, low education is associated with better glucose control, due to the fact that controls report less formal schooling than cases ($\chi^2(4)= 9.1$, $p=.048$). This association and the ones found between education and age ($P<0.001$) and between education and years of diabetes duration (P=0.019) may be due to the non-random nature of the sample, but can also reflect the socio-demographic characteristics of the Algarve. As previously reported, according to the 2011 census, 44.8% of the Algarve population over 50 years old has completed only 4 years of schooling and 20.2% has completed less than 4 years of schooling (INE 2012). Thus, T2DM patients with 50 years old and over, are expected to have a high prevalence of low schooling. This confounding effect of age may be the reason for the identification of low schooling as a protective factor for poor glucose control ($OR=0.24$, $P=0.006$). Furthermore, I did not find associations between education and occupation (P=0.215), physical activity

(*P*=0.078), number of doctor visits during the previous year (*P*=0.851), and frequency of glucose measurement (*P*=0.483), which the literature suggest as existing (Benoit et al. 2005; Buse et al. 2007; Saydah et al. 2004).

In my study, the correlation that was found between HbA1c and age at the time of data collection is not maintained when analysing only active (Pearson's *r*(37)=-0.119, *P*=0.483) or retired (Pearson's *r*(29)=-0.251, *P*=0.189) subjects. This can lead to infer that there may exist an underlying determinant of glucose control, related to employment status, which distinguishes cases from controls. Therefore, the role of employment status must be further addressed, as the literature sustains that it can substantially influence lifestyle habits, like food behaviour (in timing, number, and composition of meals) or physical activity (ADA 2013a; Benoit et al. 2005; Tahmasebi et al. 2013).

On the overall, cases and controls, as expected, show significant differences in some clinical, anthropometric and demographic variables. Nevertheless, the most surprising data are the similarities recorded in both groups of patients regarding cardiometabolic risk, obesity prevalence, doctor visits, and frequency of glucose self-measurement. As presented in the literature review, these variables are important determinants of glycaemic control, but in the subjects in this work their prevalence is not related with significantly higher odds of being part of the group of patients with HbA1c of 7% or above.

My data suggest that lifestyle habits are associated with glucose control and, as food behaviour is associated with BMI, lipid profile, and hypertension, future research focusing on the analysis of patients' eating habits and nutrition therapy can contribute to identify more adequate approaches to glucose control.

4.3. Diet and adherence to nutrition recommendations

Dietary intake was assessed by a 24h recall, which is the standard method for assessing dietary intake in epidemiological surveillance studies (Margetts and Nelson 1997; Willett 1998). I intended to accommodate the greatest detail about the food items ingested and their amounts and, although this method of food intake assessment depends on the short-term memory of the participants, it was considered the most appropriate for this study due to the fact that it did not require literacy. Furthermore, as data on food intake is recorded after consumption, this method does not alter eating behaviour.

Cases and controls were found to be significantly different in some components of their nutritional intake. The most significant difference in the nutritional composition of the diet of cases and controls is the amount of sugars ingested. Cases show a significantly higher (P=0.006) intake of sugars (*M*=128.9g, *SD*=77.92g) than controls (*M*=87.2g, *SD*=51.14g), although intake in both groups is considerably above the recommendations for T2DM patients. In general, daily consumption of sugars should not exceed 25g in women and 37.5g in men (Johnson et al. 2009), and sucrose or other added sugars in excess of 10% of TCI should be substituted by isocaloric amounts of starch, obtained from foods containing other important essential nutrients (Franz et al. 2010).

Cases also have a higher energy (P=0.03) intake than controls and these results support the evidence that glycaemic control may be more associated with total energy intake than with macronutrient distribution (Heilbronn et al. 1999; Kang and Kim 2012; Masuda et al. 2013), at least when diet carbohydrate content is moderately low.

Total energy intake has been linked to glycaemic control (ADA 2013a), with T2DM patients who exceed recommended energy intakes being reported as having a higher mean HbA1c (Bell et al. 1995; Masuda et al. 2013; Xu et al. 2007).

Nevertheless, it must be reaffirmed that all subjects presented a high prevalence of excess energy intake. Most of the subjects (72% of cases and 68% of controls) have an inadequate energy balance, failing to meet the recommended dietary reference intake

(DRI), as proposed by the literature in order to prevent or reduce overweight and obesity, and consequently, several associated complications (ADA 2013a).

The distribution of the percentage of daily TCI for each macronutrient suggests that all subjects follow a diet with adequate protein intake, high lipid intake, and a moderate carbohydrate intake.

A 2012 systematic review of the literature regarding macronutrients, food groups, and eating patterns in the management of diabetes reports a wide variability in the macronutrient distribution in the diet diabetes patients, and states that a high-carbohydrate intake is often described as a carbohydrate intake of at least 55% of total energy, whereas a low-carbohydrate intake may be described as being below 25% of total energy (Wheeler et al. 2012). The standards of care for diabetes regarding nutrition propose that the mix of macronutrients should be adjusted to meet metabolic goals of the person with diabetes (ADA 2013a), but carbohydrate distributions between 50-55% have been recommended by dietitians in order to include in patients' diet foods that are important sources of fibre, vitamins, and minerals, while maintaining dietary palatability and attending to individual preferences (Wheeler et al. 2012). Despite these recommendations, dietary intake of carbohydrates in T2DM patients is around 45%, as demonstrated by meta-analysis (Kirk et al. 2008), randomized trials (Esposito et al. 2009; Vitolins et al. 2009), and prospective (*e.g.* (Eeley et al. 1996)) and populational studies (Nelson et al. 2002), which report usual carbohydrate intakes ranging from 40% to 46% of TCI, even when dietary recommendations aim at higher intakes.

In my study, both cases and controls have a lipid distribution of at least 35% of TCI, which, when analysed taking into account the overall macronutrient distribution, seems to be an important determinant of excess energy, similarly to the results proposed by Nelson and colleagues (Nelson et al. 2002).

Considering the intake of different lipids, subjects showed a high intake of total cholesterol and saturated fatty acids (table 22). The ADA recommends limiting dietary cholesterol to levels below 200 mg/day and saturated fat intake to levels below 7% of TCI (ADA 2008), and, according to Student's t-test, both groups of patients in this study

had significantly higher intakes of both types of lipids (P>0.05). Mean total cholesterol was above 350 mg for both groups of subjects. Furthermore, controls show a mean saturated fat intake of 11.9% of TCI (*SD*=5.30%) and cases show a mean saturated fat intake of 11.5% of TCI (*SD*=4.91%), with the differences between groups being non-significant (*t*(64)=-0.319, P=0.751). Even though monounsaturated and polyunsaturated fatty acids still account for the majority of lipid intake in cases and controls, as recommended in the literature (Franz et al. 2010), these data suggest that patients should adjust their intake in order to have a more cardioprotective eating pattern.

The fibre intake recorded for both cases and controls is below the recommended intake for T2DM patients. Cases showed a mean intake of 18.3g of fibre (*SD*=8.73), while controls showed a mean intake of 17.7g (*SD*=8.13). Franz et al. (2010) suggest that diets containing 44g to 50g fibre daily improve glycaemic control, but, as these fibre contents are difficult to achieve in a diet with low carbohydrate content, and as they may be related with gastrointestinal distress, recommendations for fibre intake in T2DM patients are similar to the ones for the general population, indicating an intake of 14g of fibre for every 1000 kcal. As alternative for these recommendations, the ADA guidelines suggest a daily intake of foods containing 25g to 30g of fibre, with special attention given for soluble fibres due to their beneficial effect on lipid profile (ADA 2008).

Sodium content is another important characteristic of the nutritional composition of the diet in these subjects. When compared to non-diabetic individuals, hypertension in diabetes patients is more sodium sensitive and patients show an increased total body sodium, an increased renal tubular sodium reabsorption, and an impaired ability to excrete sodium (Underwood et al. 2012; Van Buren and Toto 2011). This has led to believe that sodium intake in diabetes patients is of major importance for the management of hypertension.

It is recommended that normotensive diabetes patients reduce dietary sodium to 2,300 mg/day or below, and that patient with hypertensions should aim for a sodium intake below 1,500 mg/day (ADA 2008). The effects of lowering intake levels below 1,500

mg/day have been demonstrated in the DASH study, which reports effects similar to antihypertensive pharmacological therapy (F. M. Sacks et al. 2001). The different diets used in the DASH study lowered blood pressure by reducing sodium intakes to 3,500 mg/day, 2,300 mg/day, and 1,150 mg/day. Blood pressure reductions were recorded among both hypertensive and non-hypertensive subjects, although the effects were greater among hypertensive participants. Subjects in this study showed a high sodium intake ($P<0.001$), recorded for both cases (M=4277.7 mg, SD=2057.04 mg) and controls (M=3921 mg, SD=1530.06 mg). Sodium intakes were not significantly different between groups ($t(64)=0.803$, $P=0.425$) and were not correlated with HbA1c (Pearson's $r(66)=0.024$, $P=0.848$), which indicates that this micronutrient, by itself, is not associated with glycaemic control.

Overall, when analysing nutrition composition of the usual diet in the subjects of this study, I found that both cases and controls show high intakes of energy, lipids (saturated fatty acids and cholesterol, especially), total carbohydrates (with sugars accounting for a considerable proportion of carbohydrate excess) and sodium. Sugars seem the type of nutrient that most significantly determines glycaemic control, but it also appears likely that the total energy intake of the diet outweighs the role of carbohydrate distribution. My results support the evidence that glycaemic control may be more associated with total energy intake than with macronutrient distribution.

Lower HbA1c is associated with worst nutrition habits, supporting one of this study's initial research hypothesis (hypothesis number 2, stating that "patients with adequate glycaemic control have a better compliance of nutrition recommendations "). Nevertheless, as described, the similarities between both groups of subjects in nutritional intake and food behaviour are also worthy of note. For instance, both cases and controls present a daily median energy intake which is over 200 kcal above individual requirements. Furthermore, both groups also showed a high intake of sodium, total cholesterol and saturated fatty acids. These results also seem linked to the perceptions of nutritional care and to an unreasonable optimism in regard with diet adequacy. Even subjects with substantially increased BMI and high excess intakes of

energy, lipids, and carbohydrates, believe they have an averagely adequate diet, independently of previous consultations with a dietitian, type of health advice received, any of the anthropometric variables collected, years of diabetes duration, and age at the time of diagnosis.

My results support the reasoning that a diet with a moderate amount of carbohydrates, privileging foods with low-sugar content, high soluble fibre, and low fat, distributed in adequate portion sizes as to not exceed recommended energy requirements, would have the most beneficial potential for glycaemic control in T2DM patients. Both cases and controls showed a moderate intake of total carbohydrates, which prompts me to believe that the promotion of an adequate diet in T2DM patients must include specific education interventions aimed at addressing the carbohydrate quality of the meals, and also other aspects of food behaviour that seem related to glycaemic control, like the number of meals. According to the data, these interventions, if effective, would benefit patients with inadequate glucose control and those with adequate glucose control, as the majority of patients in both groups have clinical (LDL cholesterol) and anthropometric characteristics (BMI, waist circumference) that the literature relates with food behaviour and with diabetes monitoring and control.

