SENSORY EVALUATION, FREQUENCY OF FOOD CONSUMPTION AND METABOLIC RESPONSES TO A TEST BREAKFAST MEAL IN MIDDLE-AGED ADULTS

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ABSTRACT

Facing the growing prevalence of type 2 diabetes (T2D), the development of nutritional interventions allowing not only optimal glycemic control but also promoting postprandial satiety and overall satisfaction constitutes an interesting therapeutic avenue. This study was carried out in two parts, with the first part informing the second one.

The **first part** was conducted in 61 middle-aged adults with or without prediabetes or T2D and aimed to assess the influences of gender/sex and health status on the relative ranking of the importance of eight common determinants of food choices as well as the sensory evaluation and the frequency of consumption of almonds, pistachios, avocados, oatmeal, and eggs. Data analysis showed that **1)** participants perceived *"taste and own food preferences*" as having the greatest influence on their food choices, **2)** women attributed more importance to their *"own food-related health beliefs"* ($p=0.040$), while men reported a higher influence of the *"recommendations of a health professional"* ($p=0.065$), **3)** almonds' and pistachios' taste was rated the highest, and **4)** taste ratings of pistachios ($\beta=0.323$, $p=0.018$) and avocados ($\beta=0.604$, $p<0.001$) were positively associated with their frequency of consumption by participants.

Based on the sensory evaluation of the five foods, almonds were included in the test meal of the **second part** of this study. The latter was conducted in 7 middle-aged men with T2D and aimed to assess the effects of the types of macronutrient subtypes contained in isocaloric macronutrient-matched meals on the postprandial glycemic, hormonal (insulin and glucagon-like peptide-1 (GLP-1)) and appetite responses. The control meal contained white bread, butter and cheese, and the test meal contained white bread and almonds. Data analysis showed that the test meal was associated with **1)** lower postprandial glycemia ($p=0.014$), **2)** higher postprandial GLP-1 serum concentrations ($p=0.044$) as well as **3)** decreased hunger ($p=0.032$) and increased fullness ($p=0.014$). There were no meal-associated differences in postprandial serum insulin concentrations.

Results highlight the importance of taste and food preferences and point out some gender/sex-related differences in the determinants of food choices. They also support the beneficial effects of almonds, a food that seemed well appreciated by men and women, on key therapeutic targets of T2D management.

RÉSUMÉ

Face à la prévalence croissante du diabète de type 2 (DT2), le développement d'interventions nutritionnelles permettant non seulement un contrôle optimal de la glycémie, mais favorisant également la satiété et la satisfaction postprandiale, constitue une avenue thérapeutique intéressante. Cette étude a été menée en deux parties, la première partie informant la seconde.

La **première partie** a été menée auprès de 61 adultes d'âge moyen avec ou sans diagnostic de prédiabète ou DT2. Cette partie avait pour but d'évaluer les influences du genre/sexe et du statut de santé sur le classement relatif de huit déterminants communs des choix alimentaires, ainsi que sur l'évaluation sensorielle et la fréquence de consommation des amandes, pistaches, avocats, gruau et œufs. L'analyse des données a permis de montrer que **1)** les participants ont perçu le *« goût et propres préférences alimentaires »* comme le déterminant ayant le plus d'influence sur leurs choix alimentaires, **2)** les femmes ont attribué plus d'importance à leurs *« propres croyances alimentaires reliées à la santé »* ($p=0.040$), alors que les hommes ont rapporté une plus grande influence des *« recommandations d'un professionnel de la santé »* ($p=0.065$), **3)** les amandes et les pistaches ont été les aliments les mieux évalués pour leur goût, et 4) l'évaluation du goût des pistaches ($\beta=0.323$, $p=0.018$) et des avocats ($\beta=0.604$, $p<0.001$) a été positivement associé à leur fréquence de consommation par les participants.

Sur la base des résultats de l'évaluation sensorielle des aliments, les amandes ont été incluses dans le repas test de la **seconde partie** de l'étude. Cette dernière a été menée auprès de 7 hommes d'âge moyen avec le DT2 et avait pour but d'évaluer l'effet des sous-types de macronutriments contenus dans des repas isocaloriques et avec des quantités identiques de macronutriments sur les réponses glycémiques, hormonales (insuline et glucagon-like peptide-1 (GLP-1)) et d'appétit. Le repas contrôle contenait du pain blanc, du beurre et du fromage, et le repas test contenait du pain blanc et des amandes. L'analyse des données a montré que le repas test était associé à **1)** une glycémie postprandiale plus basse ($p=0.014$), **2)** des concentrations sériques postprandiales de GLP-1 plus élevées ($p=0.044$), et **3)** une diminution de la faim ($p=0.032$) et augmentation de la plénitude ($p=0.014$). Il n'y avait pas de différence entre les repas pour les concentrations sériques postprandiales d'insuline.

Les résultats de l'étude soulignent l'importance du goût et des préférences alimentaires et pointent à certaines différences reliées au genre/sexe dans les déterminants des choix alimentaires. Ils supportent également les effets bénéfiques des amandes, un aliment qui a semblé être bien apprécié par les hommes et les femmes, sur des paramètres thérapeutiques clés dans la gestion du DT2.

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LIST OF ABBREVIATIONS

ADP	Adenosine diphosphate
ANOVA	Analysis of variances
ATP	Adenosine triphosphate
AgRP	Agouti-related peptide
ARC	Arcuate nucleus
AUC	Area under the curve
BF	Body fat
BG	Blood glucose
BMI	Body mass index
BW	Body weight
CANRISK	Canadian diabetes risk questionnaire
CaSR	Calcium-sensing receptor
CNS	Central nervous system
CART	Cocaine and amphetamine related transcripts
cAMP	Cyclic adenosine monophosphate
DNA	Deoxyribonucleic acid
DPP-IV	Dipeptidyl-peptidase IV
DMH	Dorso-medial nucleus of the hypothalamus
EECs	Enteroendocrine cells
FBG	Fasting blood glucose
FFAR 1-4	Free fatty acid receptors 1-4
GI	Gastro-intestinal
GLP-1	Glucagon-like peptide-1
GLP-2	Glucagon-like peptide-2
GIP	Glucose insulinotropic peptide
GLUT 1-4	Glucose transporter 1-4
GPCR	G-protein coupled receptor
GSK-3	Glycogen synthase kinase-3
HbA1C	Glycated hemoglobin
HDL-c	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic model for insulin resistance
iAUC	Incremental area under the curve

IGT	Impaired glucose tolerance
IL-6	Interleukine-6
IR	Insulin resistance
IRS-1	Insulin receptor substrate-1
ISM	Institut du Savoir Montfort
LCFAs	Long-chain fatty acids
MCFAs	Medium-chain fatty acids
mRNA	Messenger ribonucleic acid
MUFAs	Monounsaturated fatty acids
NAc	Nucleus accumbens
NDG	Nodose ganglion
NPY	Neuropeptide Y
NTS	Nucleus tractus solitarius
OGTT	Oral glucose tolerance test
PC1-2	Pro-hormone convertase 1-2
POMC	Pro-opiomelanocortine
PUFAs	Polyunsaturated fatty acids
PVN	Paraventricular nucleus
SCFAs	Short-chain fatty acids
SGLT-1	Sodium-glucose transporter 1
SFAs	Saturated fatty acids
SQ	Satiety quotient
TEE	Total energy expenditure
TEI	Total energy intake
TG	Triglycerides
TNF-α	Tumor necrosis factor-α
TCPS 2	Tri-Council Policy Statement 2
T2D	Type 2 diabetes
VASs	Visual analog scales
VTA	Ventral tegmental area
WC	Waist circumference

LIST OF SYMBOLS

>	Above
<	Below
≥	Equal or above
≤	Equal or below
ca^{2+}	Calcium
cm	Centimeter(s)
g	Gram(s)
h	Hour(s)
kcal	Kilocalorie(s)
kJ	Kilojoule(s)
kg	Kilogram(s)
L	Litre(s)
min	Minutes
mmol	Milimol(s)
%	Percent
pmol	Picomol(s)

INTRODUCTION

BACKGROUND

Type 2 diabetes (T2D) is a metabolic disorder of major public health concern due to its pandemic occurrence and its association with several physical and psychological comorbidities, as well as with a decreased overall quality of life and life expectancy [1–4]. In Canada, the highest rates of T2D are among middle-aged (45-65 years) men, with a prevalence of 13.6%, compared to 10.6% in women of the same age group, and 8.1% in the general population [1]. This disparity between men and women is mainly attributable to hormonal differences leading to a higher accumulation of abdominal fat, especially in the visceral compartment, in men [39-41]. Excessive visceral fat accumulation is associated with an increased risk of developing several cardiometabolic complications, including insulin resistance and T2D, which are both observed at lower body mass indexes (BMIs) in men than women [39, 65, 66, 73]. Some studies also suggest that men might have poorer dietary habits than women, that they could perceive healthy diets as less satisfying in terms of taste, variety, and satiation potential, and that they generally appear to have lower levels of nutrition-related knowledge than women [42-47, 116-122]. Men might indeed have a more intuitive approach towards eating, focused on internal hunger cues, pleasure, and satisfaction [117]. This is in contrast with women, who more often report making food choices and dietary changes based on dietary guidelines, appear more likely to engage in dieting behaviors, and might have a higher propensity towards cognitive restraint and emotional eating [43, 118-122]. While available literature is somewhat limited, these differences point to gender/sex-specific nutritional vulnerabilities, suggesting that men and women might benefit from somewhat different nutritional approaches and interventions. For instance, dietary approaches that are sensitive to men and women's food preferences and perceptions of healthy eating, and which incorporate antihyperglycemic and highly satiating foods, might be more effective for weight and T2D management than the current conventional dietary approach.

Food intake has both acute and chronic physiological effects. Upon its entry in the gastrointestinal (GI) tract, food is digested, and nutrients elicit the secretion of several peptide hormones. The glucagon-like peptide-1 (GLP-1) is a peptide hormone that has attracted a lot of

interest for its potential use in the management of T2D. Upon its secretion, GLP-1 acts, among others, on the pancreas and regions of the central nervous system (CNS) involved in energy homeostasis and food intake regulation. More specifically, GLP-1 positively influences blood glucose homeostasis, by stimulating insulin synthesis and secretion, and by inhibiting the secretion of glucagon [136, 137, 177, 178]. GLP-1 also appears to promote β-cells' neogenesis, as its intravenous administration was associated with increased markers of cellular proliferation and decreased markers of apoptosis [154-159]. In the CNS, by binding to its receptors on hypothalamic nuclei, GLP-1 decreases hunger, promotes satiety and inhibits food intake [186-197]. Additionally, the activation of GLP-1 receptors in regions of the CNS involved in food reward processing reduces cravings for hyperpalatable foods and might help prevent their overconsumption [200, 204, 205, 206-211]. For these well-supported actions, GLP-1 is a therapeutic target with high potential for T2D management.

Several factors influence the secretion of GLP-1, including the binding of macronutrients to G-protein coupled receptors (GPCRs) expressed by GI cells. To date, receptors that bind to carbohydrates (SGLT-1 receptor) [218-222], short (FFAR2 and FFAR3 receptors) [223-242], medium- and long-chain fatty acids (FFAR1 and FFAR4 receptors) [244-254], as well as amino acids and small peptides (CaSR and GPRC6A receptors) [255-266] have been identified and described in the literature. The affinity of these receptors for macronutrients seems to vary according to their chemical structures, and some nutrients, such as dietary fiber, proteins, monounsaturated (MUFAs) as well as omega-3 polyunsaturated fatty acids (PUFAs), appear to be more potent stimulators of GLP-1 secretion.

OVERVIEW OF THE STUDY

The study presented in this thesis was carried out in two parts with distinct methodological approaches, the first part informing the second one. Based on the knowledge presented above, a literature review was conducted to identify foods that were shown to positively influence postprandial glycemia and insulinemia, GLP-1 secretion, and subjective appetite sensations. Fourteen original articles were identified, and foods included almonds, pistachios, avocados, oatmeal, and eggs [267-

279,281]. The first part of the study was conducted in a sample of middle-aged adults with or without prediabetes and aimed to assess the influences of gender/sex and health status on 1) the relative ranking of the importance of common determinants of food choices and 2) the consumption and sensory evaluation of almonds, pistachios, avocados, oatmeal, and eggs. Based on the sensory evaluation, one of the five foods was included in the test meal of the second part of this study, whose aim was to assess the effects of macronutrient subtypes contained in isocaloric macronutrient-matched meals on postprandial glycemic, hormonal and appetite responses in middle-aged men with T2D.

THESIS OUTLINE

This thesis includes six distinct chapters:

The **first chapter** presents the literature review justifying the research objectives. Part of this literature review, mainly section 1.3.3, has been published as a review article in *Nutrition & Metabolism*. The published article is presented in *Appendix 1*. Further on, *Appendix 9* contains a statement on copyright and licensing from *BioMed Central* confirming the right to use the published article in this thesis.

The **second chapter** includes a statement of the research gaps as well as the research questions, specific objectives, hypotheses, and significance of the study.

The **third chapter** provides an overview of the methodology, which is further described in the articles presented in Chapters 4 and 5.

The **fourth chapter** includes a first original article titled "*Determinants of food choices, sensory evaluation and frequency of consumption of health-promoting foods in middle-aged adults: a pilot study"* which will be submitted for publication in *Food Quality and Preference*. This article addressed the first two research questions presented in Chapter 2.

The **fifth chapter** includes a second original article titled *"Acute effects of an isocaloric breakfast meal containing almonds on glycemic, hormonal and appetite responses in men with type 2 diabetes: a randomized cross-over study"* which will be submitted for publication in *Appetite*. This article addressed the third research question presented in Chapter 2.

The **sixth chapter** summarizes and discusses the main results of this study, its strengths and limitations, as well as its significance and contribution to the advancement of knowledge. This chapter also points to future research avenues and makes a general conclusion on the overall research project.

CHAPTER 1

Literature review

1.1 DEVELOPMENT OF TYPE 2 DIABETES

Type 2 diabetes (T2D) is a metabolic disorder with multiple aetiologies. It is defined as a state of chronic hyperglycemia accompanied by abnormalities in carbohydrate, fat and protein metabolism, resulting from insulin resistance (IR) and progressive impaired insulin secretion [5, 6]. Diagnoses of impaired glucose tolerance (IGT), a reversible prediabetic state of hyperglycemia, and T2D are made based on specific glycemic threshold values associated with the development of micro- and macro-vascular complications [6]. As it is important to fully understand the disease process of T2D, the following sections provide an overview of normal glucose metabolism, blood glucose (BG) regulation, as well as insulin secretion and functions. Thereafter, the changes occurring with the progressive development of IGT and T2D are described.

1.1.1 GLUCOSE METABOLISM AND BLOOD GLUCOSE REGULATION

The human body cells' energy requirements are principally met by glucose. Glucose is a monomeric form of carbohydrate and a product of the enzymatic degradation of more complex, polymeric forms of carbohydrates coming from the diet. Upon ingestion, dietary carbohydrates enter the gastro-intestinal (GI) tract lumen and are mainly hydrolyzed into their monomeric forms, namely into glucose, fructose and galactose [7, 8]. This is achieved through the action of several enzymes, such as the pancreatic α-amylase, and the intestinal brush border enzymes lactase, maltase and sucrose-isomaltase [7, 8]. From the GI tract lumen, these carbohydrate monomers are first absorbed into enterocytes by facilitated transport through the sodium-glucose transporter 1 (SGLT-1), and subsequently into the bloodstream by passive diffusion or by facilitated transport through the glucose transporter 2 (GLUT2) [7, 8]. Shortly after entering the bloodstream, fructose and galactose are converted to glucose in the liver, and then, recirculate [7, 8]. From the bloodstream, glucose is absorbed by the cells of several peripheral tissues, where it typically provides energy for adenosine triphosphate (ATP) formation or is stored in the form of glycogen (through glycogenesis) and/or fat (through *de novo* lipogenesis) for future use [7, 8]. Glucose

uptake into peripheral tissue cells is achieved through facilitated transport, which is mediated by the glucose transporters 1-3 (GLUT1-3), as well as by the insulin-sensitive glucose transporter 4 (GLUT4) [7–9].

In metabolically healthy individuals, BG concentrations are maintained within narrow ranges despite constant fluctuations in glucose supply and demands. More specifically, BG concentrations average ~5.0 mmol/L throughout the day, with maximal values ≤ 9.0 mmol/L and minimal values > 3.0 mmol/L [8, 9]. This is achieved through a tight homeostatic control, allowing balancing the rates of glucose entry into the circulation and the rates of glucose uptake into the peripheral tissues. Several neuro-endocrine signals orchestrate these changes, with the two most important ones being the pancreatic hormones insulin and glucagon [9–11]. The hormone insulin is produced and secreted by the pancreatic β-cells, whereas glucagon is produced and secreted by the pancreatic α-cells [9–11]. Other regulators of BG concentrations include gastrointestinal (GI) hormones (e.g., incretins), corticosteroids and adrenaline [9, 12, 13].

1.1.2 INSULIN SYNTHESIS, SECRETION AND ACTION

Insulin is the sole BG lowering hormone and is exclusively produced in the β-cell of the pancreatic islets of Langerhans [14, 15]. It is initially synthesized as a single-chain 86-amino-acid precursor – the preproinsulin [14, 15]. The latter contains an N-terminal segment that is essential for the passage into the endoplasmic reticulum, where the N-terminal 4-amino-acid fragment of preproinsulin is finally cleaved to form the proinsulin [14, 15]. Once the post-translational formation of three essential disulfide bonds is completed, the central 31-amino-acid fragment of proinsulin is cleaved at two positions by endopeptidases, producing the mature insulin and a segment called C-peptide [14, 15]. Insulin is then stored in secretory granules, which accumulate in β-cells' cytoplasm until secretion is triggered [14, 15]. C-peptide is released into the bloodstream, and can therefore be used as an indicator of insulin synthesis [14, 15]. The different steps of insulin synthesis are illustrated in **Figure 1.1**.

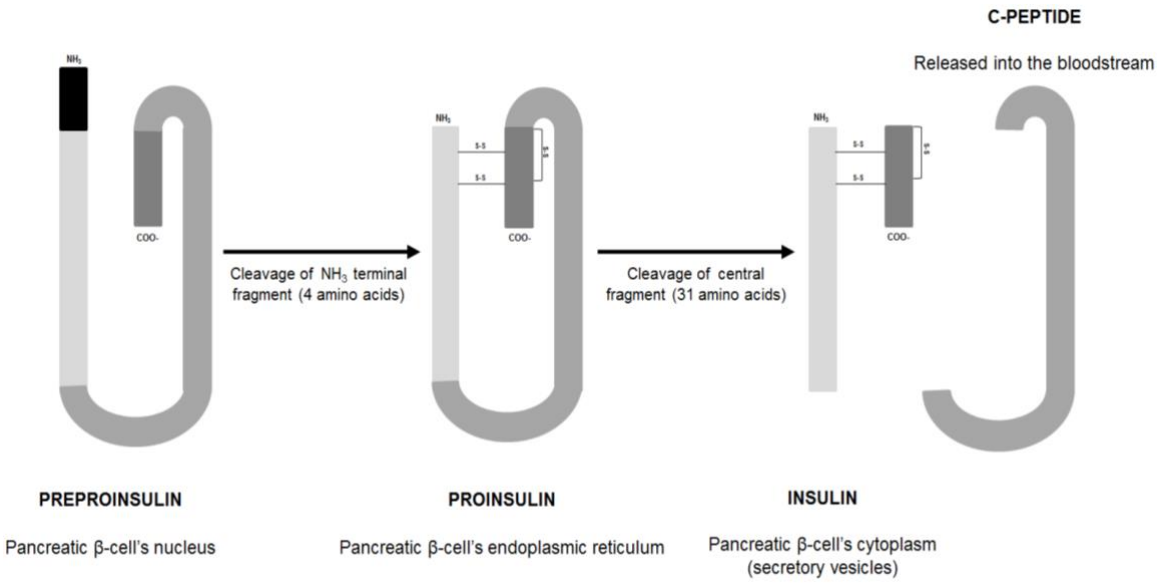


Figure 1.1 Insulin synthesis in pancreatic β-cells.

The preproinsulin is an inactive precursor of insulin – it contains an N-terminal amino-acid fragment (black segment of the preproinsulin representation) that is essential for its passage from the nucleus to the endoplasmic reticulum of the cell. In the endoplasmic reticulum, with the cleavage of the same N-terminal segment and the formation of three disulfide bonds, the preproinsulin becomes the proinsulin. The cleavage of the central 31-amino-acid fragment of proinsulin forms the active insulin (stored into secretory granules of pancreatic β-cells until secretion is triggered) and a fragment called C-peptide (released into the bloodstream).

Insulin secretion from the secretory granules of the cytoplasm is initiated when BG concentrations rise above 3.3 mmol/L [7–10]. Insulin typically exhibits a bi-phasic secretion pattern, which is the result of the influences of several metabolic and hormonal factors [7–10, 15–17]. Shortly after an elevation of BG concentrations, a transient and sharp increase of insulin secretion is observed, described as the *"first-phase insulin release"* [15–17]. A decrease to basal secretion rates follows this initial increase in insulin secretion. If exposure to glucose and other nutrients (i.e., amino acids) is prolonged, an increase in insulin synthesis as well as a more gradual and long-lasting increase in insulin secretion, described as the "second-phase insulin release", is observed [15–17]. When extracellular glucose concentrations are rising above basal levels, glucose enters the cytoplasm of pancreatic β-cells through the GLUT2 [15–17]. This leads to an increase in the ATP / adenosine diphosphate (ADP) ratio, which results in the blockade of

ATP-dependent potassium pumps and a progressive depolarization from the membrane resting potential of β-cells [15–17]. When the threshold is reached, calcium (Ca^{2+}) channels open, ultimately triggering insulin exocytosis from secretory granules [15–17]. The secretion of insulin from pancreatic β-cells is illustrated in **Figure 1.2**.

Insulin exerts several functions by interacting with its receptors expressed on insulin-sensitive cells and tissues, namely hepatocytes, adipocytes cells and myocytes [7, 9]. The binding of insulin to its receptors induces the phosphorylation of the insulin receptor substrate (IRS) [18, 19]. The IRS subsequently activates several intracellular signaling pathways [18, 19]. The limiting step in insulin-stimulated glucose absorption, and probably the most important effect of insulin, is its ability to induce the translocation of the insulin-sensitive GLUT4 from cytoplasmic vesicles to the cell membrane [7, 9]. Indeed, when BG concentrations are low, GLUT4 transporters are present in cytoplasmic vesicles [7, 9]. By interacting with its receptor, insulin allows for the fusion of those cytoplasmic vesicles with the cell membrane, thereby allowing adipocytes and myocytes to absorb more glucose [7, 9]. In the hepatocytes, the binding of insulin to its receptors also stimulates glucose storage in the form of glycogen, mainly by inactivating the glycogen synthase kinase-3 (GSK-3), an enzyme that breaks down glycogen synthase [8, 20]. In addition to promoting glucose storage, insulin inhibits glucagon secretion, as well as lipolysis and glucose production by the liver by decreasing glycogenolysis and gluconeogenesis [8].

Insulin exerts several functions by interacting with its receptors expressed on insulin-sensitive tissues, namely on liver cells, adipose tissue cells and muscle cells [7, 9]. The binding of insulin to its receptors induces the phosphorylation of the insulin receptor substrate (IRS) [18, 19]. The IRS subsequently interacts with various molecules, which results in the activation of several signaling pathways [18, 19]. The rate limiting step in insulin-stimulated glucose absorption, and probably the most important effect of insulin, is its ability to induce the translocation of the insulin-sensitive GLUT4 from cytoplasmic vesicles to the cell membrane [7, 9]. Indeed, when BG concentrations are low, GLUT4 transporters are present in cytoplasmic vesicles [7, 9]. By

interacting with its receptor, insulin allows for the fusion of those cytoplasmic vesicles with the cell membrane, thereby allowing

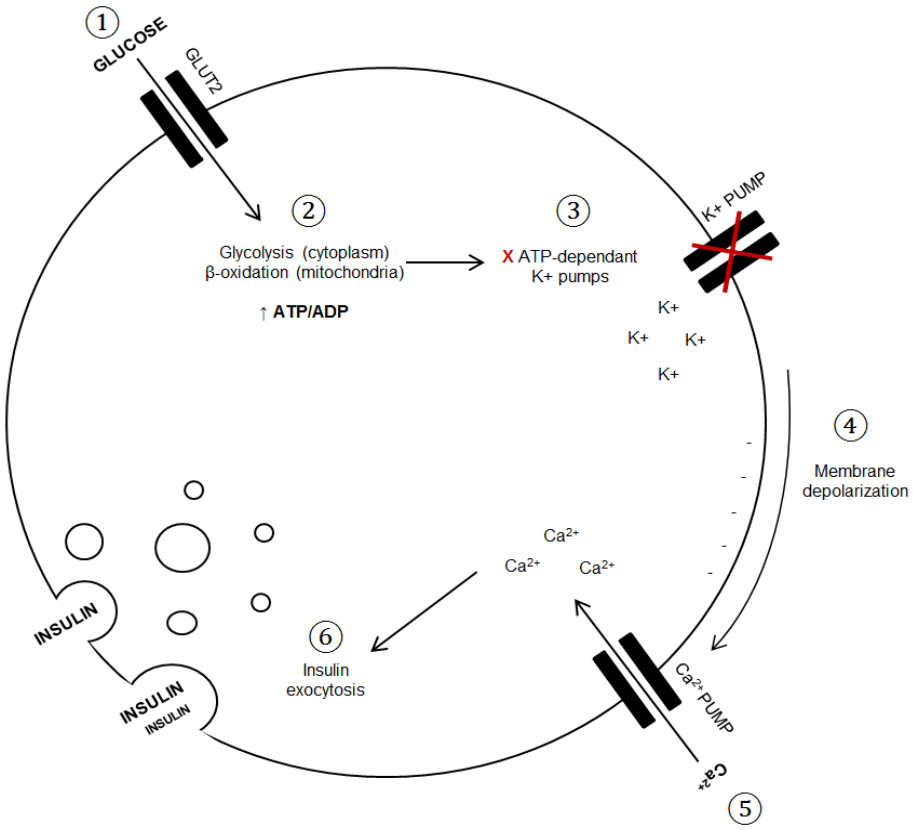


Figure 1.2 Insulin secretion from pancreatic β-cells.