The similarities in the nutritional composition of the diet of cases and controls must be further addressed in order to clarify the role that known determinants of food behaviour play in glycaemic control. The usual food intake found in both groups pf patients in the present study is significantly different from the nutritional recommendations. Subjects should receive individualized medical nutrition therapy, as it's reported that modifying intake, specifically the type and amount of dietary carbohydrates, can improve disease control (ADA 2008). Foods containing carbohydrates that are slowly digested and absorbed, included in a diet that consists largely of fresh, unprocessed fruits and vegetables, moderate levels of lean protein and beneficial fats, with minimal amounts of processed carbohydrates and saturated and *trans* fats, can significantly reduce postprandial glucose levels related to T2DM complications (ADA 2007). Evidence also suggests that dietary measures can be effective in weight reduction and glycaemic

control irrespective of the macronutrient composition (low fat or low carbohydrate), provided that there is adequate energy restriction, reduction of saturated fat to less than 7%, and adequate provision of dietary fibre (ADA 2008; Stern et al. 2004)

Nevertheless, nutrition counselling requires a contextual understanding of the patient's individual situation, in order to support and promote health behaviour change (Morris and Wylie-Rosett 2010). Despite the literature may recommend that a stricter adherence to existing guidelines and a much stronger attention to the desired therapeutic goals will allow a decrease in diabetes costs, morbidity, and mortality (Comaschi et al. 2005), the results from the socio-demographic variables I assessed provide some indication that educational, cultural or economic characteristics that may hinder compliance of nutritional recommendations must be taken into account.

Another result I propose that must be discussed is the involvement of patients in food shopping, which seems related with better glycaemic control (P=0.033). The literature on food choice and nutrition interventions has associated the participation in food shopping following nutrition counselling with better health education outcomes and greater nutrition knowledge, especially in situations where restriction of selected food items is encouraged, as in weight management diets (Saarela 2013; Saarela et al. 2013).

It is suggested that family dynamics has a significant impact in diabetes. Family provides, for example, emotional support and economic well-being, but, on the other hand, if family life is characterized by stress and conflict, subjects' health tends to be negatively affected (Miller and DiMatteo 2013). Family members of diabetes patients are also aware of their supportive role, as they report wanting to be more involved in their care (Kovacs Burns et al. 2013). The mechanism by which social support affects adherence to diabetes therapy is not yet completely understood, and this can be an area of further inquiry in diabetes and nutrition research.

On the overall, regarding diet and adherence to nutrition recommendations, the results in subjects with better glycaemic control show that these patients are also in need of effective nutrition education, as they also present a higher than expected agreement with some of the barriers presented in the literature as important determinants of

glycaemic control and nutrition therapy adherence. Furthermore, although patients believe diet is an important element in their self-care, they do not maintain their dietitian consultations for long or don't feel the need for attending any consultations.

According to my results, I propose that most patients, even if differing in their barriers perceptions, fail to comply with the recommendations for proper daily food intake. Furthermore, when analysing differences in barriers perceptions, it is of note that even with the existence of significant differences, the data that show that subjects with proper glycaemic control score several barriers above the classification scale's midpoint should not be disregarded. This means that they too experience those barriers, even if with a lower frequency or perceived importance than cases. Conversely, the significant differences found in these variables can occur due to the wide classification range between cases and controls and not necessarily due to a low perception in controls alone. For example, there are significant differences in the perceived effort that a balanced and proper diet requires, with cases reporting a higher perceived effort, but controls also report perceived mean and median scores indicating a moderate perceived effort. These results point to the existence of difficulties in translating for one's daily routine the nutritional recommendations that all patients report having previously received.

The literature refers the difficulties and complexities of the nutritional care process in T2DM, proposing that a single, uniform approach is not desirable, due to the intricacies of diabetes aetiology, complications, and glycaemia determinants (ADA 2008, 2013a; Franz et al. 2010). Recommendations for three to four sessions or consultations with a dietitian after diagnosis, each lasting from 45 to 90 minutes (ACD 2008), are difficult to upheld, and yearly follow-up to reinforce lifestyle changes and to evaluate and monitor outcomes are, in the subjects in this study, non-existent. Even though patients report having previously received nutrition recommendations, the prevalence of the feeling of confusion with nutritional information is high, especially in subjects with poor glycaemic control, which raises questions that are unanswered by this study regarding the nature and quality of nutrition recommendations. This, together with the low prevalence of

physical activity, nutritional status, and nutritional composition of the diet, allows to propose that the effectiveness of nutrition recommendations can be improved, and that further research in this field must also focus on assessing the type of counselling and the determinants of consultation prevalence.

Additional empirical observations resulting from the data collection interview raise concerns that the cost of consultations can be a barrier to nutrition recommendations, even if none of the subjects openly identified this factor as a barrier. Subjects expressed concern not only for the actual cost of the consultation, but also concern with indirect costs, like the need for transportation. Evidence for the efficacy and cost-benefit of nutrition therapy in diabetes is not new, and recent data (Franz et al. 2010; Zhuo et al. 2013) is in accordance with previous findings stating that over patient's lifetime, effective individualized nutrition interventions can be delivered by experienced dietitians with a cost-effective investment of resources, and resulting in substantial long-term savings in healthcare costs. This cost-effectiveness is enhanced when dietitians are engaged in active decision making about interventions based on the patient's needs (Franz et al. 1995; Pastors et al. 2002; Sheils et al. 1999). Subjects in the population analysed in this study are offered dietitian consultations with prices that imply that patients have to pay from around €5 to up to €20. Even this relatively low consultation cost seems to be a deterrent for consultation adherence and assessing the determinants and context of nutrition consultations is to be suggested for future research in the population for this study. Furthermore, the results from the barriers to nutrition therapy adherence also reflect patients' concerns over economic implications of a proper diet. Patients in this study, especially cases, believe that a proper diet is more expensive. This can be seen even in patients that, based on the assessment of the foods in their usual diet, seem to have a food pattern that does not often include highly expensive food items, like prime cuts of meat or expensive species of fish. As diabetes is more prevalent in older patients who are predominantly retired from their job and subsist on a pension, the costs of diabetes therapy, which regularly include poly-pharmacy, can be an important determinant of adherence to nutrition care.

Some of the barriers for nutrition therapy adherence identified in this study were expected, like the perceptions of limited food portions, or the dislike of food in the diet, but I did not predict that the economic implications were such an important predictor of glycaemic control, despite the fact that it has been described in the literature (Gazmararian et al. 2009; Jerant et al. 2005; Toobert et al. 2000; UKPDS Study Group 1995b; Vijan et al. 2005). We believe that dietitians and other healthcare professionals providing care for T2DM patients need to acknowledge the economic burden of diabetes when counselling for adequate self-care. In regard to nutrition, it seems important that the aim of education interventions must be on ways to properly construct a daily meal plan, but also on how to do so economically.

During the data collection interview, patients also made several comments stating that they have to prioritize expenses with their health care, and also stating that medication and doctor consultations were considered the most important components of care. The literature reports that although patients place a high value in a proper diet, pharmacotherapy and clinician advice are more highly regarded therapeutic tools (C. Asche et al. 2011a; Cramer 2004; Sabatâe 2003)). As beliefs and knowledge about diabetes are considered determinants of glycaemic control (Nam et al. 2011) this can explain, in part, the poor risk perception recorded, and why most studies show that adhering to a proper diet is generally non-sustainable .

A proper communication of the risk of diabetes perception and their relationship with food intake could be useful in this population, as there is evidence suggesting that an appropriate risk communication may help patients to take a more active role in their care (Paling 2003; Waldron et al. 2011). However, results from randomized controlled trials show that the evidence on the specific impact and effects of risk communication on diabetes self-care is still unclear. Risk communication seems helpful in T2DM patients (Pijl et al. 2009), but risk perception appears to improve during a short timespan after the intervention only to subside after about 12 weeks (Welschen et al. 2012). I suggest that the strategies for nutrition education in T2DM and nutrition knowledge in the

population in this study should be assessed, in order to document the association between those variables and risk perception.

Patient education enables people with diabetes to improve their knowledge, skills and confidence, allowing them to self-manage their condition. It's a critical element in diabetes care and can have a strong effect on biomedical outcomes (Funnell et al. 2011; Nyenwe et al. 2011). Patient education includes, among other goals, patient empowerment to incorporate nutritional management and physical activity into his lifestyle and the development of personal strategies to promote health and behaviour change (Funnell et al. 2011).

4.4. Consultations with health professionals

My results show a low prevalence of dietitian consultations. In the last year, only 12.5% of cases and 35% of controls sought a dietitian consultation. When compared to controls, cases went to less dietitian consultations during the last year (P=0.029), and also during all the course of the disease (P= 0.031). Additionally, in cases, a longer time since last consultation with a dietitian had passed at the time of data collection (P=0.028). These results suggest that, independently of the low prevalence of dietitian consultations, having been in a dietitian consultation during the last year is related with adequate glycaemic control. The literature describes that changes in nutrition behaviour depend on patient motivation and the quality and type of follow-up (Delamater 2006; Sabatâe 2003), with results from analytic studies evidencing the importance of low goal setting, new stimuli during the behaviour change process, proper social support, and long-term contact with therapists (Dalle Grave et al. 2010; Epstein et al. 2012) as determinants of therapeutic success. A clinical trial assessing different types of diet and their impact in weight reduction and cardiovascular outcomes also shows that, more important than the specific diet plan, maintaining adherence to the diet for one year is a determinant of weight loss and reduction of cardiovascular risk (Dansinger et al. 2005). The authors conclude that it seems plausible that for maintenance of reduced weight,

the diet needs to be matched with the patient, by adopting dietary and cognitive-behavioural strategies that increase dietary adherence.

In diabetes therapy, intensive nutrition counselling by a dietitian is believed to promote a statistically significant HbA1c reduction (Coppell et al. 2010b; UKPDS Study Group 2000), which is maintained up to 12 months after counselling and despite the use of fewer anti-diabetic drugs (Franz et al. 2010; Gæde et al. 2003; Pastors et al. 2003). While intensive pharmacological therapy seems to provide mixed results for glycaemic control (Holman et al. 2008; Turnbull et al. 2009), the current literature supports that proper nutrition is a highly valuable therapeutic tool for improving disease outcomes and patients' quality of life (ADA 2013a; Franz et al. 2008, 2010). The literature also shows that, in a primary care setting, management of diabetes guided by a registered dietitian can improve glycaemic control in patients with poorly managed disease (Huang et al. 2010), and have a significant impact in the decrease in mean energy intake at dinner and a greater increase in mean vegetable intake for the whole day, breakfast, and lunch (Adachi et al. 2013). In my study, both the time since the last consultation with a dietitian and the existence of this type of monitoring seems associated with better glycaemic control, allowing to infer that consultations with a trained dietitian are recommended for T2DM, as proposed by the standards of care for diabetes (ADA 2013a). Nevertheless, when considering the results on the prevalence of physical activity, the anthropometric indicators of nutritional status, and the nutritional composition of the diet, one must question the effectiveness of the recommendations and suggest that the type of counselling, the determinants of consultation prevalence, or the determinants of adherence to recommendations play a significant role in the results.

The analysis of the specific reasons for low prevalence of consultations, whether by referral or by own initiative, is beyond the scope of this study, but the literature suggests that low prevalence in consultations and education interventions is common. Data from the USA Diabetes Prevention and Control Programs show that only 54.3% of diabetes patients attended some type of diabetes self-management class between 2000 and 2010 (CDC 2011), and a study analysing dietitian consultations in 18,404 patients reports

that only 9.1% had at least one consultation within a 9 year period (Robbins et al. 2008). The USA health system implies that diabetes patients have a more direct cost with disease treatment and management, but similar results regarding consultation and education interventions attendance are found even in publicly-funded health care systems, where patients could access these services without direct charges (Cauch-Dudek et al. 2013).

One of the biggest therapeutic challenges in T2DM nutrition counselling is to implement strategies to assure patient adherence, as diet has significantly less compliance than pharmacological therapy (Asche et al. 2011a; Cramer 2004; Sabatâe 2003). My results show that, although patients believe diet is an important element in their self-care, they do not maintain their dietitian consultations for long or don't feel the need for attending any consultations, independently of their glycaemic control. Patients appear to believe they have moderate nutrition knowledge, as this was not clearly identified as a barrier to a proper nutrition, but cases feel more confused with the information they received. It is possible to infer that the manner in which counselling is made can be improved. Nutrition advice can be tailored to address the barriers that are more important to subjects with inadequate glucose control, such as the perceived effort, cost and foods composition in a proper diet, and the clarity of nutrition information.