When the extracellular concentrations of glucose rise above basal levels, glucose starts entering the cytoplasm trough GLUT2 (①). The entry of glucose leads to an increase of the ATP/ADP ratio in the cytoplasm (②) which results in the blockade of ATP-dependent potassium pumps (③) and a progressive depolarization from the membrane resting potential of pancreatic ϐ-cells (④). When the membrane action potential threshold is reached, Ca2+ channel open (⑤), leading to the exocytosis of insulin from secretory granules.

ADP: Adenosine diphosphate; **ATP**: Adenosine triphosphate; **Ca^{2+}**: Calcium; **GLUT2**: Glucose transporter 2; **K+**: Potassium.

adipose tissue cells and muscle cells to absorb more glucose [7, 9]. In the hepatocytes, the binding of insulin to its receptors also stimulates glucose storage in the form of glycogen, mainly by inactivating the glycogen synthase kinase-3 (GSK-3), an enzyme that breaks down glycogen synthase [8, 20]. In addition to promoting glucose storage, insulin inhibits glucagon secretion, as

well as lipolysis and glucose production by the liver by decreasing glycogenolysis and gluconeogenesis [8].

1.1.3 PATHOGENESIS OF TYPE 2 DIABETES

Type 2 diabetes is a progressive disease. Its development can therefore be viewed as several definable stages characterized by changes in BG values, insulin secretion, as well as β-cell proliferation rates and mass. **Table 1.1** illustrates those changes as the progression from 1) normal glucose metabolism and BG regulation, to 2) compensated IR, to 3) IGT, and finally to 4) T2D occurrence.

Table 1.1 Stages of change in blood glucose concentrations, insulin secretion and β-cell mass through the progressive development of type 2 diabetes.

	FBG* (mmol/L)	75g 2h-OGTT* (mmol/L)	%HbA1C*	Insulin secretion 1st phase | 2nd phase		Pancreatic β-cell mass
Stage 0 Normal glucose metabolism and blood glucose regulation	3.9 – 6.0	< 7.8	< 6.0	Normal	Normal	Normal
Stage 1 Compensated insulin resistance	3.9 – 6.0	< 7.8	< 6.0	↑	=	↑
Stage 2 Impaired glucose tolerance	6.1 – 6.9	7.8 – 11.0	6.0 – 6.4	↓ or 0	= or ↓	↓
Stage 3 Type 2 diabetes	≥ 7.0	≥11.1	≥ 6.5	0	↓	↓↓

**Diabetes Canada*'s threshold values for a diagnosis of IGT and T2D [21].

BG: Blood glucose; **FBG:** Fasting blood glucose; **HbA1C**: Glycated hemoglobin; **IGT:** Impaired glucose tolerance; **T2D:** Type 2 diabetes; **2h-OGGT**: 2-hour Oral Glucose Tolerance Test (75 g of glucose).

At the very beginning of T2D development, hepatocytes, adipocytes and myocytes become increasingly resistant to the effects of insulin [22, 23]. This translates into a decreased glucose uptake, a decreased synthesis and storage of glycogen, as well as a decreased inhibition of hepatic glucose production and lipolysis [22, 23]. At this stage, pancreatic β-cells compensate

for these changes by increasing their first-phase insulin secretion [24]. This increase in insulin secretion is thought to be mediated by an up-regulation of β-cell proliferation, resulting in an increased β-cell mass, and possibly by an increase in the amount of insulin secreted per unit of β-cell mass [25, 26]. This stage of T2D development is clinically characterized by high insulinemia, but normal fasting and postprandial BG concentrations [27]. It is a transient stage between normal glucose metabolism and IGT, which can be identified based on direct (i.e., hyperinsulinemia measured by glycemic clamp) and indirect measures (i.e., fasting blood insulin concentrations, homeostatic model for IR (HOMA-IR)), but not solely based on BG concentration values [28, 29].

Normal fasting and postprandial BG values are generally maintained until decompensation begins to occur in stage 3. The decompensation begins when the pancreatic β-cells are unable to produce sufficient insulin to overcome IR. Opposite to the stable compensation stage described above, decompensation is a result of decreased β-cell proliferation, decreased β-cell mass, as well as a significantly lower to nearly absent first phase insulin secretion, and a slightly decreased second-phase insulin secretion [25, 30]. This stage of T2D development is communally known as IGT and is clinically characterized by lower circulating insulin concentrations, as well as high fasting and postprandial BG concentrations [6, 21]. The percentage of glycated hemoglobin (%HbA1C), which is an indicator of longer-term glycemic control, might also be higher than normal [6, 21]. Impaired glucose tolerance diagnosis can be made based on fasting BG concentrations, BG concentrations 2 hours after a 75 g glucose load during an oral glucose tolerance test (75 g 2h-OGTT), as well as based on values of %HbA1C [6, 21]. The specific cut-off points of *Diabetes Canada* used for the diagnosis of IGT are presented in **Table 1.1** [21].

As the state of compensation progresses and reaches a stable point, pancreatic β-cell proliferation rates and mass, along with insulin secretion continue to decrease, whereas fasting and postprandial BG concentrations progressively increase, reaching threshold values for the diagnosis of T2D. The specific threshold values of *Diabetes Canada* used for the diagnosis of

T2D are presented in **Table 1.1** (stage 3). This state of frank T2D is characterized by an absent first-phase insulin secretion, a significantly decreased second-phase insulin secretion, and a chronic state of hyperglycemia. Moreover, β-cell mass appears to be decreased to as much as ~50% of that observed in conditions of normal BG regulation [25, 30]. This severe decrease in β-cell mass results from a decreased proliferation rate, as well as from an accentuation of β-cell apoptosis, observed with the development of T2D [25, 30]. At this stage, an increase in glucagon secretion, partly resulting from the decreased insulin secretion, also significantly contributes to the state of chronic hyperglycemia [31].

1.2 RISKS FACTORS FOR TYPE 2 DIABETES

The development of T2D is significantly influenced by a combination of risk factors, some which are non-modifiable and several which are modifiable. Well-known non-modifiable risk factors include age, sex, ethnicity, genetics, as well as a history of gestational diabetes in women [21, 32]. More specifically, the prevalence of T2D increases after 40 years old, and is higher among men and non-Caucasian ethnic groups [21, 32]. Epidemiological studies have also shown a strong genetic component [32, 33]. Indeed, having first-degree relatives with a diagnosis of T2D increases individuals' risks for its development [32, 33]. Modifiable risk factors include unhealthy diets, sedentary lifestyles, overweight, obesity, and central obesity [32, 34]. Cardiometabolic disturbances – that could in part be complications of excess adipose tissue accumulation – such as hypertension, hypercholesterolemia, hypertriglyceridemia and glucose intolerance, are also well-known risk factors for T2D [32, 34].

Studies that have been conducted in several areas of the world, as well as Canadian statistics, show that middle-aged (40-70 years) men appear to be at higher risk of developing T2D than their women counterparts [1, 35, 36]. Indeed, in Canada, more middle-aged men (13.6%) than women (10.6%) have been diagnosed with T2D, according to 2013/14 statistics [1]. As a result, sex is well-recognized as non-modifiable risk factor for the development of T2D and has been incorporated in the Canadian diabetes risk questionnaire (CANRISK) [1, 37]. Plausible

explanations for this disparity in T2D risks between sexes are, among others, the higher prevalence of overweight and obesity [32, 34], as well as the higher accumulation of fat in the abdominal area, especially in the visceral compartment, in men than women [38–41]. In addition, men appear to generally have poorer dietary habits than women which could contribute to promoting excessive weight gain, as well as the development of T2D *per se* [42–47]. While differences in the patterns of body fat accumulation are principally explained by biological difference between men and women, differences in dietary habits can be related to both sex and gender – the socially constructed roles and behaviors associated with being a man or a woman. When the roles of sex and gender cannot be clearly distinguished or are likely to both have an influence the term *"gender/sex"* will be used. Gender/sex-related vulnerability factors to the development of T2D are described in further details in the following sections.

1.2.1 OVERWEIGHT, OBESITY AND CENTRAL OBESITY

Overweight, obesity and central obesity are defined as an excessive fat accumulation that increases health risks [48, 49]. The most commonly used classifications of excess weight accumulation are body mass index (BMI) and waist circumference (WC) [48, 49]. Body mass index, which is equal to body mass (in kg) divided by height (in m) squared, is correlated to total body fat content, whereas WC is correlated to the abdominal fat content [48, 49]. Specific cut-off points, associated with higher health and overall mortality risk, have been developed for both BMI and WC. In men and women, overweight and obesity are defined as a BMI ≥ 25.0 kg/m^2 and ≥ 30.0 kg/m^2, respectively [48, 49]. Moreover, in men, abdominal obesity is defined as a WC ≥ 94 cm or ≥ 90 cm, depending on the ethnicity [49, 50]. In women, abdominal obesity is defined as a WC ≥ 80 cm. Those cut-off points and the associated health risk are presented in **Table 1.2**.

It is widely accepted that obesity, especially excessive fat accumulation in the abdominal area, is the most powerful predictor of T2D development. Indeed, 60 to 90% of T2D appears to be related to obesity and weight gain [51]. Similarly, obesity and weight gain can increase the risks for T2D development by twenty to more than ninety folds [52–55]. Excessive fat accumulation promotes

IR, possibly by increasing the secretion of pro-inflammatory cytokines, such as the tumour necrosis factor-α (TNF-α) and interleukine-6 (IL-6) [56–58]. Those inflammatory markers have several detrimental metabolic and cellular effects, including a down-regulation of the expression of the insulin-sensitive GLUT4 [59, 60] and of the insulin receptor substrate-1 (IRS-1) [60–62], as well as an increase in lipolysis [63, 64]. In Canada, statistics show that the prevalence of overweight and obesity is higher among middle-aged men (69.5%) than women (51.9%), which could be a contributor to their higher risk of developing T2D [65]. Additionally, several studies have shown that men tend to develop T2D at lower BMI values, which supports the concepts that body fat distribution and patterns of body fat storage may have a significant impact on T2D development risk [66, 67].

Table 1.2 Classification* of excess weight and health risk according to body mass index and waist circumference in men and women.

			Cardiometabolic disease risk, relative to normal weight and waist circumference (cm)			
	BMI (kg/m^2)	Obesity class	Men WC < 90§ WC < 94**	Women WC < 90	Men WC ≥ 90§ WC ≥ 94**	Women WC ≥ 90
Underweight	< 18.5	-	-		-	
Normal	18.5 – 24.9	-	-		-	
Overweight	25.0 – 29.9	-	Increased		High	
Obesity						
Mild	30.0 – 34.9	I	High		Very high	
Moderate	35.0 – 39.9	II	Very high		Very high	
Severe	≥ 40.0	III	Extremely high		Extremely high	

*Cut-off points of the World Health Organization [48, 49] and the National Cholesterol Education Program (NCEP) Expert Panel [50].

Ethnic-specific WC cut-off points for: **Europids; §South Asians, Chinese, Japanese, South and Central Americans, Sub-Saharan Africans

BMI: Body mass index; **WC:** Waist circumference

1.2.2 BODY FAT DISTRIBUTION AND PATERNS OF ACCUMULATION

Health risks associated with obesity vary according to the location of adipose tissue [68, 69]. When total energy intake (TEI) is greater than total energy expenditure (TEE), excess energy is stored in the human body is the form of glycogen, proteins and, mostly in the form of

triglycerides (TG) in white adipose tissue [68, 70]. White adipose tissue is distributed throughout different anatomical regions (e.g., gluteal and abdominal areas), as well as in different body compartments (e.g., subcutaneous and visceral adipose tissue) [69, 71, 72]. Excessive accumulation of fat in the abdominal area, higher in visceral adipose depots and linked to ectopic fat accumulation (presence of TG in tissues other than adipose tissue), is associated with increased risks of developing cardiometabolic diseases compared to the accumulation of fat in gluteal regions [69, 71, 72]. Meaningful sex differences in body fat distribution and fat storage patterns have been described and those are thought to have been primarily modulated by evolutionary adaptation [38]. Indeed, on average, for the same BMI value, men have higher abdominal and ectopic fatty acid depots, higher fasting BG and blood TG concentrations, as well as lower high-density lipoprotein cholesterol (HDL-c) concentrations than their women counterparts [39, 66, 67, 73].

Men tend to accumulate more fat in the abdominal area (android or *"male pattern"* distribution), whereas premenopausal women generally accumulate more fat subcutaneously (gynoid or *"female pattern"* distribution) [38–41]. Physiology studies have shown that visceral adipose tissue TG uptake is greater in men than in women [40, 74]. However, this is still controversial, some studies also suggest that androgen hormones facilitate visceral adipose tissue accumulation. Clear examples illustrating this effect are changes in adipose tissue distribution in female-to-male transsexual transition, as well as higher abdominal fat deposition in women with polycystic ovary syndrome (syndrome associated with abnormally high testosterone levels) [75, 76]. In contrast, circulating estrogen concentrations have been inversely correlated with visceral fat, and the decline in estrogen concentrations occurring during menopause has been linked to an increase in visceral fat area and higher cardiometabolic risks [77–79]. An important characteristic of visceral fat is its high lipolytic activity allowing a rapid response to immediate energy needs [40]. As men were historically more responsible for hunting and gathering which necessitate more rapid energy mobilization, storing TG in an area with a greater lipolytic activity was advantageous [40]. On the other hand, having a lower lipolytic activity, subcutaneous fat is better suited to respond to chronic changes in energy demands, such as

those occurring during gestation and lactation [38]. In the context of the current epidemic of obesity and T2D, these evolutionary adaptations put men at higher risk of developing cardiometabolic diseases and confer a certain protective effect to pre-menopausal women.

1.2.3 NUTRIENTS, FOOD GROUPS AND DIETARY PATTERNS

Several dietary factors impact the risk of developing cardiometabolic diseases, including T2D. Some components of the diet, considered beneficial, can promote health and decrease the risk of developing several cardiometabolic disorders, whereas other components of the diet, viewed as detrimental, especially in large quantities, have the opposite effects. Energy intake is a central dietary factor due to its direct impact on energy balance, and consequently on body fat accumulation and body weight. On the other hand, several epidemiological studies have identified a number of nutrients, foods and dietary patterns which impact the risk for its development independently of the energy balance. Findings from several cross-sectional and prospective studies, as well as meta-analyses, are summarized in **Table 1.3**.

The impact of diet on the risk of T2D development has been studied from various angles. Several studies have focussed on the effect of single nutrients, some have examined the effects of specific foods or food groups, and others have investigated the effects of dietary patterns. Nutrients are the main components of food and can be subdivided into macro- and micronutrients. Macronutrients – namely carbohydrates, lipids and proteins – provide the energy that ensures the functioning of all body cells, whereas micronutrients – namely vitamins and minerals – provide several co-factors that are essential for many physiologic processes. Macronutrients can be subdivided into several categories based on their chemical characteristics. In this regard, the intake of dietary fiber – a subtype of carbohydrates which cannot be digested and absorbed by the intestinal cells – has been associated with a decreased risk of developing IR and T2D [80, 81]. In particular, soluble fibers have been shown to have benefits for BG control and normalization of elevated blood TG and cholesterol concentrations [82]. Similarly, in some studies, the intake of omega-3 polyunsaturated fatty acids (PUFAs) [83, 84], as well as

monounsaturated fatty acids (MUFAs) [84], have also been associated with a decreased risk of developing IR and T2D. Regarding micronutrient intake, some studies have shown a negative association between vitamin D [85–87], calcium [85–87] and magnesium [80, 88] intakes and the risk for T2D development, whereas the intake of heme-iron [89] has been positively associated to T2D risk in men only, likely due to its association with foods high in saturated animal fats, as well as to the pro-oxidative effects of iron.

Compared to studies on single nutrients, studies that investigate the effects of food and food groups take into account some interactions between the nutrients available in foods. Such studies have found a negative association between the intake of whole grain foods [82, 90], vegetables and fruits [91, 92], low-fat dairy products [93, 94], fish [95, 96] and nuts [97, 98] and the risk of IR and T2D development. Inversely, a positive association was found in several studies between the intake of refined carbohydrates [90], sugar-sweetened beverages and juices [99, 100], as well as red and transformed meats [101, 102]. Finally, several cross-sectional and prospective studies conducted in different areas of the world have investigated the effects of dietary patterns on the risk of IR and T2D. This approach complements the study of single nutrients and foods by considering the complexity of the diet and allowing the examination of the synergistic effects of dietary intake. These studies have shown that “Western”, “Atherogenic” or “Unhealthy” dietary patterns, characterized by a high intake of refined grains, sweets and dessert, high-fat dairy products, as well as red and transformed meats are associated with an increased risk of IR and T2D development [103–111]. Inversely, “Prudent” or “Healthy” [103–112], as well as the Mediterranean [113–115] dietary patterns, characterized by a higher intake of whole grain products, vegetable and fruits, low-fat dairy products, poultry, fish and seafood, nuts and pulses, as well as olive oil, herb and spices have been associated with a decreased risk of developing IR and T2D.

Studies comparing men and women’s dietary intakes showed that men might be more likely to adopt typical Western or unhealthy dietary patterns; they had lower intakes of vegetables and fruits [42–44], and higher intakes of red and transformed meats [45], sodium [46], alcohol

[47], and sugar-sweetened beverages [47]. In Baker & Wardle's (2003) study, men also rated their liking of vegetables significantly lower than women and rather favored meat-dominated meals, which they perceived as more pleasurable [43]. Along the same lines, in a qualitative study of barriers to healthy eating, men reported perceiving healthy foods and diets as being less satisfying in terms of taste, variety, as well as for their satiation and satiety potentials [116]. Men appear to have a

Table 1.3 Nutrients, food groups, dietary patterns and the risks of insulin resistance and type 2 diabetes.

	↑ risks of IR and T2D	↓ risks of IR and T2D
Nutrients	↑ intake of heme-iron-rich foods (men) [89]	↑ intake of dietary fiber [80–82] ↑ intake of omega-3 PUFAs [83, 84] ↑ intake of MUFAs [84] ↑ intake of vitamin D [85–87] ↑ intake of calcium [85–87] ↑ intake of magnesium [80, 88]
Foods and food groups	↑ intake of refined carbohydrates [90] ↑ intake of sweet beverages and juice [99, 100] ↑ ***intake in men than in women*** [47] ↑ intake of red and transformed meats [101, 102] ↑ ***intake in men than in women*** [45]	↑ intake of whole grain foods [82, 90] ↑ intake of vegetables and fruit [91, 92] ↓ ***intake in men than women*** [43, 44] ↑ intake of low-fat dairy products [93, 94] ↑ intake of fish [95, 96] ↑ intake of nuts [97, 98]
Dietary patterns	***"Western"***, ***"Atherogenic"*** or ***"Unhealthy"*** dietary pattern [103–111]: ↑ intake of refined carbohydrates, sweets and desserts, high-fat dairy products, and red and transformed meats.	***"Prudent"*** or ***"Healthy"*** dietary pattern [103–112]: ↑ intakes of whole-grain foods, vegetables and fruit, low-fat dairy products, poultry, and meat. **Mediterranean** dietary pattern [113–115]: ↑ intake of whole grain foods, vegetable and fruit, fish and seafood, nuts and pulses, olive oil, and spices.

IR: Insulin resistance; **MUFAs:** Monounsaturated fatty acids; **PUFAs:** Polyunsaturated fatty acids; **T2D:** Type 2 diabetes.

more intuitive approach towards eating focussed on internal hunger cues, pleasure, and satisfaction [116–120], which is in contrast with women, who more often report making dietary changes that are towards meeting dietary guidelines, are more likely to engage in dieting behaviours, and might have a higher propensity towards cognitive restraint and emotional eating [43, 117–119, 121–124]. While available literature is not very abundant, these differences point to gender/sex-specific nutritional vulnerabilities, suggesting that men and women might benefit from slightly different nutritional approaches and interventions.

1.3 MANAGEMENT OF TYPE 2 DIABETES

The management of T2D is a multifaceted and dynamic process which main goals are to promote optimal BG control, to alleviate symptoms and to decrease the risks of long-term complications. Along with anti-hyperglycemic pharmaceutical agents, targeting modifiable risk factors for T2D plays a key role in achieving these goals. In this regard, the 2018 Clinical Practice Guidelines of *Diabetes Canada* reemphasized the integral role of nutrition and weight management in individuals with T2D [125, 126].

1.3.1 EXCESS BODY WEIGHT REDUCTION AND MANAGEMENT

As described in the sections above, excessive body fat accumulation is a major risk factor for the development of T2D. It is indeed estimated that 80 to 90% of individuals who develop T2D are either overweight or obese [126]. After the onset of T2D, excessive body fat accumulation also promotes hyperglycemia, and contributes to increasing the risks for T2D comorbidities and overall mortality rates [126–128]. Therefore, weight maintenance is advised for individuals with T2D having a body weight qualified as *"normal"* [49, 126]. Similarly, achieving and maintaining a reduced body weight is strongly recommended for individuals with overweight and obesity [49, 126]. Even a weight loss corresponding to 5 to 10% of the initial body weight has been associated with significant improvement in insulin sensitivity, glycemic control, as well as obesity- and T2D-

associated comorbidities [129–133]. Current overweight and obesity management options include lifestyle, behavioural, pharmacological and bariatric surgical approaches. The selection of a weight management strategy is based on the assessment of overweight severity, health complications involved, as well as individual's readiness to change [49, 126]. In adults with a BMI ≥ 25.0 kg/m^2 or a WC above cut-off points (see **Table 1.2**), a lifestyle modification program combining a reduction in daily energy intake (i.e., ↓ 500-1000 kcal/day), with a progressive increase in physical activity levels (i.e., when medical condition allows, progression from 30 min of moderate intensity physical activity 3-5 times/week to ≥ 60 min most days), as well as cognitive-behavior therapy is recommended [49, 126]. A pharmacological adjunct to lifestyle modifications is recommended when the weight loss (i.e., at least 0.5 kg/week) goal is not achieved by 3 to 6 months after lifestyle modification program initiation [49]. Finally, in adults with a BMI ≥ 35.0 kg/m^2 with medical comorbidities (i.e., hyperlipidemia, hypertension, IGT or T2D, etc.), bariatric surgery is considered if all others weight loss attempts have failed [49].

1.3.2 NUTRITION AND DIETARY RECOMMENDATIONS

Healthy nutrition is a key component of both weight and T2D management. Depending on weight reduction or maintenance goals, average daily TEI should be inferior or equal to average daily TEE.

Table 1.4 Macronutrient recommendations* for the management of type 2 diabetes.

Macronutrients	Percentage of daily TEI (%)	Specific recommendations
Carbohydrates	45 – 60	To prioritize: low glycemic index and high-fiber carbohydrate-containing foods. Daily fiber intake: 25 – 50 g/day Daily added sugar intake: ≤ 10% of TEI
Lipids	20 – 35	Daily SFAs intake: < 7% of TEI Daily MUFAs intake: ≤ 20% of TEI Daily PUFAs intake: ≤ 10% of TEI

Proteins	15 – 20	

*Recommendations of *Diabetes Canada* [125].

MUFAs: Monounsaturated fatty acids; **PUFAs:** Polyunsaturated fatty acids; **SFAs:** Saturated fatty acids; **T2D:** Type 2 diabetes; **TEI:** Total energy intake

Although the ideal macronutrient intake and distribution for adequate management of T2D may vary depending on the quality of the macronutrient source, the fixed goals, the individual's preferences and actual lifestyle, *Diabetes Canada* recommends a diet containing 45 to 60% of daily TEI in the form of carbohydrates, 20 to 35% in the form of fat, and 15 to 20% in the form of proteins [125]. *Diabetes Canada* further recommends prioritizing high-fiber foods, as well as reaching a daily intake of dietary fiber of 25 to 50g [125]. Ideally, the daily intake of saturated fatty acids (SFAs) should not exceed 7% of TEI, while the daily intake of MUFAs and PUFAs can reach up to 20% and 10% of TEI, respectively [125]. These dietary recommendations are summarized in **Table 1.4**

1.3.3 GLUCAGON-LIKE PEPTIDE-1: A THERAPEUTIC TARGET FOR TYPE 2 DIABETES MANAGEMENT?

Food intake has both acute and chronic physiological effects. Upon its entry in the GI tract, food is digested, and nutrients elicit the secretion of several peptide hormones. In this regard, the signaling pathways between the GI tract, the brain, and the pancreas are receiving increasing attention as potential targets for improving glycemic control in individuals with T2D as well as for weight management. This interest emerged, among others, from the discovery and characterization of incretin GI peptide hormones, in particular, the glucagon-like peptide-1 (GLP-1) [134–136]. Indeed, the positive influences of GLP-1 on many metabolic disturbances associated with T2D, as well as on crucial determinants of weight loss and maintenance, make it a therapeutic target with good potential. As a result, since 1980, over fifteen pharmaceutical

agents that are either mimicking GLP-1's effects or acting on GLP-1's metabolism have been developed and are increasingly used for the management of T2D and obesity [135–137].

In another yet similar vein, since the endogenous secretion of GLP-1 is mainly stimulated by the presence of nutrients in the GI tract and knowing that the chemical characteristics of those nutrients can influence the secretory response, there is an opportunity for identifying dietary interventions that could promote GLP-1's positive effects. The following sections defend the therapeutic superiority of GLP-1 as compared to another GI peptide, the glucose-stimulated insulinotropic peptide (GIP), detail its metabolism and actions in the pancreas and the central nervous system (CNS), and describe the effects of nutrients and specific foods on its endogenous secretion.

1.3.3.1 INCRETIN PEPTIDE HORMONES

Incretins are peptide hormones secreted by enteroendocrine cells (EECs) of the GI tract in response to oral food ingestion; they can explain part of the postprandial insulin secretion, a process which is referred to as the *"incretin effect"* [138–140]. The incretin effect is more specifically defined as the differential augmentation in insulin secretion observed after oral glucose intake, compared to intravenous glucose administration resulting in the same BG concentrations [138–140]. Among the vast array of GI peptide hormone secreted following food ingestion, only two – the GIP and GLP-1 – have significant incretin effects, namely [138, 139]. Together, these two incretins, account for up to 70% of the total postprandial insulin secretion [141].

Several differences in the physiologies of GIP and GLP-1 have been identified; these, along with changes occurring with the development of T2D, are summarized in **Table 1.5**. First, GIP and are secreted by different types of EECs and have different actions in the pancreas. GIP is secreted by K-cells which density is higher in the proximal part of the small intestine and which express receptors binding available carbohydrates and fatty acids [139, 140, 142]. GLP-1, on the other hand, is secreted by L-cells which density is higher in the distal part of the small intestine and the proximal portion of the colon, and which bind carbohydrates, fatty acids, small peptides,

and amino acids [139, 140, 143]. As for their actions in the pancreas, GLP-1's have been shown to be more numerous. While GIP's actions are limited to insulin and somatostatin secretion [142, 144–146], GLP-1 also acts on insulin synthesis, glucagon secretion, as well as β-cell's differentiation and apoptosis [141, 146–155].