A gradually implemented, patient-centred care, recognizing patient autonomy but providing continuity of care with frequent contact with health professionals (Delamater 2006), could constitute a model for nutrition counselling aimed at sustaining the beneficial changes beyond the intervention.

4.5. Glucose self-monitoring

Glucose self-monitoring was also similarly infrequent in cases and controls. Although the optimal frequency for glucose self-monitoring in T2DM patients who follow a non-insulin pharmacotherapy is still a topic of debate (ADA 2013a), it is believed that it results in early therapeutic changes and can help prevent asymptomatic hypoglycaemia and hyperglycaemia (Garg and Hirsch 2014).

In this study, empirical observations resulting from patients' own anecdotal reports during the data collection interview allow to infer that the population under study has poor knowledge on how to self-measure blood glucose using a portable glucometer, and also lacks the skills to properly interpret the data and to act if the results are too high or too low. This can be an important aspect of diabetes care and providing additional education on self-monitoring must be considered.

The self-monitoring of glucose in T2DM patients who are not treated with insulin is still a controversial topic in the literature. There is evidence from randomized controlled trials (Garcia de la Torre et al. 2013) and different prospective studies (Henderson et al. 2013; Schnell et al. 2013) stating its efficacy in reducing HbA1c, but also evidence stating that the improvements in quality-adjusted life years are not cost-beneficial and that are only visible if patients have a high compliance with monitoring (Cameron et al. 2010; Simon et al. 2008; Tunis 2011). It seems that the evidence skews on the side of supporting glucose monitoring in non-insulin treated patients, mostly due to the improvements in diabetes management reported in real world clinical settings (Lalic et al. 2012), and also to the fact that patient-obtained glucose readings can provide valuable real-time feedback on glycaemic responses to meals and exercise, and provide the patient with guidance on the day-to-day management of their disease (Garcia de la Torre et al. 2013). Nevertheless, for self-monitoring to be most effective, it should be performed in a structured format where information obtained from this measurement is used to guide treatment, considering that both patients and health care professionals require education on how to respond to the data.

In Portugal, diabetes patients receive their measuring strips and glucometers almost completely funded by the Health Service, with a prescription by a doctor. Data modelling for Italy and Spain, where payer reimbursement practices are similar, has provide data to consider self-monitoring as cost effective across a 40-year time horizon (Tunis et al. 2010). This timespan can be a deterrent for promoting widespread self-monitoring in T2DM patients not using insulin, but it also must be considered that the benefits of self-monitoring may not be limited to HbA1c improvements.

Integration of glucose self-monitoring into basic T2DM management improves glycaemic control, but psychosocial outcomes, such as benefits to self-efficacy and diabetes-related distress must also be assessed. Furthermore, the increasing technology in glucose monitoring and all the novel care strategies that can improve doctor and patient communication may aid to detect clinical outcomes, such as hypoglycaemia, and to implement therapeutic changes. Results from self-monitoring may will help clinicians to adjust OADA therapy.

For self-measurement of blood glucose to be successfully incorporated into diabetes self-management, health care professionals must also be motivated to explain their rationale to patients and also to show them their importance and meaning. The literature reports that is not unusual for patients to make a note of glucose measurements without really understanding what they mean or how they should use the information, and also to feel frustrated when healthcare professionals take little interest in their diligence in recording glucose values. Glucose self-monitoring must be integrated into a comprehensive and structured training programme in which these issues are expressly addressed (Heller 2014; Polonsky et al. 2014)

Considering the results in the present study, glucose-self monitoring also constitutes the only practical way to identify glucose excursions after a meal. Due to the similarities in PPG that seem independent of HbA1c, self-monitoring results may help to provide clinicians with information that can be used to reduce cardiovascular risk in T2DM patients. Further research is needed in order to assess the benefits and costs of glucose self-monitoring considering additional outcomes other than improvements in HbA1c and also cardiovascular risk.

4.5. Perceptions and barriers to nutrition therapy adherence

As proposed in this study's hypothesis number 3, patients with poor glycaemic control identify barriers to nutrition recommendation compliance differently from those identified by patients with adequate glycaemic control ($P<0.05$). Subjects with poor glycaemic control believe that a balanced and proper diet takes too much effort, is more expensive than other diets, implies different meals from the rest of the family, and is composed by less than enough food. Additionally, they also have an increased agreement with the statements indicating that diet doesn't seems to affect glucose control, confusion with nutrition information, and insufficient knowledge about nutrition in diabetes.

The results of the agreement with the statements regarding confusion with the nutrition information received and with the need for more advice on what is a proper diet seem to reflect a concern of diabetes patients with the knowledge and skills related to self-care and food intake. Confusion and perceived high complexity of diet is correlated with low adherence (Mata et al. 2010) and in the cases in my study agreed more with the feeling of confusion with nutrition information.

The results in this study show evidence of an unreasonable optimism in regard with diet adequacy that is visible in cases and in controls, even in individuals with substantially increased BMI and high excess intakes of energy, lipids, and carbohydrates, and in individuals that seem confused with the nutritional information they received and state they would like to know more about nutrition in diabetes. In this study, the existence of optimistic bias in perceived diet adequacy is not related to a particular characteristic or set of characteristics and the mean difference in the classification of diet adequacy on the Likert response scale is not correlated ($P>0.05$) with consultations with a dietitian, HbA1c, BMI, WC, energy intake, carbohydrate intake, duration of diabetes, and age at the time of diagnosis.

It is believed that individuals have a general optimism about the outcome of an event, related with a strong but unjustified sense of immunity. When asked to classify their agreement with the likelihood of an event, individuals are also more unjustifiably

optimistic when they perceive having some form of control over that event (Neil D. Weinstein 1980). This can explain the difference in perceived diet adequacy, as individuals have more control over their own diet, and thus perceive the outcomes of their diet in a favourable way. According to the literature, the tendency to believe that one's own outcomes of an event are more favourable than that of others can partly explain why health education messages can be ineffective (Weinstein and Klein 1995).

As health education can even exacerbate unrealistic optimism (Weinstein and Klein 1995), the communication of nutrition practices in T2DM should be made with care, by skilled professionals. Diet and proper eating behaviour are widely prevalent diabetes counselling topics and, as is shown in my results, even the patients who never had a consultation with a dietitian were previously advised to follow a diet or meal plan. I propose that, although repeated and intensive counselling can be correlated with better disease outcomes (Franz et al. 2010), it should be promoted by skilled nutrition professionals (Pastors et al. 2002; Spahn et al. 2010) due to its effectiveness in facilitating health and food behaviour change and in improving glycaemic control, but also due to its possible association with the accentuation of unrealistic optimism, which, in turn, can be a determinant of diabetes self-care (Tahmasebi et al. 2013; Weinstein 2003).

4.6. Postprandial glycaemia

In order to assess glucose response, all patients were offered a controlled breakfast, constructed according to the dietetic recommendations for patients with T2DM (ADA 2008; Franz and Bantle 2012), and composed of foods traditionally consumed in a Mediterranean culture and obeying to usual eating habits in the region. It was decided that the breakfast should account for approximately 400 kcal, based on the prediction equations of the IOM (2002) that estimate a daily energy requirement of 2000 Kcal for adults over 50 years old with a lifestyle that includes only the light physical activity associated with typical day-to-day life, and considering that a nutritionally balanced breakfast should account for 20% to 25% of the daily energy intake (Leidy et al. 2009;

Leidy 2013; Schusdziarra et al. 2011). In this study, cases and controls did not significantly differ in glycaemia up to 120 minutes post-meal (P>0.05).

In non-diabetic individuals, PPG peaks 60 min after the start of a meal and rarely exceeds 140 mg/dl, before decreasing to pre-prandial levels within up to 180 minutes (ADA 2001). This evidence, together with the association of postprandial hyperglycaemia with several diabetes complications, like macrovascular disease, increased risk of retinopathy, oxidative stress, inflammation, and endothelial dysfunction, has prompted the proposal of guidelines suggesting a PPG level below 140 mg/dl for 2 hours after the start of a meal as adequate (Ceriello et al. 2008; Franc et al. 2010).

All of the subjects in this study presented a PPG level above 140 mg/dl, indicating a postprandial glycaemia associated with diabetes complications. Furthermore, it is also recommended that the difference between pre-prandial and postprandial glucose should not exceed 40 mg/dl (Ceriello et al. 2008). All but 4 subjects (2 cases and 2 controls) had differences above 40 mg/dl, which can be classified as glucose excursions (*i.e*. elevated differences between pre-prandial and postprandial glucose).

The previous results in this study indicating that a high proportion of subjects have a usual diet that is inadequately high in energy, sugars, total carbohydrates, and lipids, besides the correlations these variables showed with HbA1c, lead me to suggest that the glucose excursions that resulted from the experimental breakfast may have been less pronounced than the ones subjects' experience in their daily diet. It can be proposed that outside the experimental setting for this study, some patients can choose to have a breakfast which can be classified as less nutritionally adequate than the one that was offered during data collection. Analysis of the dietary data makes it safe to assume that, due to the high intake of total carbohydrates and sugars, subjects can experience postprandial hyperglycaemia, independently of their perceived glycaemic control, measured by HbA1c. As previously reported, excess intakes were common in both cases and controls, and excess intake of energy and sugars is associated with poor glycaemic control.

My results confirm this study's hypothesis number 1, allowing to conclude that there is no significant difference in PPG between patients with adequate glycaemic control and those with poor glycaemic control. Mean glycaemia values were similar in cases and controls up to 120 minutes after a meal.

Although the group of subjects in this study is a particular one (doing only metformin as OADA), if we consider the high prevalence of excess energy and carbohydrates intake reported, diabetes patient's cardiovascular risk can be high in subjects who, based on HbA1c levels, believe themselves in a proper state of glycaemic control.

Similarities in PPG also extend to the mean difference between pre-prandial and postprandial glucose and further studies should be promoted in order to analyse the role of different OADA in PPG in subjects with adequate HbA1c.

The similarities in PPG between the subjects also add to the evidence that HbA1c, despite being considered an adequate predictor of glycaemic control that can be used for establishing a diagnosis, does not account for daily fluctuations of glucose (S. Colagiuri 2011; Sakuma et al. 2011; Woerle et al. 2007). The mean values for glucose excursions in both cases (*M*=57.1 mg/dl, *SD*=13.29 mg/dl) and controls (*M*=63.0 mg/dl, *SD*=19.73 mg/dl) were significantly above the recommendations stating that this value should not exceed 40 mg/dl (Ceriello et al. 2008) and may imply an added risk for cardiovascular events (Coutinho et al. 1999). Self-measure of blood glucose is the most appropriate way to identify PPHG and the results from this study show that patients should be empowered to overcome their low prevalence of glucose self-measure, as regular data of postprandial glycaemia can help to adjust diabetes care plans.

4.7. Diabetes complications perception and glycaemic control

This section of the data collection interview used a set of questions based on the Risk Perception Survey for Diabetes Mellitus (RPS-DM) questionnaire (Walker et al. 2007a). This set of questions was analysed prior to its application by a test-retest method, where a sample of eight T2DM patients was used to assess its reliability.

The sample was interviewed using only the set of questions regarding diabetes complications perception and, a week after, they were retested with the same version of the scale. According to the Wilcoxon signed ranks test for paired samples, the scale's scores did not significantly differ between test and retest moments ($P>0.05$). The scales had an acceptable internal consistency, with Cronbach's alphas between 0.7 and 0.8, and all original items were retained because there would be no increase in Cronbach's alpha with the deletion of any item (Streiner and Norman 2008).

Although this adaptation and translation process does not validate the subscales of the RPS-DM for this population, I suggest that the items used can be considered reliable and allowed to achieve this study's objectives regarding risk perception.