Excess weight accumulation and metabolic changes occurring with the development of T2D are associated with a significantly reduced incretin effect. Interestingly, when assessed individually, GIP and GLP-1 appear to be both impacted differently by the development of T2D. This can be explained by the fact that the reduced incretin effect can arise from a decrease in incretin hormone secretion, a reduction in the sensitivity of target cells to their actions, or a combination of both. In this regard, studies have shown that GIP's secretion is unaffected by T2D, while the sensitivity of pancreatic cells to its effects are significantly reduced, nearly completely lost [156, 157]. Conversely, both GLP-1's fasting blood concentrations and postprandial secretion are reduced in individuals with T2D [158–160], while the sensitivity of target cells to its actions are mostly conserved, thus providing an opportunity for the development of pharmacological agents and other strategies for promoting GLP-1's actions [156, 157, 161].

1.3.3.2 GLUCAGON-LIKE PEPTIDE-1 SYNTHESIS, SECRETION AND METABOLISM

GLP-1 is a peptide hormone resulting from the differential processing of proglucagon. Proglucagon is a 160-amino acid inactive precursor of several peptide hormones, including glucagon, oxyntomodulin and GLP-1 [140, 162]. Proglucagon encoding gene is expressed in the intestine, the pancreas, as well as the CNS [140, 162]. Several studies have confirmed that the gene encoding proglucagon produces identical messenger ribonucleic acids (mRNAs) transcripts in the intestine, the pancreas and the CNS, but is translated and processed differently, thus producing different biologically active peptides depending of the expressing tissue [143, 163]. GLP-1 is principally produced and secreted by the enteroendocrine L-cells of the GI tract, and also to a lesser extent by the nucleus tractus solitarius (NTS) of the brainstem[164, 165]. In intestinal enteroendocrine L-cells, the production of GLP-1 appears to be attributed to the tissue-specific expression of the pro-hormone convertases 1 and 3 (PC1, PC3) which cleave

proglucagon [166]. The synthesis and differential processing of proglucagon is illustrated in **Figure 1.3**.

Table 1.5 Differences in the glucose-stimulated insulinotropic peptide (GIP) and glucagon-like peptide-1's (GLP-1) syntheses and secretions, effects on the pancreas and pancreatic secretions, and changes occurring with the development of type 2 diabetes.

	GIP	GLP-1
Synthesis and secretion		
- **Secretory EECs:**	*K-cells** [142]	*L-cells*** [143]
- **Nutrients ↑ secretion:** [139, 140]	*Available carbohydrates* *Fatty acids*	*Carbohydrates* *Fatty acids* *Peptides and amino acids*
- **Postprandial concentrations:**	↑ *10 – 20x* [142]	↑ *3 – 4x* [140, 143]
Effects on the pancreas and pancreatic secretions		
- **Insulin** (acute effects):	↑ *secretion* [142, 144, 145]	↑ *secretion* [141, 148]
- **Insulin** (chronic effects):	*Ø*	↑ *biosynthesis* [149]
- **Glucagon:**	*Ø direct effect* [146]	↓ *secretion* [146, 150, 151]
- **Somatostatin:**	↑ *secretion* [146]	↑ *secretion* [146]
- **Pancreatic β-cells:**	*Ø*	↑ *β-cells differentiation* [152–154] ↓ *β-cells apoptosis* [147, 153, 155] ↑ *β-cells mass* [152]
Changes occurring with T2D development		
- Secretion:	Ø [158]	↓ [158–160]
- Incretin effect:	*Neary lost* [156, 157]	*Preserved* [156, 157, 161]

* Higher density in the duodenum.

** Higher density in the distal part of the ileum and proximal part of the colon.

EECs: Enteroendocrine cells; **GIP:** Glucose-dependent insulinotropic peptide; **GLP-1:** Glucagon-like peptide-1. ↑ = increase; ↓ = decrease; **Ø** = no change/effect.

The EECs are a type of intestinal cell specialized in the production and the secretion of peptide hormones [167, 168]. Based on their structure, EECs can be subdivided into close- and

open-type cells [167, 168]. A unique characteristic of open-type EECs is that they possess microvilli that are in direct contact with nutrients present in GI lumen after food ingestion [167, 168]. On their microvilli, open-type EECs express various macronutrient-sensing G-protein coupled receptors (GPCRs) [167, 168]. In response to the binding of macronutrients to their GPCRs, open-type EECs secrete a wide range of peptide hormones, including GLP-1 [169, 170]. Based on their distribution throughout the GI tract, their GPCRs expression and their secretory profile, several types of open-type EECs have been identified [169, 170]. Those include G-cell, K-cells, I-cells, as well as L-cells. The latter are producing and secreting GLP-1 [169, 170].

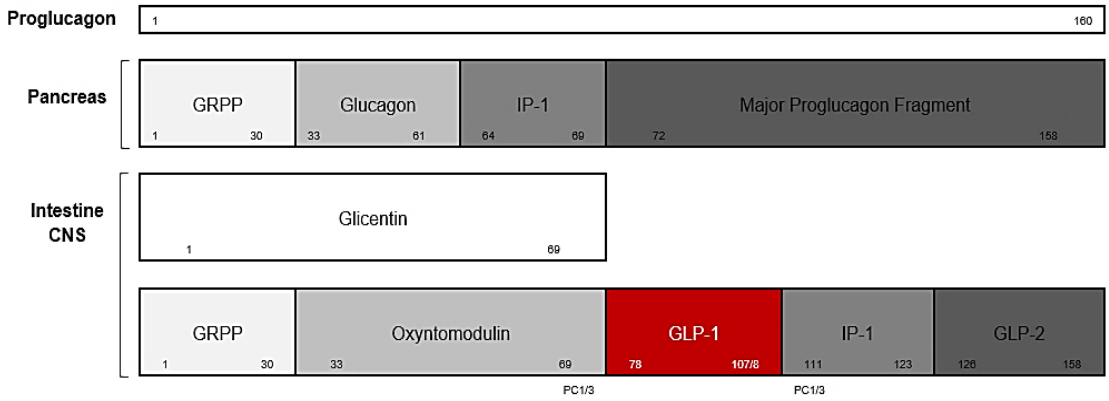


Figure 1.3 Differential processing of proglucagon in the pancreas, the intestine and the central nervous system.

The proglucagon gene is expressed in pancreas, the CNS and the intestine. The proglucagon encoding gene produces identical mRNAs in all three locations, but is translated and processed differently, thus producing different biologically active peptides depending of the expressing tissue. In intestinal enteroendocrine L-cells, the production of GLP-1 is attributed to the tissue-specific expression of the PC1 and PC3.

CNS: Central nervous system; **GLP-1:** Glucagon-like peptide-1; **GLP-2:** Glucagon-like peptide-2; **GRPP:** Glicentin-related pancreatic polypeptide; **IP-1**: Intervening peptide 1; **IP-2:** intervening peptide-2; **mRNAs:** messenger ribonucleic acids; **PC1:** Pro-hormone convertase 1; **PC3:** Pro-hormone convertase 3.

Enteroendocrine L-cells are expressed over a large portion of the GI tract, starting in the proximal small intestine and progressively increasing in density throughout the small intestine and the colon [169, 170]. Thus, the contact of L-cells with macronutrients present in the GI lumen also increases progressively as they move down the GI tract. Accordingly, GLP-1 exhibits a two-phase release profile: 1) an initial phase, which is thought to represent the release of GLP-1 from the

proximal small intestine, and 2) a second phase, which represents GLP-1 release in response to the arrival of macronutrients in the distal part of the small intestine and the colon [171]. The binding of macronutrients to L-cells GPCRs leads to a rise in intracellular cyclic adenosine monophosphate (cAMP) levels, followed by an increase in intracellular Ca^{2+} levels, which ultimately triggers GLP-1 exocytosis from secretory granules [140]. GLP-1 then diffuses into nearby capillaries and reaches the systemic circulation through the portal vein [140]. In humans, fasting plasmatic levels of GLP-1 range between 5 pmol/L and 15 pmol/L, and increase two- to four-folds after a meal, depending on its energy and macronutrient content [140]. More specifically, GLP-1 blood concentrations increase within 15 min after food ingestion, and peak at ~40 min, before reaching a plateau [140]. GLP-1 is highly susceptible to the catalytic activity of the enzyme dipeptidyl peptidase IV (DPP-IV), which cleaves the two NH_2-terminal amino acids of the active forms of GLP-1 (i.e., 7-36 amide, 7-37 amide), leading to the production of the biologically inactive forms of GLP-1 (i.e., 9-36 amide, 9-37 amide) [172–174]. This results in a half-life of GLP-1 in systemic circulation that is of approximately 1 to 2 min [173, 174]. Animal and in vitro studies have shown that less than 25% of the newly secreted GLP-1 reaches the liver in its active form [173, 174]. Further catalytic activity takes place in the liver, resulting in only ~10-15% of the newly secreted GLP-1 reaching the systemic circulation in its active form [173, 174]. GLP-1 metabolism is illustrated in **Figure 1.4**.

1.3.3.3 GLUCAGON-LIKE PEPTIDE-1 ACTION

Upon its secretion from enteroendocrine L-cells, GLP-1 exerts its actions by directly interacting with its receptors (endocrine pathway), as well as by stimulating the vagus nerve (neural pathway) [140, 162, 175]. The GLP-1Rs are GPCR type and are highly expressed by the pancreatic β-cells, as well as on pancreatic α-cells and several areas of the CNS [164, 165, 176–179]. Furthermore, GLP-1Rs are expressed in the nodose ganglion of the vagus nerve, which conveys afferent projections to GLP-1-expressing neurons of the NTS [178].

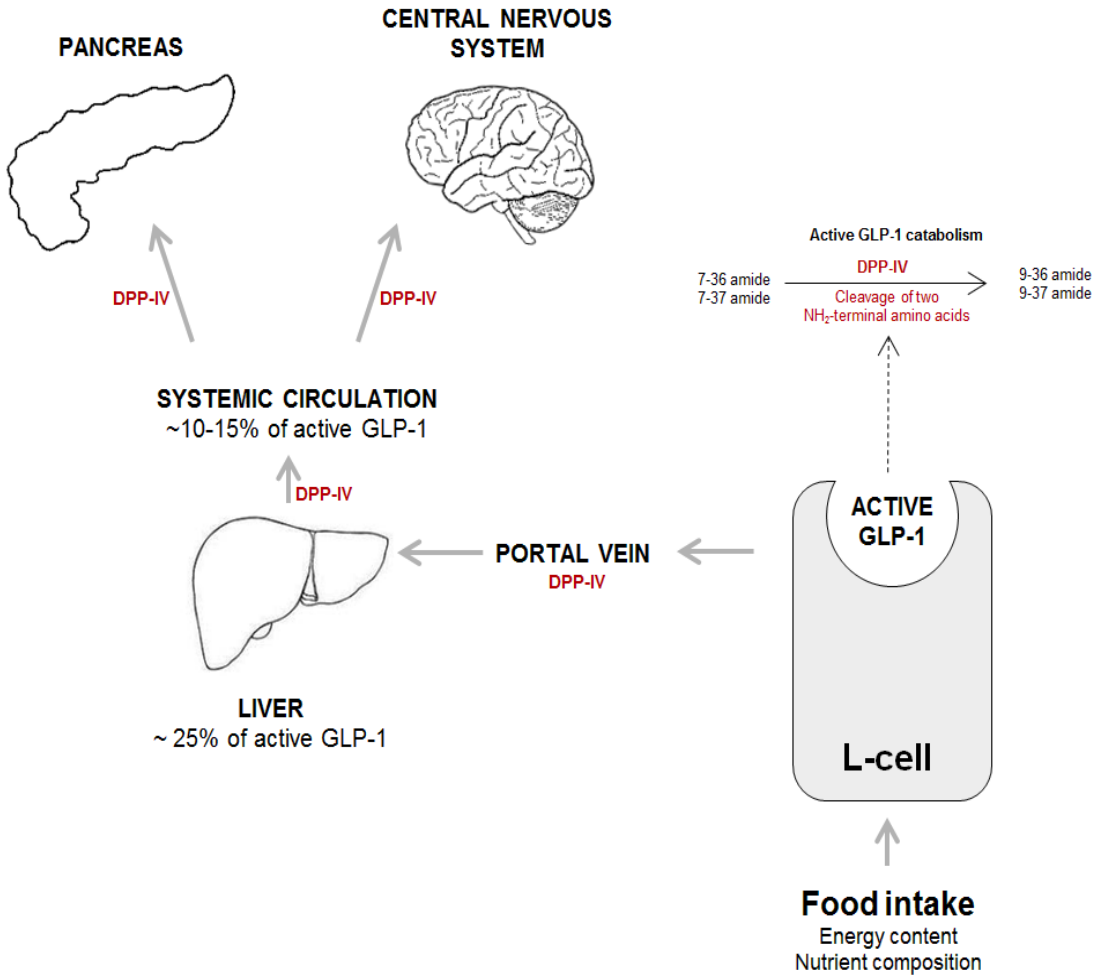


Figure 1.4 Glucagon-like peptide-1 metabolism.

GLP-1 half-life is of approximately 1 to 2 min. Less than 25% of the newly secreted GLP-1 reaches the liver in its active form where further catalytic activity takes place. This leaves only ~10-15% of the newly secreted GLP-1 reaching the systemic circulation in its active form.

DPP-IV: Dipeptidyl peptidase IV; **GLP-1:** Glucagon-like peptide-1.

1.3.3.3.1 GLUCAGON-LIKE PEPTIDE-1 ACTION IN THE PANCREAS

One of the best-known and most important effects of GLP-1 is its ability to stimulate insulin secretion in response to carbohydrate consumption [141, 148, 180, 181]. In this regard, GLP-1 appears to be responsible for nearly half of the total insulin secretion occurring after a meal [138]. Upon food ingestion, GLP-1 is released from L-cells and increases intracellular Ca^{2+} concentrations in β-cells, thus promoting insulin exocytosis from secretory granules [141, 148].

GLP-1 has also been shown to promote insulin gene transcription and biosynthesis [149]. GLP-1 appears to, at least partly, exert its effects on pancreatic β-cells through the endocrine pathway, by directly interacting with its receptors. Indeed, the inhibition of the GLP-1Rs of pancreatic β-cells in rodents and humans resulted in a significant inhibition of insulin secretion, as well as in an impaired glucose tolerance [180, 181]. The glucose-lowering effects of GLP-1 are not solely related to its insulinotropic effect, but also to its strong inhibition of glucagon secretion from pancreatic α-cells [139, 140]. This effect appears to be partly mediated by the increased insulin and somatostatin secretion from pancreatic islets (indirect effect), as well as by GLP-1 interaction with its receptors on pancreatic α-cells (direct effect) [146, 150, 151]. In addition to its acute effects, GLP-1 exhibits trophic effects on pancreatic β-cells as its intravenous infusion has been associated with increased markers of proliferation, as well as decreased markers of apoptosis, effects which promoted β-cell growth [147, 152, 153, 155].

1.3.3.3.2 GLUCAGON-LIKE PEPTIDE-1 ACTION IN THE CENTRAL NERVOUS SYSTEM

GLP-1 plays a role in both homeostatic (related to energy status) and non-homeostatic (related to reward and motivation) regulation of food intake, which occur in different areas of the CNS [182, 183]. The homeostatic regulation of food intake is mainly taking place in the hypothalamus and the NTS of the brainstem, which receive, convey and integrate numerous peripheral signals [182, 183]. The hypothalamus contains several interconnected nuclei, including the arcuate nucleus (ARC), the paraventricular nucleus (PVN), as well as the dorso-medial nucleus (DMH) [182, 183]. Due to its anatomical position, the ARC plays a critical role in conveying peripheral information related to energy and nutrient status to other structures of the SNC. Indeed, the ARC is situated at the bottom of the hypothalamus, where the blood-brain barrier has a higher permeability, and thus, it is likely exposed to circulating factors reaching the CNS [182]. The ARC contains two distinct populations of neurons: 1) the orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) expressing neurons, and 2) the anorexigenic pro-opiomelanocortine (POMC), and cocaine and amphetamine-regulated transcript (CART) expressing neurons [182, 183]. Additionally, POMC is also a precursor of the α-melanocyte

stimulating hormone(α-MSH), another potent anorexigenic neuropeptide [182, 183]. Upon release, POMC and α-MSH activate neurons of the PVN, which inhibits food intake [182, 183]. By inhibiting the PVN neurons' activation, NPY and AgRP have the stimulate food intake [182, 183]. Opposite to the PVN, DMH neurons are activated by NPY and AgRP, which promotes food intake, and are inhibited by POMC and α-MSH, which reduces food intake [182, 183].

The GLP-1Rs are widely expressed in the hypothalamus, with the highest expression in the POMC neurons, in the PVN neurons, and to a lesser extent in the DMH neurons [164, 165, 176–179]. A small quantity of GLP-1 appears to diffuse through the blood-brain barrier and directly bind to its receptors on POMC neurons, as well as on the NTS neurons, which share dense connections with neurons of the ARC [184]. However, endogenous GLP-1 exerts its action on the CNS mainly by indirectly stimulating neurons of the NTS and the ARC via the activation of vagal afferent neurons [185]. The GLP-1Rs have been identified on neurons of the nodose ganglion of the vagus nerve [178, 186, 187]. The implication of the vagal pathway in the regulation of food intake by GLP-1 has been confirmed in rats, where vagal deafferentation decreased the effects of intraperitoneally administered GLP-1 [188]. In rodents, acute intraperitoneal, subcutaneous or intravenous administration of GLP-1 and GLP-1 analogs reduce meal size, as well as cumulative food and energy intake [189–194]. Similarly, in healthy adults, as well as adults with obesity or T2D, acute intravenous administration of GLP-1 and GLP-1 analogs resulted in a decrease in appetite, hunger and food intake, as well as increased fullness and satiety sensations [195–200].

In addition to physiological energy needs, food intake is driven by non-homeostatic central pathways involved in reward processing and reward-motivated behavior [201, 202]. The palatability of food is a crucial determinant of the decision to eat, as a result highly palatable food can trigger food intake in the absence of physiological energy needs [201, 202]. Central structures, such as the orbitofrontal cortex, the insula, the amygdala and the striatum play an important role in the processing and evaluation of food cues [203]. Increased activation of those areas of the CNS in response to visual and olfactory food cues (referred as "anticipatory food

reward") is associated with increased craving for highly palatable foods [204, 205]. Furthermore, upon food ingestion, dopaminergic neurons project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and other forebrain areas [201, 202]. Dopamine release in those areas of the brain is well correlated with meal pleasantness in healthy individuals [206]. Blunted activation of those areas of the brain in response to food consumption (referred as "consummatory food reward") is associated with compensatory overeating [203–205, 207, 208]. The GLP-1Rs have been identified in areas of the brain involved in anticipatory and consummatory food reward processing, and neurons of the NTS also share dense neuronal connection with those areas [209, 210]. Exogenous administration GLP-1 and GLP-1 analogs, have been associated with decreased anticipatory food reward, increased consummatory food reward and decreased intake of hyperpalatable foods – which are typically high in energy, lipids, simple carbohydrates – in humans and rodents [203, 207, 208, 211–214].

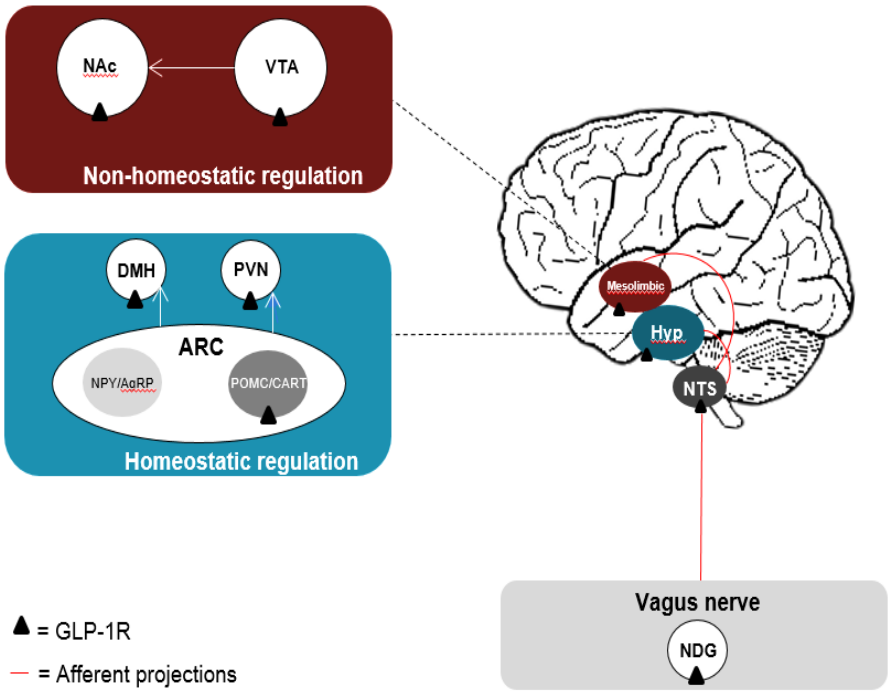


Figure 1.5 Routes of action of glucagon-like peptide-1 in the central nervous system.

The GLP-1Rs are widely expressed in the hypothalamus, with the highest expression in the POMC and PVN, and to a lesser extent in the DMH neurons. A small quantity of GLP-1 appears to diffuse through the blood-brain barrier and directly binds to its receptors on POMC neurons. Nonetheless, endogenous GLP-1 exerts its action on the CNS mainly by indirectly stimulating neurons of the NTS and the ARC via the activation of vagal afferent neurons. The GLP-1Rs have

been identified on neurons of the nodose ganglion of the vagus nerve. The implication of the vagal pathway in the regulation of food intake by GLP-1 has been confirmed in rats, where vagal deafferentation decreased the effects of intraperitoneally administered GLP-1.

AgRP: Agouti-related peptide; **ARC:** Arcuate nucleus; **CART:** Cocaine and amphetamine-regulated transcript; **DMN:** Dorso-medial nucleus; **Hyp:** Hypothalamus; **NAc:** Nucleus accumbens; **NDG:** Nodose ganglion; **NPY:** Neuropeptide Y; **NTS:** Nucleus tractus solitarius; **PVN:** Paraventricular nucleus; **VTA:** Ventral tegmental area.

1.3.3.4 GLUCAGON-LIKE PEPTIDE-1 SECRETION MODULATION BY NUTRIENTS AND SINGLE-NUTRIENT FOODS

According to the dietary profile of the food ingested, the content of the GI lumen varies considerably between individuals, as well as within the same individual over the course of the day. Hence, EECs require several specific GPCRs to appropriately detect the macronutrient content of the GI lumen and generate endocrine responses. In this regard, L-cells express GPCRs that binds several products of food breakdown, including monosaccharides, short-chain fatty acids, medium and long-chain fatty acids, as well as amino acids and peptides. There is some evidence suggesting that the macronutrient composition of the diet may directly influence GLP-1 secretion. The following sections will describe macronutrient sensing mechanisms, as well the effects of macronutrients on GLP-1 secretion.

1.3.3.4.1 CARBOHYDRATES

Carbohydrates are the primary source of energy in the diet and can be divided into several categories depending on their characteristics [215]. Chemically, carbohydrates are divided into three main groups depending on their degree of polymerization [215]. The most complex carbohydrates are polysaccharides (≥ 10 monosaccharides), followed by oligosaccharides (3-9 monosaccharides), and by simple sugars (≤ 2 monosaccharides) [215]. Polysaccharides and oligosaccharides can be further subdivided into digestible and non-digestible carbohydrates [215]. Upon ingestion, digestible carbohydrates undergo enzymatic degradation and are absorbed in the form of glucose, and to a lesser extent in the form of galactose and fructose. In addition to being broken down to monosaccharides, some carbohydrates, namely the non-digestible type, escape digestion and reach the distal part of the small intestine and the colon. The colon is a site with high anaerobic bacteria activity, where

these undigested carbohydrates undergo fermentation, leading, depending on their type, to the production of various amounts of short-chain fatty acids (SCFAs) [216–218]. SCFAs are carboxylic acids that contain fewer than 6 carbons, the most abundant ones being acetate, butyrate and propionate [219]. In humans, SCFAs concentrations range from ~130 mmol/L in the caecum to ~80 mmol/L in the ascending colon. Acetate appears to be the most abounded SCFA in the colon, followed by propionate and butyrate, with an overall colonic molar ratio 50-60:15-20:10-20, respectively [219, 220].

Glucose absorption by the enterocytes, as well as its stimulation of GLP-1 secretion from enteroendocrine L-cells appears to be mediated by the sodium-glucose transporter-1 (SGLT-1), a membrane transport protein [8, 221–225]. Moriya and colleagues investigated the mechanisms underlying glucose-stimulated GLP-1 secretion by administering glucose and Phloritzine, a competitive inhibitor of SGLT-1, in the small intestine of mice [221]. While glucose administration alone significantly increased circulating GLP-1, co-administration of glucose and Phloritzine blocked first-phase glucose-induced GLP-1 secretion [221]. Similarly, compared to controls, SGLT-1 knockout mice had decreased first-phase GLP-1 secretion and developed glucose and galactose malabsorption, which testifies of the importance of SGLT-1 in GI absorption of glucose, as well as galactose [222]. An ulterior study investigated the prolonged effect of SGLT-1 pharmaceutical inhibition in mice [223]. While confirming an inhibition of first-phase GLP-1 secretion and an increase in luminal glucose concentrations, it was found that the second-phase GLP-1 secretion was significantly increased, and that BG excursions were decreased over a 6-hour postprandial period [223]. These results were confirmed in two clinical studies conducted in healthy adults, as well as in adults with T2D [224, 225]. Taken together, results from these studies strongly suggest that SGLT-1 plays an important role in luminal glucose absorption and glucose-mediated GLP-1 secretion. Furthermore, the increase in second-phase GLP-1 secretion that was observed in three studies suggests that SGLT-1 inhibition enhances another mechanism that promotes GLP-1 secretion from the distal part of GI tract. In this regard, it has been proposed that the inhibition of glucose and galactose absorption in the small intestine increases the amount of undigested carbohydrates that reach the colon, which could potentially increase the production