One of the determinants of diabetes self-care is the perception of harmful effects resulting from the disease and its complications (Day 2000; Frostholm et al. 2007; Griva et al. 2000; Tahmasebi et al. 2013). Although research on diabetes self-care has tried to identify determinants for adherence to professional recommendations, there is limited evidence on the relationship between risk perceptions and health behaviours that reduce the risk of disease (Weinstein 2003). Nevertheless, the literature suggests that adherence to treatment and management of T2DM is influenced by patients' illness perception (Harrison et al. 2003).

In this study, both cases and controls seem to have a biased diabetes complication perception, favouring less individual likelihood of diabetes complications. My data supports the evidence that diabetes patients significantly underestimate their risk for diabetes complications (Calvin et al. 2011; Meltzer and Egleston 2000). The group of cases, with mean HbA1c that is associated with higher incidence of macrovascular

disease, appears to believe that they are less likely to experience diabetes complication. When analysing the agreement with a lower likelihood of serious health problems, and not only diabetes complications, the results are similar.

A bias in perceived risk, reflecting an unreasonable optimism can be inferred by the results, with cases appearing to have a poorer awareness of the complications of diabetes and of the risk of other serious health problems. When considering the perception of individual disease risk, both cases and controls also reflect a biased assessment, with a predominance of the perception that they have "almost no risk" or "slight risk" for several health outcomes.

The biased risk perception in the subjects is also reflected in their environmental risk. The events or outcomes analysed in this type of risk where considered moderately probable, with a mean score for environmental disease risk that is statistically similar ($P>0.05$) to the mean score for personal disease risk, in both cases (mean personal disease risk=1.9 and environmental disease risk=2.2) and controls (mean personal disease risk=2.0 and environmental disease risk=2.1).

The high perceived health risk from pesticides and extreme weather reflects current knowledge on risk perception, stating that individuals tend to attribute a higher risk to situations which they cannot control and that associated to a greater sense of dread (Brewer et al. 2007; Walker et al. 2007b), like the effects of extreme weather, that are usually presented as catastrophic.

The optimistic bias subscale in the set of questions used to assess diabetes complications perception has a high score in both cases (M=3.4) and controls (M=3.3), which indicates an unreasonable optimism in diabetes risk perception.

Cases and controls also score their personal disease risk in a way that indicates low risk perception. Cases present a significantly lower risk perception for personal disease ($P=0.03$). These results are incongruent with the physiologic, anthropometric and nutritional data I collected, as these indicate a moderate or high risk for diabetes complications in most of the subjects.

The literature reports associations between risk perception and risk knowledge and communication (Fischhoff et al. 1993; Fisher et al. 2002). In the subjects of this study, I tested for association between previous counselling and risk perception, but did not find any significant correlation.

The associations between risk perception and consultations with health professionals are erratic, with negative and positive correlation between the scales of risk perception and the same variable (e.g., between nurse consultations in the last year and risk perception in controls), with widely varying significance, which I believe to be related with the random nature of the measurement.

My data does not support the evidence in the literature associating lower education with a higher optimistic bias (Walker et al. 2007b), but I infer that the homogeneity in education in the participants in this study may have led to these results. Approximately 40% of the subjects had only completed primary education, corresponding to 4 years of schooling, and 20% of patients only had 6 years of schooling. The literature suggests that individuals with higher education can incur in a more adequate self-care management due to a greater knowledge of diabetes (Cauch-Dudek et al. 2013) and, consequently, may have a better risk perception for diabetes complications.

The lack of diabetes symptoms is another factor that the literature associates with poor perceived risk for diabetes complications (Frijling et al. 2004), as they are considered motivators of protective behaviour (Stover et al. 2001). In the sample, previous diagnosis of diabetes complications was low, which may have led subjects to have an unreasonably low risk perception, as they feel their disease is under control.

When assessing the odds ratio for optimistic bias, I found that 65 out of the 66 subjects in this study presented an unreasonably optimistic view of their risk for complications (value above 2 points in the scale's score) while the remaining subject was more associated with a realistic or pessimist perception (score below 2 points in the optimistic bias scale). This implies that I would not find a significant odds associated with inadequate glycaemic control due to the high prevalence of optimistic bias in both cases and controls.

These results further support the need for health education interventions in both groups, regarding risk perception and risk knowledge.

These results confirm this study's hypothesis numbers 4 and 5. Patients show an optimistic bias in the risk perception for diabetes complications, reporting a lower likelihood of experiencing diabetes related complications than the likelihood of health problems caused by environmental risk factors, like riding an automobile, extreme weather, or pesticides. Patients, even those with poor glycaemic control, also report a lower individual risk for diabetes complications when asked to compare themselves to other patients.

Nevertheless, as proposed in hypothesis number 5, there is a significant difference in risk perception for diabetes complications between patients with adequate glycaemic control and those with poor glycaemic control. The optimistic bias recorded in the risk perception for personal disease is stronger in subjects with poor glycaemic control.

More studies on diabetes risk perception are needed to enlighten its role as a determinant of glycaemic control, but my results show that patient's diabetes knowledge, together with the way that risk is communicated to patients, must be improved.

4.8. Statistical model for prediction of inadequate glucose control

When analysing risk perception data by creating classification cut-offs in the scales' midpoint and computing the odds ratio associated with the likelihood of being in the group of cases, I confirm the results obtained when analysing mean differences in risk perception scales indicating that a low personal disease risk perception is associated with a poor glycaemic control (section, 3.4., table 32).

When assessing the odds ratio for optimistic bias, I found that 65 out of the 66 subjects in this study presented an unreasonably optimistic view of their risk for complications (value above 2 points in the scale's score) while the remaining subject was more associated with a realistic or pessimist perception (score below 2 points in the optimistic

bias scale). This implies that I would not find a significant odds associated with inadequate glycaemic control due to the high prevalence of optimistic bias in both cases and controls.

These results, together with the associations of glycaemic control with socio-demographic (age, education), anthropometric (BMI), nutritional (high energy and sugars intake), and psycho-behavioural (perceived barriers to proper nutrition, engaging in food shopping, and personal disease risk perception) characteristics, prompted me to construct a binary logistic regression model, in order to identify covariates that predict poor glycaemic control.

For this procedure, I first produced a multilevel method, with covariates entered by ascending order of the statistical significance previously determined in parametric and non-parametric tests for correlations and group comparisons, which resulted in a predictive model that did not fit the data. The Hosmer-Lemeshow goodness-of-fit statistic was considered non-significant (P=0.321) and I recorded several interactions between covariates. One example of such interactions is the confounding effect of age in the correlation between occupation and glycaemic control, as previous analysis shows that the significant predictor of glycaemic control should be subjects' age. Older subjects are more likely to be retired, resulting in a statistically significant association between employment status and glycaemic control when the data are not age adjusted.

Due to these results and to the exploratory nature of this study, I conducted a backward stepwise covariate selection, based on the probability of the likelihood-ratio statistic, as proposed by Hosmer and collaborators (Hosmer et al. 2013). From the variables entered in the analysis, the most parsimonious resulting model identified age, personal disease risk, and BMI above 29 kg/m^2 as significant predictors of glycaemic control (table 37):

Table 38. Predictors, coefficients, and odds ratio in the logistic regression model for inadequate glycaemic control

Predictors	Beta	SE	Wald statistic	Wald statistic p-value	Odds ratio	95% CI for odds ratio
Age at data collection	-0.103	0.041	6.18	0.013*	0.902	0.832 - 0.978
Personal disease risk	2.801	1.125	6.20	0.013*	0.061	0.007 - 0.551
BMI above 29 kg/m^2	1.308	0.616	4.51	0.034*	3.70	1.11 – 12.36
Model constant	11.062	3.730	8.79	0.003*	-	-

SE – Standard error
CI – Confidence interval
* Statistical significant statistica at the 0.05 probability level

I found that the model had a good fit to the data, according to the Hosmer-Lemeshow statistic ($\chi^2(7)$= 14.97, P=0.036), and moderate effect sizes (Cox & Snell R^2=0.27, Nagelkerke R^2=0.36). By assessing the Wald statistic and its significance, I also concluded that each covariate has a significant contribution to the prediction of the outcome.

These results allow to propose that younger subjects, with low individual disease risk perception, and BMI above 29 kg/m^2 have a high probability of presenting poor glycaemic control. The odds ratio values associated with each predictor allows to analyse their role in glycaemic control. Increased age is associated with an odds of 0.902 for the outcome under study, or, conversely, a decrease of approximately 10% (considering the difference between 1, the maximum probability of an outcome, and 0.902) in the predicted probability for inadequate glycaemic control. A good (high) perceived personal disease risk implies a decrease of approximately 94% in predicted probability for inadequate glycaemic control, while BMI over 29 kg/m^2 implies an increase of 270% in predicted probability.

The logistic regression model provided the predictor coefficients that can be used in the logistic equation formula (figure 12), from which probability of an event can be predicted.

$$P(Y) = \frac{1}{1 + e^{-(b_0 + b_1 X_{1i} + b_2 X_{2i} + \ldots + b_n X_{ni})}}$$

Figure 12. Logistic regression equation (Hosmer et al. 2013).

Using the equation constant and coefficients, the probability of inadequate glycaemic control associated with different values in the predictor covariates can be predicted. For example, a 57 year old subject, with a score of 1.57 in personal disease risk, and a BMI over 29 kg/m^2 is expected to have a probability of 89.5% of having inadequate glycaemic control.

Although this model does not include other variables that appear to be associated with group differences, this analysis identified age, personal disease risk, and BMI above 29 kg/m^2 as the strongest predictors of glycaemic control. In previous analyses regarding age, both current age and age at the time of T2DM diagnosis seem to be associated with glycaemic control and allow the inference that younger patients have higher HbA1c levels. Nevertheless, the number of years of disease duration did not correlate with glycaemic control nor was a significant predictor in the regression model, which seems incoherent with the data from all other age-related variables. Regarding this topic, data from the UKPDS describing a patient follow-up for 11 years shows that as disease progresses, the prevalence of poor glycaemic control increases (UKPDS Study Group 1998a). This happens after a period of lower HbA1c, which is thought to be due to pharmacotherapy. It is known that patients with an early diagnosis may have a more severe form of the disease, as the pathophysiological mechanisms involved with diabetes onset are associated with a higher degree of insulin resistance (D'Adamo and Caprio 2011). Diabetes treatment aims at normalizing glycaemia and, if successful, patients will experience a period of lower HbA1c. As diabetes progresses, most

individuals require an increasing number and higher doses of medications to achieve glucose, lipid, and blood pressure targets to prevent and/or delay chronic complications. This can be a predictor for proper glycaemic control in older individuals, which I could not assess in this study due to the sample selection and case-control study design. As the mean number of years of diabetes duration were moderately low (6.0 years in cases and 6.4 years and controls) and did not significantly differ between groups ($t(54)=-0.34$, P=0.730), the analysis of the impact of years of diabetes duration in glycaemic control was not comprehensive. Thus, as diabetes duration in the participants in this study presents a mean value around 6.2 years (SD=4.48 years), the regression model is believed to be valid if applied to subjects that are in the first decade of disease duration. I propose that these results can contribute to the monitoring and counselling of T2DM patients, as health professionals can assess in a fast, inexpensive, and non-invasive way the predictors identified by the regression analysis.

4.9. Study limitations

One of the limitations of this work is the fact that I did not assess nutrition knowledge and the specific nature and frequency of previous nutrition advice, apart from collection of data on the prevalence of dietitian consultations. An analysis of the way that nutrition education is offered to these patients could help to further enlighten patient motivations and barriers to the adherence to a proper diet.

The assessment of PPHG was also limited due to the fact that patients did not interrupt their usual OADA therapy for the purpose of data collection. The rationale for this methodological aspect in this study was that I aimed to replicate as closely as possible patient' daily routine, in order to eliminate bias resulting from the experimental setting. I propose that additional data collection moments in these patients, using different experimental meals, could have helped to discuss the impact of PPHG on glycaemic control, and also of the relation between nutritional composition of the meal and glucose excursions.

Lastly, I suggest that although this study's results were obtained in subjects that were all selected from the same population, in an effort of assuring that both cases and controls share the same opportunity for exposure to the predictor variables under study, the sample size can have affected the ability to extrapolate from the data. This study's inclusion criteria implied that subjects must not differ in their pharmacotherapy, in order to prevent biases in PPHG. This resulted in a reduced sampling universe, which was further reduced by some patients' refusal in being a part of this study due to the expected duration of data collection interview, even if the data collection schedule was constructed according to patients' availability. The fact that the target population is composed only of patients receiving metformin or even no OADA restricts the applicability of this study's results to a subset of T2DM patients. Nevertheless, on the overall, I propose that this study provides evidence that patients with T2DM should be targeted in health education interventions, even the ones with adequate glycaemic control, providing that strategies for education must be carefully considered.

Chapter 5: Conclusions and recommendations

5.1. Conclusions

The data analysed in the present study provided answers to the research questions and confirmed all research hypotheses.

I conclude that younger age, high BMI, and biased personal disease risk perceptions are important predictors of glycaemic control and should be addressed by education interventions.

I verified that there are no significant differences in PPG between T2DM patients with adequate glycaemic control and those with poor glycaemic control. The glucose response to a mixed-meal containing 75 of carbohydrates did not significantly differed up to 120 minutes after ingestion. I conclude that patients which are considered as having a proper glucose control may be unaware that they exceed the recommended rise in PPG, and thus may be at a higher than expected risk for macro and microvascular events.

The data from the present study show that the prevalence of blood glucose self-monitoring is low and independent of glycaemic control, especially in low-schooled, older patients. As self-monitoring is the only practical way to detect PPG, efforts should be made to promote regular glucose self-monitoring.

Patients with adequate glycaemic control can be classified has having a better compliance of nutrition recommendations, due to their lower intake of energy and sugars. Nevertheless, both patients with adequate glycaemic control and patients with inadequate glycaemic control present excess intakes of energy, total cholesterol, saturated fatty acids, and sugars, when compared with their individual nutritional estimates. Additionally, the majority of the subjects were overweight and did not engage in recommended levels of physical activity. I conclude that all patients are in need of nutrition counselling addressing these issues, even those with apparently adequate glycaemic control.

Inadequate glycaemic control is related to a greater agreement with the existence of barriers to the adherence to nutrition recommendations. Subjects with poor glycaemic

control believe that a balanced and proper diet takes too much effort, is more expensive than other diets, implies different meals from the rest of the family, is composed by less than enough food distributed by too many daily meals, is incompatible with social gatherings, and doesn't seems to affect glucose control. These patients are also more confused with the nutrition information they have received.

Both patients with adequate glycaemic control and patients with poor glycaemic control show an optimistic bias in their risk assessment of diabetes complications.

There is a significant difference in risk perception of diabetes complications between patients with adequate glycaemic control and those with poor glycaemic control. The latter group of patients has a more biased opinion of their likelihood of personal disease risk. Additionally, the risk of health complications due to environmental risks is perceived similarly to the personal disease risk. Exposures such as medical tests, air pollution, pesticides, or household chemicals, are considered as likely to cause health problems as several known and common diabetes complications, like high blood pressure or cardiovascular disease.

Overall, adhering to nutrition therapy in T2DM seems to present several challenges, especially for patients with inadequate glycaemic control, who seem more prone to experience difficulties in integrating the nutrition recommendations into their daily life activities.

I propose that just as it is important for individuals with diabetes to have regular consultations with a doctor for assessing health status and disease monitoring, it is also important for T2DM patients to receive continuing nutrition education and support for lifestyle changes. Consultations with a dietitian are associated with better glycaemic control, and so they should be encouraged for all patients with T2DM. Furthermore, T2DM management is achieved primarily by patient self-care, and health professionals must be aware of the multiplicity of barriers that can constitute an obstacle for self-care.

Health professionals need to consider specific patient characteristics in order to provide proper clinical assessment, treatment, education, and continued medical care. Nutrition

education should be tailored to the perceptions of patients and should positively discriminate subjects above or below the internationally proposed HbA1c cut-points for glycaemic control.

I conclude that, when counselling individuals to make changes in their nutrition behaviour, besides considering food preferences, cultural practices, environmental factors, and the patient's willingness to implement changes, dietetics and nutrition professionals must also consider the existence of unreasonable optimism in the perception of diabetes complications.

5.2. Recommendations

Following the analysis of the data and the conclusions that can be drawn, I propose the following recommendations, which consist in care practices that currently are not common in the Algarve and, in my opinion, can contribute to the improvement of the quality of life of T2DM:

I. All patients should be referred to a dietitian after diagnosis for a set of nutrition education sessions, with the first session with the lowest possible cost for the patient. Not all patients had a consultation with a dietitian after being diagnosed, and if the patient is first diagnosed in the public Health Service, the price of each consultation is expected to be around €2.5 for the patient;

II. Educational materials for quick assessment of overall diet quality should be used as a screening tool in diabetic consultations, independently of the health professional conducting them. The prevalence of poor eating behaviour is expected to be high and this procedure can help clinicians to reassess current treatment and plan future interventions. Short, concise questions, currently used by skilled dietitians to assess time between meals, number of daily meals, and to estimate the number of carbohydrate servings ingested daily, can provide valuable information on overall diet quality and can constitute a reproducible inquiry tool for use in a structured nutrition education program;

III. Structured nutrition education is needed in all patients, independently of recorded glycaemic control. A sustained, structured program for nutrition education should be put in place and offered to all patients. It is imperative that this program is organized in multiple sessions, planned at set time intervals, which must also include physical activity promotion, clear information about nutrition in diabetes, and how to properly shop and prepare healthy, low-cost meals;

IV. Postprandial glucose measurement should be more thoroughly recommended by clinicians and be the subject of additional research. Similarities in subjects with different HbA1c makes this the only way to record PPHG and provide data for changing the course of treatment and monitoring regimens. All patients should be advised to, at least once a day for a period of one to two weeks before their consultation with a doctor, record their PPG to properly assess their glycaemic control and cardiovascular risk;

V. Clinicians should ensure that the use of glucometers is adequate and promote educational interventions in patients focused on the proper procedure to record PPG.

VI. Health professionals providing diabetes care should be aware of novel technologies for glucose monitoring, like phone applications, and consider their use.

VII. Educational interventions must consider that patients have a poor risk perception of diabetes complications and a proper risk communication should be promoted.

VIII. Additional research on the determinants for dietitian consultation adherence should be encouraged.

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Annex 1 – Interview script

(ENGLISH) – Interviewer's guide ID: ☐☐ Date: ☐☐/☐☐/☐☐☐☐

Before data collection, reaffirm that all information provided is confidential and that collaboration is invaluable!

I - Patient file data and demographics
(Confirm demographics with subject)

1. Age: ☐☐ years old

2. Sex: ☐ Male ☐ Female

3. Marital status

☐ Married ☐ Widower
☐ Never married ☐ Divorced/separated

4. Persons in the household: ☐☐

5. Occupation:

☐ Employed ☐ Unemployed; Retired

6. Years of schooling: ☐☐ years

7. Age at diabetes onset: ☐☐ years
("When were you first told you had diabetes?)

8. Previous diagnosis of:

	Yes	No	Date (DD/MM/YYYY)
Excess weight	☐	☐	☐☐.☐☐.☐☐☐☐
Renal disease	☐	☐	☐☐.☐☐.☐☐☐☐
CV disease	☐	☐	☐☐.☐☐.☐☐☐☐
Retinopathy	☐	☐	☐☐.☐☐.☐☐☐☐
Hypertension	☐	☐	☐☐.☐☐.☐☐☐☐

9. In the last 12 weeks, measurement of:

	Value		Date (DD/MM)
HbA1c	☐☐	(%)	☐☐.☐☐
Cholesterol	☐☐☐	(mg/dl)	☐☐.☐☐
LDL cholesterol	☐☐☐	(mg/dl)	☐☐.☐☐
HDL cholesterol	☐☐☐	(mg/dl)	☐☐.☐☐
Triglycerides	☐☐☐	(mg/dl)	☐☐.☐☐

II – Anthropometry and blood pressure

10. Blood pressure: ☐☐☐/☐☐☐ (syst/diast)
11. Height: ☐☐☐.☐☐ (cm)
12. Weight: ☐☐☐.☐ (kg)
13. Waist circumference: ☐☐☐.☐ (cm)

III – Glucose response

14. Glycaemia measurements:

	Value		Time	
Fasting (T_0)	☐☐☐	(mg/dl)	☐☐h	☐☐m
$T_{30\ minutes}$	☐☐☐	(mg/dl)	☐☐h	☐☐m
$T_{60\ minutes}$	☐☐☐	(mg/dl)	☐☐h	☐☐m
$T_{90\ minutes}$	☐☐☐	(mg/dl)	☐☐h	☐☐m
$T_{120\ minutes}$	☐☐☐	(mg/dl)	☐☐h	☐☐m

IV – Lifestyle and diabetes care

15. How many times during the last 12 months did you visit with:

Doctor	☐☐
Dietitian	☐☐
Nurse	☐☐

16. When was your last visit? On that occasion did you decided to go or were you referred by other health care professional?

		Self-init.	Refered
Doctor	☐☐☐ months ago	☐	☐
Dietitian	☐☐☐ months ago	☐	☐
Nurse	☐☐☐ months ago	☐	☐

17. How often do you measure your blood glucose?

☐☐ times each day ☐ month ☐
week ☐ year ☐

18. Do you currently smoke? "

No, never ☐ month ☐
Ex-smoker ☐ week ☐
Smoker ☐ -> ☐☐ cigarettes each day ☐

19. Regarding shopping and meal preparing, you:
(Check one response in each topic)

Don't engage in food shopping	☐
Share food shopping duty	☐
Are the main food shopper	☐

Don't engage in meal planning/ preparing ☐
Share meal planning/preparing duty ☐
Are the main meal planner/preparer ☐

20. Have you ever been told by a health care provider to:

	Yes	No	Not sure
Follow an exercise program	☐	☐	☐
Follow a diet or meal plan	☐	☐	☐
Weigh or measure your food	☐	☐	☐
Keep a record of your meals	☐	☐	☐
Use food lists to plan your meals	☐	☐	☐

21. How often do you:

	Never 1	2	Sometimes 3	4	Always 5
Follow a regular schedule for meals and snacks?	☐	☐	☐	☐	☐
Weight or measure the food for your meals?	☐	☐	☐	☐	☐
Keep a record of your meals?	☐	☐	☐	☐	☐
Use food lists to plan your meals?	☐	☐	☐	☐	☐

Physical activity guidance:

Vigorous activities - activities that take hard effort and make you breathe much harder than normal.

Moderate activities - activities that take moderate effort and make you breathe somewhat harder than normal.

22. During the last 7 days, on how many days did you spent at least 10 min. at a time doing vigorous activities like heavy lifting, or fast bicycling? How much time did you spent in vigorous activities on one of those days?

☐ days with vigorous activities

☐☐☐ minutes of activity

23. During the last 7 days, on how many days did you spent at least 10 min. at a time doing moderate activities like carrying light loads or cycling at a regular pace? How much time did you spent in moderate activities on one of those days? Do not include walking.

☐ days with moderate activities

☐☐☐ minutes of activity

24. During the last 7 days, on how many days did you walk for at least 10 min. at a time? This includes walking at work and at home, walking from place to place, and any other walking that you did solely for recreation, sport, exercise or leisure. How much time did you usually spend walking on one of those days?

☐ days walking for at least 10 minutes

☐☐☐ minutes of walking.

25. During the last 7 days, how much time did you spent sitting in week days? Include time spent at work, at home, while doing course work, and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television.

☐☐☐ minutes seated on a weekday

26. Do you currently follow any type of special diet? If so, what kind of diet?

No ☐
Yes ☐ Diet: _____

Food intake recall for the last 24h guidance:

Do not forget plain water, snacks, and food items like chewing gum or candy. Use the images for amount assessment.