of SCFAs. Fermentable dietary fiber, as well as its metabolites the SCFAs, seem to promote GLP-1 secretion by L-cells by interacting with two GPCRs. Indeed, enteroendocrine L-cells have been shown to express the free fatty acids receptor 2 and 3 (FFAR2, FFAR3), two receptors that bind to SCFAs [226–232]. An in vitro study showed that propionate was the most potent agonist for both FFAR2 and FFAR3, and that acetate was more selective for FFAR2, and butyrate more active on FFAR3 [228]. In colonic cell cultures, physiological concentrations of acetate, butyrate and propionate were shown to stimulate GLP-1 secretion [233]. The implication of FFAR2 and FFAR3 in the SCFA-induced GLP-1 secretion was confirmed, as this effect was lost in FFAR2 and FFAR3 knockout cells [233]. Similar results were found in vivo, where the colonic administration of propionate significantly increased GLP-1 secretion in rodents [233]. This effect was lost in FFAR-2 knockout animals [234]. In adults with overweight or obesity, acute targeted delivery of propionate in the colon stimulated postprandial GLP-1 secretion and reduced food intake [235]. Furthermore, the long-term delivery of propionate in the colon significantly reduced body weight, as well as abdominal fat and lipid accumulation in hepatocytes [235]. In addition to the direct effect of SCFAs, the effects of diets rich in fermentable dietary fiber – which are expected to promote the production of SCFAs in the colon – have been investigated in animal models and humans. In this regard, compared to a standard control diet, the consumption of a diet enriched in fermentable fiber for 35 days increased GLP-1 concentrations in the proximal colon and the portal vein of rodents, effects which were associated with an increased expression of proglucagon in the colon [236]. Similar results were found in streptozotocin-treated diabetic rats, where the consumption of a diet enriched in fermentable fiber for 6 weeks increased GLP-1 concentrations in the colon and the portal vein, as well as insulin concentrations in the pancreas and the portal vein [237]. These effects were associated with an increased expression of proglucagon and pro-hormone convertase 1 (PC1) in the colon [237]. To determine the importance of GLP-1Rs-dependent mechanisms for the effects of fermentable fiber on insulin production, the effects of a diet rich in fermentable fiber have been compared with those of the same diet combined with a GLP-1R antagonist as well as those of a GLP-1R knockout group of diabetic rats [238]. The group of rats receiving the diet rich in fermentable fiber only exhibited

decreased fasting BG concentration, improved glucose tolerance, as well as an enhanced glucose-stimulated insulin secretion [238]. These effects were significantly diminished by the GLP-1R antagonist and were abolished in the GLP-1R knockout group of rats [238]. In healthy humans, a pilot study showed that the daily supplementation with 16 g of fermentable fiber for a two-week period significantly increased postprandial satiety, and decreased hunger, as well as prospective food consumption [239]. GLP-1 blood concentrations were not assessed in this study [240]. In adults with IR, the daily consumption of a high wheat-fiber cereal (test group, 24g/day of fiber from the cereal), compared to a low-fiber cereal (control group, 0.5g/day of fiber from the cereal) for one year, significantly increased acetate and butyrate production, as well as GLP-1 blood concentrations [241]. More specifically, at 9 months into the intervention, acetate and butyrate blood concentrations were significantly higher in the test group [241]. Furthermore, at the end of the one-year intervention, fasting and postprandial GLP-1 blood concentrations were significantly increased in the test group compared to baseline values, as well as compared to the control group [241]. Together, these results provide evidence for the beneficial effect of dietary fiber, as well as their metabolites the SCFAs, on BG, insulin secretion, appetite sensations, food intake, as well as body weight management. Results from these studies also suggest that one possible mechanism by with fiber and SCFAs could exert these effects is by promoting GLP-1 secretion form EECs via their interaction with the FFAR2 and FFAR3.

Table 1.5 Acute[a] and chronic[b] effects of non-digestible carbohydrates on glucagon-like peptide-1 (GLP-1) secretion and associated outcomes.

Studies	Experimental model	Dietary intervention	Main outcomes measured
Cani 2005a [240]	〉Male Wistar rats	Oligofructose (10% of diet[c])	↑ GLP-1 concentrations in the proximal and medial colon ↑ Proglucagon mRNA concentrations in the caecum and proximal colon ↓ Triglyceride blood and hepatic concentrations ↓ Food and energy intake ↓ Body weight gain
Cani 2005b [237]	〉Streptozotocin-treated diabetic rats	Oligofructose (10% of diet[c])	↑ Proglucagon mRNA concentrations in the proximal colon ↑ Pro-hormone convertase 1 mRNA concentrations in the proximal colon ↑ GLP-1 concentrations in the portal vein ↑ Glucose tolerance ↑ Insulin and C-peptide blood concentrations ↑ Pancreatic β-cell mass ↓ Food and energy intake
Cani 2005c [239]	〉Healthy men and women	Oligofructose (16g/day)	↓ Energy intake over 24 hours ↑ Satiety ↓ Hunger ↓ Prospective food consumption
Cani 2006a [238]	〉Male C57BL/6J mice with high-fat feeding-induced diabetes	Oligofructose (10% of diet[c])	↑ GLP-1 concentrations in the proximal colon ↑ GLP-1 concentrations in the portal vein ↑ Proglucagon mRNA concentrations in the proximal colon ↑ Blood and pancreatic insulin concentrations ↓ Fasting and postprandial blood glucose concentrations

Cani 2007 [242]	〉Male Wistar rats	Oligofructose (10% of diet[c])	↑ GLP-1 concentrations in the portal vein and proximal colon ↑ Proglucagon mRNA concentrations in the proximal colon ↑ L-cell number in the proximal colon ↑ Neurogenin-3 and Neuro-D mRNA concentrations in the proximal colon ↓ Food and energy intake ↓ Body weight gain
Zhou 2008 [243]	〉Sprague-Dawley rats 〉Streptozotocin-treated C57BL/6J mice	Resistant starch (53% of diet[c])	↑ GLP-1 blood concentrations ↑ PYY blood concentrations ↓ Variation in blood glucose and insulin concentrations ↑ Proglucagon and PYY colonic mRNA concentrations ↑ Glucose tolerance in diabetic mice
Olli 2015 [244]	〉Men and women with obesity (n = 18)	Polydextrose (15 g) as part of a high-fat meal	↑ GLP-1 plasma concentrations ↓ Lactic acid plasma concentrations ↓ Hunger ↑ Satisfaction
Zhao 2018 [245]	〉Men and women with T2D 〉Germ-free C57BL/6J mice	Dietary recommendations for a high-fiber diet + arcabose	↓ Fasting blood glucose concentrations Changes in gut microbiota ↑ Fecal butyric acid concentrations* ↓ Fecal pH* ↑ Postprandial GLP-1 blood concentrations* ↑ Fasting PYY blood concentrations*

GLP-1: Glucagon-like peptide-1; **mRNA:** messenger ribonucleic acid; **PYY:** Peptide tyrosine-tyrosine.

* Changes observed following the transplant of the post-intervention microbiota in germ-free mice

[a] 6 hours

[b] 10 days - 1 year interventions

[c] weight : weight proportion

1.3.3.4.2 LIPIDS

Similar to carbohydrates, lipids can be divided into several categories based on their chemical characteristics. Dietary lipids encompass triglycerides (TG), phospholipids, as well as sterols, such as cholesterol [246]. The majority of dietary lipids are TG, which are composed of one glycerol molecule, and three fatty acids [246]. Upon ingestion, TG undergo hydrolysis by lipases and are absorbed by enterocytes in the form of glycerol and free fatty acids (FFAs) [246]. FFAs can be subdivided in several categories based on their length, as well as their degree of saturation [246]. Saturated FFAs acids carry the maximum possible number of hydrogen atoms, and do not contain any double bonds [246]. Inversely, unsaturated FFAs lack ≥ 2 hydrogen atoms compared to the maximum number that can be carried, and contain at least one double bond between carbon atoms [246]. Unsaturated FFAs can be further subdivided into MUFAs and PUFAs. MUFAs lack 2 hydrogen atoms and contain only one double bond [246]. Oleic acid is the predominant MUFA in the diet – it is contained in olive oil, a variety of nuts and seeds, avocados, as well as eggs, poultry and meat [246]. Polyunsaturated fatty acids lack ≥ 4 hydrogen atoms and contain at least two double bounds [246]. The predominant forms of PUFAs in the diet are omega-6 (e.g., linoleic acid) and omega-3 (e.g., α-linolenic acid) FFAs [246]. Saturated, as well as MUFAs and PUFAs, can have various chain lengths, and are classified as either medium- (i.e., 6 to 10 carbon atoms) chain fatty acids (MCFAs) or long- (i.e., 12 to 24 carbon atoms) chain fatty acids (LCFAs) [246].

FFAs are potent stimulators of GLP-1 release through interactions with the free fatty acids receptors 1 and 4 (FFAR1, FFAR4) [256, 257]. More specifically, the secretion of GLP-1 has been shown to be significantly increased by unsaturated MCFAs and LCFAs. Thompsen and colleagues (1999, 2003) were the first to assess GLP-1 responses following an olive oil containing meal in healthy adults, as well as adults with a diagnosis of T2D [247, 248]. Compared with a meal containing butter, which is high in SFAs, the ingestion of the olive oil containing meal resulted in significantly higher GLP-1 blood concentrations [247, 248]. No significant differences in BG, nor insulin blood concentrations were observed [247, 248]. In a subsequent study

Table 1.6 Acute[a] and chronic[b] effects of monounsaturated fatty acids (MUFAs) and omega-3 polyunsaturated fatty acids (PUFAs) on glucagon-like peptide-1 (GLP-1) secretion and associated outcomes.

Studies	Experimental model	Dietary intervention	Main outcomes measured
Thomsen 1999 [247]	〉Healthy men and women	MUFAs from olive oil[a] (80g)	↑ GLP-1 blood concentrations ↑ GIP blood concentrations
Thomsen 2003 [248]	〉Men and women with T2D	MUFAs from olive oil[a] (80g)	↑ GLP-1 blood concentrations ↓ Triglyceride blood concentrations ↑ High-density lipoprotein cholesterol blood concentrations
Hirasawa 2005 [249]	〉Male C57/B6 rats	α-linolenic acid (0.1 µmol)[a]	↑ GLP-1 blood concentrations ↑ Insulin blood concentrations
Prieto 2005 [250]	〉Wistar rats	MUFAs from olive oil[b,c]	↑ GLP-1 blood concentrations ↑ Glucose-stimulated insulin secretion ↑ Glucose tolerance
Cancelas 2006 [251]	〉Streptozotocin-treated diabetic rats	MUFAs from olive oil[b,c]	↑ GLP-1 postprandial secretion ↑ Insulin sensitivity ↓ Weight gain
Adachi 2006 [252]	〉Male C57BL/6J mice 〉Diabetic male NSY mice 〉C3H/He mice	α-linolenic acid (0.3 µmol)[a]	↑ GLP-1 blood concentrations ↑ Insulin blood concentrations ↓ Blood glucose concentrations
Paniagua 2007 [253]	〉Insulin resistant men and women	MUFAs from an olive-oil containing Mediterranean diet (23% of total energy intake)[b]	↑ Postprandial GLP-1 concentrations ↑ Insulin sensitivity ↓ Postprandial insulin secretion ↓ Fasting and postprandial blood glucose concentrations
Tanaka	〉Male Wistar rats	α-linolenic acid	↑ GLP-1 blood concentrations

2008 [254]		(3 µmol)[a,b]	↑ pancreatic β-cell number and mass
Cheshmehkani 2015 [255]	〉Male Sprague-Dawley rats	Fish or flaxseed oil[b,d] (10% of diet)	↑ FFAR4 expression in the colon ↓ TNFα blood concentrations

FFAR4: Free fatty acid receptor 4; **GIP:** Glucose insulinotropic peptide; **GLP-1:** Glucagon-like peptide-1; **MUFAs:** Monounsaturated fatty acids; **SCFAs:** Short-chain fatty acids; **TNFα:** tumour necrosis factor-α.

[a] Acute effect (5 minutes post-consumption)

[b] Chronic effect (28 to 50 days of consumption)

[c] Specific MUFA content not known

[d] weight : weight proportion

conducted in rodents, the prolonged administration (i.e., 50 days) of an olive oil-enriched diet resulted in an increased GLP-1 secretion, which also coincided with a higher glucose-stimulated insulin secretion, as well as an improved glucose tolerance by the 36th day of the intervention [250]. In humans with obesity or T2D, ingestion of a Mediterranean diet rich in MUFAs from olive oil for 28 days resulted in significantly higher GLP-1 blood concentrations, as well in decreased fasting BG concentration and HOMA-IR index (improved sensitivity to insulin), when compared to a diet rich in SFAs or carbohydrates [253]. Some studies have also shown that the acute ingestion, as well as the colonic administration of α-linolenic acid, increased GLP-1 blood concentrations and insulin secretion in rodents and in vitro [249, 252]. Similarly, while also resulting in increased GLP-1 blood concentrations, long-term administration of α-linolenic acid has been shown to increase β-cells proliferation in rodents [254]. As GLP-1 has been shown to decrease apoptosis, as well as to increase neogenesis of β-cells, it has been hypothesized that the increased β-cells proliferation was mediated by the increase in GLP-1 concentrations induced by α-linolenic acid [254]. A recent study showed that fish oil and flaxseed oil, which are rich in α-linolenic acid, increased FFAR4 expression in rodent colon [255]. Taken together, the results of these studies suggest that diets that have similar energy content but are richer in MUFAs or omega-3 PUFAs than in SFAs, could increase GLP-1 secretion from EECs, which may be a mediator for the increase in insulin secretion, β-cell proliferation, as well as the improved glucose tolerance observed in animal models and in humans.