Attach the recall to this questionnaire

V – Risk perception of diabetes complications

Please consider the following scale:

Strongly disagree	Disagree	Agree	Strongly agree
1	2	3	4

Consider your risk of having diabetes health problems and classify your agreement with these two sentences:

27. *"Compared to other people with diabetes of the same age and sex, I am less likely than they are to get diabetes complications."*

Agreement ☐ (1 to 4)

28. *"Compared to other people with diabetes of the same age and sex, I am less likely to have serious health problems."*

Agreement ☐ (1 to 4)

29. For the following list of health problems and diseases, please rate the risk they can imply for your own personal health

	Almost no risk	Slight risk	Moderate risk	High risk
Heart attack	☐	☐	☐	☐
Foot amputation	☐	☐	☐	☐
Cancer	☐	☐	☐	☐
Vision problems	☐	☐	☐	☐
High blood pressure	☐	☐	☐	☐
Numb feet	☐	☐	☐	☐
Stroke	☐	☐	☐	☐
Blindness	☐	☐	☐	☐
Kidney failure	☐	☐	☐	☐

30. Consider the following list of possible hazards or dangerous conditions in the environment around most of us and rate the risk they imply for your own personal health.

	Almost no risk	Slight risk	Moderate risk	High Risk
Medical tests (e.g., X-rays, MRI)	☐	☐	☐	☐
Violent crime	☐	☐	☐	☐
Extreme weather (hot or cold)	☐	☐	☐	☐
Driving/ riding in an automobile	☐	☐	☐	☐
Illegal drugs	☐	☐	☐	☐
Air pollution	☐	☐	☐	☐
Pesticides	☐	☐	☐	☐
Household chemicals	☐	☐	☐	☐
Cigarette smoke from people smoking around you	☐	☐	☐	☐

31. Please consider a numbered agreement scale from 1 ("strongly disagree") to 5 ("strongly agree") and rate your agreement with each of the following statements:

	Agreement (1 to 5)
My diet is balanced and adequate to my needs.	☐
In general, population in my age group has a balanced diet.	☐
A balanced and proper diet takes too much effort.	☐
Whatever I eat, my diabetes doesn't seems to be affected by my diet.	☐
The amount of food in a balanced diet is less than enough for me.	☐
The type of food items in a balanced diet is not to my liking.	☐
I do not have enough time to prepare meals.	☐
I do not have enough time to eat all the meals in a proper diet.	☐
A proper diet implies different meals from the rest of the family.	☐
I often eat out or attend to social gatherings and there are no adequate meal options.	☐
A proper diet is more expensive.	☐
I feel I don't know enough about nutrition in diabetes.	☐
I am confused with the nutrition information I received.	☐
I feel I need more advice on what is a proper diet.	☐

32. Do you often experience any other barriers to following a proper diet?

Finalize interview by asking the patient if there are any questions and by thanking the collaboration.

(PORTUGUÊS) Guião de entrevista

ID: ☐☐ Data: ☐☐/☐☐/☐☐☐☐

Antes da recolha de informação, referir novamente confidencialidade e agradecer a colaboração!

I – Dados demográficos e clínicos
(Confirmar dados presentes no processo clínico)

1. Idade: ☐☐ anos

2. Sexo: ☐ Masculino ☐ Feminino

3. Estado civil

☐ Casado ☐ Viúvo
☐ Solteiro ☐ Divorciado/Separado

4. Elementos do agregado familiar: ☐☐

5. Ocupação:

☐ Empregado ☐ Desempregado

6. Anos de escolaridade: ☐☐ anos

7. Idade no diagnóstoco: ☐☐ anos
("Quando lhe disseram pela primeira vez que tinha diabetes?)

8. Diagnóstico prévio:

	Sim	Não	Data (DD/MM/YYYY)
Excesso peso	☐	☐	☐☐.☐☐.☐☐☐☐
Doença renal	☐	☐	☐☐.☐☐.☐☐☐☐
Doença CV	☐	☐	☐☐.☐☐.☐☐☐☐
Retinopatia	☐	☐	☐☐.☐☐.☐☐☐☐
Hipertensão	☐	☐	☐☐.☐☐.☐☐☐☐

9. Valores de, nas últimas 12 semanas:

	Valor		Data (DD/MM)
HbA1c	☐☐	(%)	☐☐.☐☐
Colesterol	☐☐☐	(mg/dl)	☐☐.☐☐
LDL colesterol	☐☐☐	(mg/dl)	☐☐.☐☐
HDL colesterol	☐☐☐	(mg/dl)	☐☐.☐☐
Triglicéridos	☐☐☐	(mg/dl)	☐☐.☐☐

II – Antropometria e pressão arterial

10. Pressão arterial: ☐☐☐/☐☐☐ (syst/diast)
11. Altura: ☐☐☐.☐☐ (cm)
12. Peso: ☐☐☐.☐ (kg)
13. Perímetro da cintura: ☐☐☐.☐ (cm)

III – Glicemia

14. Medição da glicemia:

	Valor		Tempo	
Jejum (T_0)	☐☐☐	(mg/dl)	☐☐h	☐☐m
$T_{30\ minutos}$	☐☐☐	(mg/dl)	☐☐h	☐☐m
$T_{60\ minutos}$	☐☐☐	(mg/dl)	☐☐h	☐☐m
$T_{90\ minutos}$	☐☐☐	(mg/dl)	☐☐h	☐☐m
$T_{120\ minutos}$	☐☐☐	(mg/dl)	☐☐h	☐☐m

IV – Estilo de vida e cuidados com a diabetes

15. Nos últimos 12 meses, quantas vezes visitou:

Médico	☐☐
Dietista	☐☐
Enfermeiro	☐☐

16. Quando foi a última visita? Foi por iniciativa própria?

			Iniciat.	Refer
Médico	☐☐☐	meses	☐	☐
Dietista	☐☐☐	meses	☐	☐
Enfermeiro	☐☐☐	meses	☐	☐

17. Frequência de medição da glucose?

☐☐ vezes por dia ☐ mês ☐
Semana ☐ ano ☐

18. Fuma?

Não, nunca ☐ mês ☐
Ex-fumador ☐ semana ☐
Sim ☐ -> ☐☐ cigarros por dia ☐

19. Compras e preparação de refeições:
(Uma resposta cada tópico)

Não vai às compras de alimentos	☐
Colabora na compra de alimentos	☐
É quem vai às compras de alimentos	☐
Não planeia ou prepara refeições	☐
Colabora no planeamento preparação	☐
É quem planeia e prepara refeições	☐

20. Alguma vez um profissional de saúde lhe disse para:

	Sim	Não	Não sabe
Fazer exercício físico	☐	☐	☐
Seguir dieta ou plano alimentar	☐	☐	☐
Pesar ou quantificar alimentos	☐	☐	☐
Fazer um registo das refeições	☐	☐	☐
Usar listas de equivalentes	☐	☐	☐

21. Com que frequência:

	Nunca 1	2	**Às vezes** 3	4	**Sempre** 5
Segue um horário regular de refeições e merendas?	☐	☐	☐	☐	☐
Pesa ou quantifica os alimentos?	☐	☐	☐	☐	☐
Regista as refeições?	☐	☐	☐	☐	☐
Usa lista de equivalentes?	☐	☐	☐	☐	☐

Atividade física:

Atividades vigorosas – atividades que requerem muito esforço e que o fazem respirar muito mais dificilmente que o normal.

Atividades moderadas – atividades que requerem esforço moderado e que fazem respirar mais dificilmente que o normal.

22. Nos últimos 7 dias, em quantos despendeu pelo menos 10 minutos seguidos em atividades vigorosas, como levantar objetos muito pesados ou pedalar depressa? Quanto tempo num desses dias?

☐ dias com atividade vigorosa

☐☐☐ minutos de atividade

23. Nos últimos 7 dias, em quantos despendeu pelo menos 10 minutos seguidos em atividades moderadas, como carregar pesos leves ou pedalar a ritmo regular? Quanto tempo num desses dias? Não incluir andar..

☐ dias com atividade moderada

☐☐☐ minutos de atividade

24. Nos últimos 7 dias, em quantos despendeu pelo menos 10 minutos seguidos a caminhar? Quanto tempo num desses dias?

☐ dias a caminhar pelo menos 10 minutos

☐☐☐ minutos de atividade

25. Nos últimos 7 dias, quanto tempo esteve sentado, por dia de semana? Incluir tempo no trabalho, em casa, a ler ou ver televisão.

☐☐☐ minutos sentado, num dia de semana

26. Segue, atualmente, algum tipo de dieta especial? Se sim, qual?

Não ☐

Sim ☐ Dieta:_____

Questionário às 24h:

Não esquecer água, merendas e alimentos como rebuçados ou pastilhas elásticas.

V – Perceção do risco de complicações da diabetes

Considere a seguinte escada:

Discorda completamente	Discorda	Concorda	Concorda completamente
1	2	3	4

Considere o seu risco de ter complicações de saúde por causa da diabetes e classifique as seguintes frases:

27. *"Comparado com outros diabéticos da mesma idade e sexo, é menos provável que tenha complicações de saúde por causa da diabetes."*

Concordância ☐ (1 a 4)

28. *"Comparado com outros diabéticos da mesma idade e sexo, é menos provável que tenha problemas graves de saúde"*

Concordância ☐ (1 a 4)

29. Diga, para cada um dos seguintes problemas de saúde, o risco que implicam para a sua própria saúde:

	Quase nenhum risco	Algum risco	Risco moderado	Risco elevado
Ataque cardíaco	☐	☐	☐	☐
Amputação de pés	☐	☐	☐	☐
Cancro	☐	☐	☐	☐
Problemas de visão	☐	☐	☐	☐
Pressão arterial alta	☐	☐	☐	☐
Pés dormentes	☐	☐	☐	☐
Enfarte	☐	☐	☐	☐
Cegueira	☐	☐	☐	☐
Falência renal	☐	☐	☐	☐

30. Considere os seguintes perigos à nossa volta e classifique o risco que podem implicar para a sua saúde:

	Quase nenhum risco	Algum risco	Risco moderado	Risco elevado
Exames médicos (e.g., Raios-X, RM)	☐	☐	☐	☐
Crime violento	☐	☐	☐	☐
Clima extremo (calor ou frio)	☐	☐	☐	☐
Conduzir/ andar de automóvel	☐	☐	☐	☐
Drogas ilegais	☐	☐	☐	☐
Poluição atmosférica	☐	☐	☐	☐
Pesticidas	☐	☐	☐	☐
Produtos químicos em casa (e.g. detergentes)	☐	☐	☐	☐
Fumo de tabaco de pessoas à sua volta	☐	☐	☐	☐

31. Considere, por favor, uma escala numérica entre 1("Discordo completamente") e 5 ("Concordo completamente") e classifique a sua concordância com as seguintes afirmações:

	Concordância (1 a 5)
Acho que a minha alimentação é equilibrada e adequada às minhas necessidades.	☐
Acho que a população da minha idade, no geral, tem uma alimentação adequada.	☐
Uma alimentação adequada exige muito esforço.	☐
Não importa o que coma, a minha diabetes parece não estar controlada.	☐
A quantidade de alimentos aconselhada para mim não é suficiente.	☐
Os alimentos aconselhados não são do meu agrado.	☐
Não tenho tempo suficiente para preparar as refeições.	☐
Não tenho tempo suficiente para comer todas as refeições recomendadas.	☐
Sigo uma dieta diferente do resto da família e não gosto que isso aconteça	☐
Como fora de casa frequentemente, onde não há opções alimentares adequadas.	☐
Uma dieta adequada é mais cara.	☐
Sinto que não sei o suficiente sobre alimentação na diabetes	☐
Estou confuso com a informação que recebeu sobre alimentação na diabetes.	☐
Sinto que necessito de mais aconselhamento sobre alimentação.	☐

32. Há algumas barreiras que consiga identificar na sua vida que o impeçam de ter uma alimentação adequada?

Finalizar a entrevista disponibilizando tempo para questões e agradecendo a colaboração!

Annex 2 – Informed Consent Form

(ENGLISH) INFORMED CONSENT FORM **ID:** ☐☐

You are being invited for a research project regarding nutrition and type 2 diabetes. Please read this form carefully and afterwards, place all questions you feel necessary to the researcher providing this document. If you agree to be a part of this project, sign your full name in the appropriate space at the bottom.

1. **Purpose of the study:** To collect data regarding nutrition in type 2 diabetes and regarding your perceptions on health complications;
2. **Procedures:** We will offer you a breakfast composed by bread, ham, apple and milk and, after your meal, we will measure your blood glucose using a similar device to the one you may have used before for self-monitoring. We will measure your blood glucose before breakfast and 30, 60, 90, and 120 minutes after. Then, we will interview you about your eating habits and lifestyle. Finally, we will measure, with your consent, your weight, height, and waist circumference;
3. **Time involved:** We expect your participation to last approximately 2 hours and 45 minutes;
4. **Possible risks and discomfort:** There will be a minimal risk of discomfort, associated with the procedures of glucose measure;
5. **Possible benefits:** The data collected in this study may help improve the quality of care provided by your healthcare professional. Additionally, immediately after the data collection interview, you may place any questions you have regarding nutrition and type 2 diabetes to a registered dietitian;
6. **Costs and compensations:** Your collaboration does not imply any costs or any monetary compensation for your time;
7. **Confidentiality:** Your identity will be kept private and we will not divulge any information that allow your identification. All results from this study will not include your name or personal information;
8. **Right to disallow:** You may disallow the use of your data at any time, without any consequences. All questions regarding your collaboration can be answered at this moment or at a later time, directly with the researcher responsible for the study, through the phone number 966 472 993 or through the e-mail address epinto@ualg.pt.

Your informed consent: **ID:** ☐☐

I declare that I have understood the research project outlined above and that I freely consent to collaborate.

Participant's signature: _____ ____/____/_____

Researcher's signature: _____ ____/____/_____

(PORTUGUÊS) DOCUMENTO DE CONSENTIMENTO INFORMADO **ID: ☐☐**

Está a ser convidado a participar numa investigação sobre alimentação e diabetes tipo 2. Para aceitar participar deve ler a descrição da sua colaboração até ao fim e assinar no espaço apropriado, por favor.

1. **Propósito do estudo:** Recolher informação para estudar a alimentação na diabetes tipo 2;
2. **Procedimento:** Vai ser-lhe realizada uma entrevista sobre os seus hábitos alimentares e opinião sobre a diabetes e registado o seu peso, altura e circunferência da cintura. Depois, vamos pedir-lhe que ingira um pequeno-almoço composto por pão com fiambre, leite e maçã e que consinta que, após 30, 60, 90 e 120 minutos lhe façamos uma punção capilar para obtenção da glicemia pós-prandial em aparelho portátil.
3. **Tempo envolvido:** Prevê-se que a sua participação demore 2 horas e 45 minutos;
4. **Possíveis riscos e desconforto:** Há riscos e desconforto mínimos associados à sua participação, relacionados com a medição da glicemia;
5. **Possíveis benefícios:** A informação recolhida neste estudo poderá ajudar o seu prestador de cuidados de saúde; Para além disso, no final da entrevista poderá colocar todas as questões que considerar pertinentes acerca da alimentação na diabetes a um dietista.
6. **Considerações financeiras:** A sua colaboração não implica compensação nem tem custos associados;
7. **Confidencialidade:** A sua identidade é confidencial e não será divulgada informação que comprometa o seu anonimato. Todos os resultados deste trabalho, como eventuais publicações científicas, não incluirão o seu nome ou outra informação pessoal;
8. **Os seus direitos:** Se decidir participar tem o direito de retirar o seu consentimento a qualquer altura, sem qualquer prejuízo ou consequência. Todas as questões ou dúvidas sobre a sua participação podem ser esclarecidas agora, diretamente com o responsável, ou através do telefone 966 472 993 ou endereço de correio eletrónico epinto@ualg.pt.

Consentimento: **ID: ☐☐**

Declaro que li e compreendi este documento e que participo voluntariamente na investigação.

Assinatura do participante: _____ ____/____/_____

Assinatura do responsável: _____ ____/____/_____

Annex 3 – Approval from the Cranfield University Health Research Ethics Committee

Cranfield,
Bedfordshire,
MK43 0AL, England
Tel +44 (0) 1234
758349
Fax +44 (0) 1234
758380
www.cranfield.ac.uk

Date 21st March 2015

Dear Dr Newman

Project Reference No 13/15: Glycaemic control: The role of nutritional intake, postprandial glycaemia, nutrition therapy adherence and diabetes complications.

Thank you for submitting the CUHREC approval form.

I can confirm that your study has been granted ***retrospective*** ethical approval from the CUHREC Committee.

Subsequent to approval being given by the committee, applicants are responsible for:

- Destruction of personal data within the specified time period.

Yours sincerely

Dr Ruth Bevan
Vice Chairman
Cranfield University Health Ethics Committee

Annex 4 – Approval from the Algarve Regional Health Directorate

Administração Regional de Saúde
do Algarve, I.P.

Ministério da Saúde

Exmº. Senhor
Dr. Ezequiel Pinto
epinto@ualg.pt

Sua Referência	Seu Fax	Nossa Referência
		005/12 D.E.P. **11-01-2012**

ASSUNTO: Pedido de parecer para projecto de investigação sobre "**Aporte alimentar, percepções e comportamento em pacientes com DMT2**"

Serve o presente para comunicar que o Conselho Directivo da ARS Algarve, analisou o parecer e os fundamentos apresentados pela Comissão de Ética referentes ao pedido de autorização de V. Exa. para a realização do estudo em epígrafe, decidindo concordar com o teor do mesmo, o qual se transcreve:

"... Foi aprovado por unanimidade, um parecer favorável para a realização do referido estudo, considerando que estão reunidas todas as condições legais e éticas exigidas para o efeito".

Com os melhores cumprimentos,

Drª Ana Costa
Vogal do Conselho Directivo
da ARS Algarve, I.P.

Largo do Carmo, 3 – 8000 – 148 Faro
Telf. 289889900 – Fax. 289829849
http://www.arsalgarve.min-saude.pt

ENGLISH TRANSLATION OF THE TEXT OF THE ETHICS COMITTE APPROVAL FROM THE ALGARVE HEALTH DIRECTORATE

11-01-2012

SUBJECT: Submission for approval of a research project on nutritional intake, perceptions, and behaviour in patients with T2DM

The present letter intends to report that the Directive Council of the ARS Algarve has analysed your submission and the report of the Ethics Commission regarding the proposed study and decided to authorize the research project, as stated in the excerpt of the meeting transcription presented below:

"…The request for the conduction of the study was approved by unanimity, considering that all of the required legal and ethical conditions are guaranteed".

Kindest regards,

Annex 5 – Study Protocol

Cranfield UNIVERSITY

– Study Protocol –

Glycaemic control: The role of nutritional intake, postprandial glycaemia, nutrition therapy adherence and diabetes complications

Supervisor: Dr. Jeff Newman

Co-supervisor: Dr. Nídia Braz

Author: Ezequiel Pinto

Student number: 154599

1. Study title

The intended study is titled “Dietary intake, postprandial glucose and nutrition therapy adherence in T2DM patients”

2. Project background

Treatment and prevention approaches for type 2 diabetes (T2DM) focus on achieving glycaemic control, in order to manage the disease and to prevent or slow its related health complications. General management of patients with diabetes consist of patient education, medical nutrition therapy, physical activity, and pharmacological therapy with oral hypoglycaemic agents or insulin [1]

Patient education enables people with diabetes to improve their knowledge, skills and confidence, allowing them to self-manage their condition. It’s a critical element in diabetes care and can have a strong effect on biomedical outcomes [1, 2]. Patient education, defined as diabetes self-management education (DSME) by a task force jointly convened by the American Association of Diabetes Educators and the American Diabetes Association, consists in “the on-going process of facilitating the knowledge, skill, and ability necessary for diabetes self-care”, and includes, among other goals, patient empowerment to incorporate nutritional management and physical activity into his lifestyle and the development of personal strategies to promote health and behaviour change [2].

Individuals who have diabetes should also receive individualized medical nutrition therapy to achieve treatment goals, preferably provided by a registered dietician, familiar with the components of diabetes nutrition therapy [3]. Modifying the type and amount of dietary carbohydrates can improve disease outcomes. Foods with a lower glycaemic index contain carbohydrates that are more slowly digested and absorbed and a diet that consists largely of fresh, unprocessed fruits and vegetables, moderate levels of lean protein and beneficial fats, minimal amounts of processed carbohydrates and saturated and *trans* fats can significantly reduce postprandial glucose levels [4]. Evidence also suggests that dietary measures can be effective in weight reduction and glycaemic control irrespective of the macronutrient composition (low fat or low carbohydrate), provided that there is adequate energy restriction, reduction in saturated fat to less than 7%, and adequate provision of dietary fibre [3, 5].

The role of postprandial glycaemia (PPG) in overall glycaemic control and as a risk factor for cardiovascular complications has also been considered in the literature, as patients with good glycaemic control (measured by HbA1c) can show elevated PPG. According to the American Diabetes Association, [6] HbA1c levels below or around 7% are associated with long-term reduction in macrovascular disease and a reasonable A1C goal for T2DM adult patients is 7%. A 2009 review [7] shows that the relative contribution of PPG in the overall glycaemic control is around 70% in patients with HbA1c below 7.3%, independently of the timing of the meal during the day, stating also that postprandial hyperglycaemia is common in T2DM patients, even in those who are considered to have good overall glycaemic control. In fact, achievement of target HbA1c and fasting plasma glucose levels does not necessarily indicate that good glycaemic control is continuous throughout the day [8]. Furthermore, a meta-analysis by Coutinho *et al.* [9] showed an exponential relationship between the incidence of cardiovascular events and elevated glycaemia 2 hours after a meal, resulting in an increased mortality risk, also reported in a large European patient sample [10]. A 2010 review [8] shows that PPG values 1 hour after breakfast were predictive of all-cause mortality and suggests that hyperglycaemia after meals is associated with increased cardiovascular risk independent of fasting hyperglycaemia, adding to the evidence indicating that PPG may be a more dominant cardiovascular risk factor than fasting hyperglycaemia.

International Diabetes Federation has developed clinical guidelines for PPG and recommend that 2 hour post-meal glucose levels are kept below 7.8 mmol/L [11] and delta postprandial glycaemia is considered normal between 30 and 50 mg /dl [12]. Furthermore, considering PPG variations throughout the day and between different meals, influenced by the blood glucose level before the meal, the nature and quantity of carbohydrate consumed or the anti-diabetic treatment [8], the management and treatment of T2DM must also consider this important marker of diabetes complications [13].

Although the goals and objectives of treatment approaches for T2DM are known, their translation into daily routine seems difficult. Studies that have evaluated adherence do dietary recommendations have shown poor results, especially those with T2DM patients [14, 15], who appear to have high calories and saturated fat intakes, accompanied by low fibre intake [16]. In fact, self-reported adherence is higher for pharmacological therapy than for a proper diet, even if weight loss trough diet and exercise also results in an improved glycaemic control [17]. Although medical nutrition therapy can be successful, diabetics treated by diet alone in a general

practice setting have significant rates of complications and are less likely than those on medication to be adequately monitored [18]. This can imply that compliance with dietary recommendations can be improved and that inadequate patient education strategies are being used.

Barriers to chronic disease self-management and to diabetes care have also been identified. Daly et al. [19] suggest that the type and duration of diabetes, illness and other health conditions and psychosocial factors, medication use, meal plans, exercise and home glucose testing are factors that influence diabetes treatment. Gazmararian et al. [20], using a focus group design, identified the emotional toll from the diagnosis and lifestyle changes to treat diabetes, the failure to recognize the risks and consequences of an asymptomatic condition, the perception of lack of follow-up on patient education interventions (refresher courses, support group discussions, for example) and the availability of different education modalities as barriers to diabetes care. Despite all these known barriers, few studies have specifically examined the reasons for the low adherence to dietetic recommendations or how patients view dietary restrictions [21].

Interventions aimed at improving patients' ability to modify their diet need to consider preferences and barriers when setting goals for treatment and more research is needed to successfully translate the benefits of interventions to individuals in the community, outside the controlled research environment. [17]. This implies that the assessment of patient's characteristics, their motives and motivations to comply with nutrition therapy, considering also the traditional Mediterranean style diet associated with Portugal, may offer some insight into the skills and adjustments needed to promote the adequacy of current nutrition therapy guidelines in a clinical, on the field, setting. Furthermore, although the health risks of poor diabetes care are well known by the scientific community, the general population is yet to fully appreciate the hazards of this condition [1]. Additionally, considering the effect of PPG in glycaemic control and its role as a cardiovascular risk factor, and that PPG measures provide immediate feedback on the effect of foods and meals [22], an investigation considering the associations between socio-demographic characteristics, nutrition recommendations compliance, meal composition and PPG could contribute to the discussion of the optimal nutrition therapy in T2DM and to the design of strategies to reduce the burden of diabetic complications.

3. Study aims

The aim of the present study is to undertake a comparative analysis regarding PPG, nutritional therapy adherence, and risk perceptions of diabetes complications in patients with T2DM.

The specific research questions in this research are:

- Does adherence to nutrition recommendations differ between patients with adequate glycaemic control and those with poor glycaemic control?
- What barriers patients identify in the adherence to nutrition recommendations?
- What is the association between PPG levels and HbA1c?
- How do patients with T2DM with different glycaemic control perceive their risk of diabetes complications?

4. Recruitment and consent

4.1. Study population

The study population is composed by patients with T2DM receiving health care in a Diabetes Clinic in the municipality of Faro, in the Portuguese region of the Algarve. The clinic is integrated in a regional association of diabetes patients (AEDMADA).

4.2. Inclusion and exclusion criteria

The inclusion criterion for this study were:

- Male or female patients with medical diagnosis of T2DM for at least 12 complete weeks, obtained by previous assessment and identification of one or more of the following: HbA1c ≥ 6.5%, FPG ≥ 126 mg/dl (7.0 mmol/l), 2h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during a OGTT, or presence of classic hyperglycaemia symptoms and a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l);
- Age below 85 years

The exclusion criteria were:

- Undergoing a pharmacotherapy regimen with insulin or any ADOA other than metformin;
- Diagnosis of degenerative disorder of the central nervous system;
- Following a lactose-free or gluten-free diet;

4.3. Recruitment

The subjects in the study population will be invited to be a part of this study in the diabetology consultations in the AEDMADA Diabetes Clinic. Patients who conform to the inclusion criteria will be approached by the physician conducting the consultations, who will briefly explain the study and ask for patient permission to a later contact by the researcher. Having been provided with the contact details by the physician, the researcher will contact the patients by telephone and explain the study, setting up an individual appointment with each patient that manifests interest in being recruited. In this initial contact, patients will informed that they should attend the appointment before any intake of food and that a breakfast will be provided, free of charge, whether they accept or not to be a part of the study. Furthermore, it will be clearly stated at this time that participants will not be compensated monetarily for their collaboration or reimbursed for their expenses with any trips to attend the appointment.

The individual appointments will be held in the School of Health of the University of Algarve, conducted solely by the researcher. In this appointment, the study protocol will be discussed thoroughly with each patient and the final consent will be taken through an informed consent form. Annex 1 presents the informed consent form in Portuguese and in English.

For this inquiry to take place, it was recommended by the AEDMADA clinic that a written approval by the Regional Health Directorate should be sought. A copy of this study protocol was submitted for evaluation and the Regional Health Directorate gave its approval to the study. The written approval is presented in Annex 2, in its original form and translated into English by the researcher, as the Regional Health Directorate stated that an English version could not be provided.

5. Study methodology

The data for this study will be collected during an individual interview conducted by the researcher, predicted to last between 150 minutes and 180 minutes and to start between 8:00h A.M. and 9:00h A.M, according to patients' convenience. The interviews will be conducted according a previously prepared interview script and will follow a semi-structured pattern. Annex 3 presents a copy of the interview script, in Portuguese and in English.

The interviews will be held in a consultation office.

The inquiry will include the collection of data under five categories:

VI. Clinical and socio-demographic data
VII. Anthropometric assessment;
VIII. Glucose response to a meal;
IX. Lifestyle and care assessment;
X. Risk perception of diabetes complications and optimistic bias.

5.1. Clinical and socio-demographic data

Clinical data on the patient will be collected from the clinical file of the patient that exists at the AEDMADA diabetes clinic. This will be done on the day of the interview but after it has been held and after patient consent. This data will include the date of diagnosis, previous diagnosis of diabetes related complications, lipid profile levels, and the HbA1c level. Lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) and HbA1c are routinely measured in each patient consultation at the diabetes clinic, which are held once in every trimester for all of the patients. The HbA1c assays are done by an accredited laboratory under the guidelines proposed by the Portuguese Ministry of Health for all assays in the National Health System and for all Clinical Laboratories [23]. This guideline directs that blood samples must processed by the same laboratory, with a method certified by the National Glycohemoglobin Standardization Program and calibrated according to the standards of the International Federation of Clinical Chemistry and Laboratory Medicine.

During the course of the interview, patient will also be asked to provide some socio-demographic data, namely age, gender, marital status, number of persons living in the household, occupation, and years of schooling.

5.2. Anthropometry and blood pressure assessment

During the interview, patients will be asked consent for the interviewer to measure their height to the nearest centimetre and weight to the nearest 0.1kg, using a stadiometer (Seca, Model 217, Seca, United Kingdom) and a scale (Seca, Model 899, Seca, United Kingdom), appropriated for medical use and calibrated according to the manufacturer's instructions. Waist circumference will also be measured, using an extensible measuring tape (Seca, Model 218, Seca, United Kingdom).

All the measurements will follow the International Standards for Anthropometric Assessment procedures [24], following also the guidelines for patients' intimacy and comfort.

Blood pressure will also be collected during this stage, using a digital sphygmomanometer (OMRON, M6 Confort, OMRON Healthcare Co., Ltd., Japan) for upper-arm measurements, validated for clinical use in adults through the European Society of Hypertension International Protocol [25]. Patients will be seated and the left arm will be used for blood pressure measurement. Three blood pressure measurements will be conducted and the data used in this study will correspond to the mean value of the three measurements.

5.3. Glucose response to a meal

In order to assess glucose response, all patients will be offered a controlled breakfast, constructed according to the dietetic recommendations for patients with T2DM [26, 27], and composed of foods traditionally consumed in a Mediterranean culture and obeying to usual eating habits in the region.

The experimental meal will have the following nutritional composition (table 1):

Table 1. Foods and nutritional values for the experimental breakfast

Food	Amount (g)	Energy (Kcal)	Protein (g)	Fat (g)	Carbohydrates (g)	Sugars (g)
Wheat bread	80	231.13	6.72	1.76	45.84	1.68
Ham	30	90.98	5.40	7.65	0.15	0.15
Milk	200	93.68	6.60	3.20	9.80	9.80
Apple	135	76.78	0.27	0.68	18.09	18.09
	Total	492.6	19.0	13.3	73.9	29.7

Glucose will be measured with a portable blood glucose monitoring system (Freestyle Lite, MK-23, Abbot, USA) before breakfast and then in 30 minute intervals, up to 120 minutes after breakfast.

The same device will be used for all patients to minimize variability and test strips will be from the same batch. The blood samples for testing will be obtained by puncture in the fingers of the left hand and all the strictest safety and hygiene procedures will be assured.

5.4. Lifestyle and care assessment

The interview will also include questions on dietary and physical activity habits, and assessment of tobacco and alcohol use.

Physical activity will be assessed with the short-form version of the International Physical Activity Questionnaire (IPAQ) [28], translated to Portuguese [29].

This assessment of food intake will be achieved by the recall of all the food items ingested by the patient in the previous day, plus questions regarding usual eating habits, both aided by the use of images representing usual food items and different portions [30], which were presented to the patients for clarification of their description.

Patients will also be enquired regarding their agreement with different barriers to nutrition therapy adherence identified in the literature [17, 20, 21, 31, 32]. The data will be collected using a Likert-type scale with 5 points and, also, with an open-ended question, in order to collect data

on the views of this specific population on the barriers to a proper diet and on the reasons behind the adherence to nutrition therapy.

5.5. Risk perception of diabetes complication and optimistic bias

The interview will included items adapted from the in-person completion form of the Risk Perception Survey for Diabetes Mellitus (RPS-DM) questionnaire [33]. The items were translated and adapted into Portuguese and face validity of the subscales was ensured by translating the original English version into European Portuguese according to recommendations for cross-cultural research [34]. The scales were translated and then back-translated by two independent translators, without access to the original version. These versions were evaluated by a Psychology and Linguistics expert with English skills, in order to ensure the accuracy of the final version. All the items in this scale have a straightforward translation, due to the fact that literal equivalents exist in Portuguese.

5.6. Interview and data collection steps

The flow of the interview will be as follows: first, the patient will be explained the purpose of the study and read the informed consent form. Those who choose to be a part of the study will have their blood glucose measured and then offered the experimental breakfast. Patients who decline participation will be thanked for their time and provided with a free breakfast voucher, to be used inside the university's grounds.

Participants will go through the anthropometric assessment and afterwards offered the experimental breakfast in a room next to the interview room. They will have their breakfast seating down, alone. After breakfast, they will be conducted to the interview room and the data collection interview will proceed. The interviewer will be monitoring the time and, at the designated hours for glucose monitoring, will stop the interview and proceed with the glucose assessment.

The last data to be collected will be regarding blood pressure.

6. Data analysis

Data will be analysed with IBM-SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). Patient description and characterization will be presented as mean values, median values, and standard deviations.

The Kolmogorov-Smirnov test will be used to assess adherence to the Normal distribution and, accordingly, parametric or non-parametric statistical procedures will be used to compare groups. For comparisons between two groups, Student's t-test or Mann-Whitney test will be used computed, while a one-way analysis of variance (ANOVA) with Bonferroni *post-hoc* correction is intended for multiple group comparisons.

The statistical procedure for analysing the differences between cases and controls in qualitative variables is expected to be the chi-square test, or Fisher's exact test, were applicable.

Statistical significance in all procedures will be determined by two-tailed analysis and set at 0.05.

7. Dissemination of information

All the resulting information from this study can eventually be published in peer-reviewed journals, after following all patient anonymity and confidentiality requirements. Furthermore, the researcher will also write a brief report on the nutritional analysis that each patient dataset will be subjected and deliver it in a signed and sealed envelope directly to the physician responsible for the diabetes consultations at the AEDMADA clinic. In this way, participants and their physician will be informed of the results of the nutritional assessment.

8. Ethical issues

This study implies a slight discomfort for the participants, associated with the finger punctures needed to assess glucose on the day of data collection. Nevertheless, as this measurement can constitute a usual disease self-monitoring behaviour for some of the patients, it is expected the discomfort to be minimal.

9. Data protection

Only the physician responsible for the diabetes consultations will know the identity of the participants and, at the end of the study, will be given access to the data regarding nutritional assessment.

The collection of data from the patients' clinical files will be conducted after a written formal consent is given and only the researcher will have access to the files.

Throughout all of the study, only the researcher will be responsible for coding the informed consent forms and for data collection, and will be the only one who will have access to the entire dataset.

The dataset will be stored in a password protected computer belonging to the University of Algarve, exclusively used by the researcher. When the data is no longer needed, the researcher will ensure the safe deletion of the data file.

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