1.3.3.4.3 PROTEINS

Dietary protein is generally described as the most satiating nutrient, an effect which appears to be partly mediated by the stimulation of anorexigenic GI peptides secretion, including that of GLP-1 [258–260]. Upon ingestion, proteins are broken down by acid hydrolysis and proteases to produce peptones, tripeptides, dipeptides and single amino acids. Products of protein breakdown have been shown to stimulate GLP-1 secretion by binding to the calcium-sensing receptor (CaSR) and the class C, group 6, subtype A GPCR (GPCR-C6A). The CaSR binds to peptones, dipeptides and amino acids, with a higher affinity for aromatic amino acids

[261–268]. Conversely, GPCR-C6A preferentially binds to the basic amino acids, L-arginine, L-lysine, and L-ornithine, and do not bind to aromatic amino acids [269].

1.3.3.5 GLUCAGON-LIKE PEPTIDE-1 SECRETION MODULATION BY MIXED-NUTRIENT FOOD

In contrast with single nutrients and single-nutrient foods (e.g., oil), more complex foods containing a mix of nutrients are more representative of what humans consume and could allow targeting a combination of enteroendocrine pathways that would synergistically enhance GLP-1 secretion. Regarding T2D management, clinical guidelines recommend carbohydrate intake from high-fiber foods such as vegetables, fruit, legumes and whole grains, while limiting SFAs intake and promoting that of MUFAs and omega-3 PUFAs [125], all of which have been associated to different extents with an increased GLP-1 secretion.

Some experimental studies conducted with healthy individuals have examined the effects of several specific foods on glycemic response, subjective appetite sensations as well as energy intake at a subsequent meal [153–166]. The main findings of these studies are summarized in **Table 1.7**. Several researchers have investigated the effects of high-fiber grain products, which could enhance GLP-1 secretion by binding to SGLT-1, FFAR2 and FFAR3. In this regard, two recent studies compared appetite responses after isoenergetic breakfast meals containing ready-to-eat breakfast cereals (low-fiber) or oatmeal (high-fiber) among healthy young adults [270, 271]. Compared to ready-to-eat breakfast cereals, oatmeal (66.8 g) increased fullness, and reduced hunger, desire to eat, as well as subjective prospective food intake [270, 271]. Furthermore, oatmeal decreased energy intake at the following meal [271]. Likewise, in adults with insulin resistance, daily consumption of a high wheat-fiber breakfast cereal (test group, 24 g/day of fiber from the cereal) for one year, significantly increased colonic SCFAs production, as well as GLP-1 blood concentrations compared to low-fiber breakfast cereals (control group, 0.5 g/day of fiber from the cereal) [241]. More specifically, at 9 months into the intervention, acetate and butyrate plasma concentrations were already significantly higher in the test group [241].

The addition of foods with a high protein, MUFAs and fiber content, such as almonds (30.0 to 90.0 g) or pistachios (28.0 to 85.0 g) to a high-carbohydrate meal has also been shown to improve postprandial glycemic responses in a dose-dependent manner [272–278]. Jenkins and colleagues (2006, 2008) also found a decrease in insulin secretion in healthy adults and adults with hyperlipidemia following acute and prolonged almond consumption [272, 274]. Similarly, daily intake of 50.0 g of pistachios for 12 weeks decreased C-reactive protein blood concentrations, systolic blood pressure, and body mass index in adults with T2D [278]. Only two of these studies assessed GLP-1 blood concentrations [275, 277]. Mori et al. (2011) found no significant differences in GLP-1 blood concentrations following the addition of 42.5 g of almonds to a carbohydrate-containing meal, which could be due to the small sample size of the study [275]. Indeed, with a larger sample size, Kendall et al. (2014) found higher GLP-1 and glucose insulinotropic peptide blood concentrations following the addition of 85.0 g of pistachios to a carbohydrate-containing meal in adults with metabolic syndrome [277].

Consumption of eggs (2 to 3), which are high in protein and also contain MUFAs, for breakfast or lunch, has been shown to improve subjective postprandial appetite sensations [279–282]. Furthermore, when compared to a bagel breakfast, consumption of a breakfast containing eggs (3) in adult men was associated with lower postprandial blood glucose concentrations, decreased hunger, and reduced energy intake in the next 24 hours [280]. Men also reported higher subjective satisfaction after eating eggs [280]. While GLP-1 blood concentrations were not measured in these studies, Liu and al. (2015) found a significant increase in postprandial blood concentrations of PYY in adolescents following ingestion of an egg-containing breakfast compared to an isocaloric bagel breakfast [282]. Since GLP-1 and PYY are co-released from L-cells [284], it is plausible that eggs may also promote postprandial GLP-1 secretion. One study also showed that adding avocado (50 to 90 g), which is high in fiber and MUFAs, to a high-carbohydrate isocaloric meal improved subjective satiety sensation and satisfaction [283].

Table 1.7 Summary of experimental studies assessing the effects of mixed-nutrient foods on glucagon-like peptide-1 (GLP-1) secretion and associated outcomes.

Studies	Subjects		Dietary intervention		Main outcomes measured
	N	Characteristics	Food	Duration	
Rebello 2013 [270]	48	〉Healthy[a]	Oatmeal[b] (66.8 g)	4h	↑ Fullness ↓ Hunger ↓ Desire to eat ↓ Prospective food consumption
Rebello 2016 [271]	48	〉Healthy	Oatmeal[b] (66.8 g)	4h	↑ Fullness ↓ Hunger ↓ Desire to eat ↓ Prospective food consumption ↓ Energy intake at the next meal
Jenkins 2006 [272]	15	〉Healthy	Raw almonds[b] (60.0 g)	4h	↓ Blood glucose postprandial concentrations ↓ Insulin postprandial blood concentrations ↓ Oxydative damage to proteins measured in blood serum
Josse 2007 [273]	9	〉Healthy	Raw almonds[c] (30, 60 and 90 g)	4h	↓ Blood glucose postprandial concentrations[d]
Jenkins 2008 [274]	27	〉Hyperlipidemia	Raw almonds- (37.0 and 73.0 g)	1 month	↓ 24-hour insulin secretion
Mori 2011 [275]	14	〉Impaired glucose tolerance	Raw almonds[c] (42.5 g)	8h	↓ Blood glucose concentrations ↑ Insulin blood concentrations ↓ Non-esterified fatty acid blood concentrations after a second meal ↑ Fullness
Kendall 2011 [276]	10	〉Healthy	Pistachios[b] (28.0, 56.0 and	2h	↓ Blood glucose concentrations[d]

			84.0 g)		
Kendall 2014 [277]	20	〉Metabolic syndrome	Pistachios[c] (85.0 g)	3h	↑ GLP-1 postprandial blood concentrations ↑ Glucose-insulinotropic peptide postprandial blood concentrations ↓ Blood glucose postprandial concentrations ↑ Insulin postprandial blood concentrations
Parham 2014 [278]	48	〉Type 2 diabetes	Pistachio[d] (50.0 g per day)	12 weeks	↓ Fasting blood glucose concentrations ↓ Percentage of glycated blood hemoglobin ↓ Systolic blood pressure ↓ Body mass index ↓ C-reactive protein blood concentrations
Wal 2005 [279]	30	〉Overweight women	Whole eggs[b] (2)	36h	↑ Satiety ↓ Energy intake at the next meal and over 24 and 36 hours
Ratliff 2010 [280]	21	〉Healthy men	Whole egg[b] (3)	24h	↓ Blood glucose postprandial concentrations ↓ Ghrelin postprandial blood concentrations ↓ Insulin postprandial blood concentrations ↓ Hunger ↑ Satisfaction ↓ Energy intake at lunch and over 24 hours
Pombo-Rodrigues 2011 [281]	31	〉Healthy	Whole eggs[b] (2)	4h	↑ Fullness ↓ Desire to eat ↓ Prospective food consumption
Liu 2015 [282]	28	〉Healthy children and adolescents	Eggs[b]	3h	↑ PYY postprandial blood concentrations
Wien 2013 [283]	26	〉Overweight	Fresh avocado[b] (50.0 to 90.0 g)	3h	↓ Insulin postprandial blood concentrations ↓ Desire to eat

	↑ Satisfaction

GLP-1: Glucagon-like peptide-1; **PYY:** Peptide tyrosine-tyrosine; **SCFAs:** Short-chain fatty acids.

[a] Unless otherwise mentioned, study samples include adults of both sexes.

[b] Isocaloric test and control meals, however, not matched for macronutrient contents.

[c] Test and control meals matched for carbohydrate content only.

[d] In a dose-dependent matter.

CHAPTER 2

Research gaps, research questions, specific objectives, and significance

2.1 GENERAL SUMMARY AND RESEARCH GAPS

Several studies have shown that middle-aged men are at increased risk of developing T2D due to biological, as well as to some diet-related lifestyle risk factors [1, 35, 36]. Gender/sex-related differences surrounding nutrition are often brought up in the scientific literature as being obvious; however, the actual evidence from the current literature is rather small. Indeed, gender/sex-related differences in dietary intakes are very often supported only by a small number of studies (e.g., only one study using dietary records supports each of the following intakes: red and transformed meat [45], sodium [46], sugar-sweetened beverages in men than women) and studies that focussed on differences between men and women's perceptions of healthy eating were often published or used data collected over fifteen years ago [116–119, 122]. While scarce, available literature points to some gender/sex-specific nutritional vulnerabilities, suggesting that men and women might benefit from nutritional approaches better adapted to their needs. Perhaps, dietary intervention including well-appreciated foods, allowing optimal glycemic control and also promoting postprandial satiety and overall satisfaction, could be an interesting nutritional avenue for T2D management. Such an approach could be more acceptable for men particularly, as according to several studies, they tend to perceive healthy eating as less satisfying in terms of taste, variety and postprandial appetite sensations [116–120].

Based on the well-supported actions of GLP-1 in the pancreas and CNS, as well as the increasing use of GLP-1 analogs in the management of T2D and excess weight, there is an opportunity for using dietary manipulations to promote GLP-1's endogenous secretion. In the previous chapter, we summarized the effects of several nutrients and single-nutrient foods on the endogenous secretion of GLP-1 and identified five foods – almonds, pistachios, avocados, oatmeal, and eggs – that contain a combination of these nutrients. In comparison to nutrients alone and single-nutrient foods, foods containing a mix of nutrients theoretically constitute a more promising and practical approach as they can allow targeting several enteroendocrine pathways. The main limitation of studies assessing the metabolic effects of almonds, pistachios, avocados, oatmeal, and eggs, is that it is impossible to distinguish the specific impact of macronutrient

subtypes (e.g., MUFAs *vs.* PUFAs *vs.* SFAs) from the impact of the amount of their intake *per se* because the experimental meals were not matched for macronutrient content [270, 271, 273–276, 278–283]. Furthermore, several studies [273, 277, 279] did not use isocaloric test and control meals. Since the test meal was always the meal with the highest energy content, it is hard to tell whether the observed effects are attributable to the tested foods and their specific nutrient profile, or their energy content.

2.2 RESEARCH QUESTIONS AND OBJECTIVES

Three research questions and the associated specific objectives are presented below. The research project presented in this thesis was carried out in two parts, with distinct methodological approaches. The first part of the study was in line with the first two research questions and informed the second part of the study, which was in line with the third research question presented below. More specifically, the findings for the first specific objective of the second research question allowed determining the composition of the test meal used in the second part of the study. This is described in further details in Chapter 3.

Research question 1:

"How do gender/sex and health status influence the relative ranking of the importance of common determinants of food choices in middle-aged adults?"

Specific objectives:

1. To identify the most important determinant of food choices within the whole study sample as well as within each subgroup of participants (i.e., men, women, healthy participants, participants with prediabetes or T2D).

2. To compare the relative ranking of the importance of common determinants of food choices between male and female participants.

3. To compare the relative ranking of the importance of common determinants of food choices between healthy participants and participants with prediabetes or T2D.

Research question 2:

"How do gender/sex and health status influence the consumption and the sensory evaluation of almonds, pistachios, avocados, oatmeal, and eggs in middle-aged adults?"

Specific objectives:

1. To compare the taste ratings of the five foods.
2. To compare the frequency of consumption as well as the ratings for appearance, smell, taste, texture, and palatability of the five foods between men and women.
3. To compare the frequency of consumption as well as the ratings for appearance, smell, taste, texture, and palatability of the five foods between healthy participants and participants with prediabetes or T2D.
4. To assess the association between taste ratings and frequency of consumption of the five foods.

Research question 3:

"How do the subtypes of macronutrients contained in isocaloric macronutrient-matched meals influence postprandial glycemic, hormonal and appetite responses in middle-aged men with T2D?"*

**e.g., for the same total lipid content, different proportions of SFAs, MUFAs and PUFAs*

Specific objectives:

1. To assess the influence of the subtypes of macronutrients contained in isocaloric macronutrient-matched meals on postprandial glycemia of middle-aged men with T2D.

2. To assess the influence of the subtypes of macronutrients contained in isocaloric macronutrient-matched meals on postprandial serum concentrations of insulin and GLP-1 of middle-aged men with T2D.

3. To assess the influence of the subtypes of macronutrients contained in isocaloric macronutrient-matched meals on postprandial subjective appetite sensations of middle-aged men with T2D.

2.3 HYPOTHESES

The hypotheses for each of the specific objective were:

Research question 1:

Objective 1: Taste and food preferences are the most important determinants of food choices.

Objective 2: The relative ranking of the importance of common determinants of food choices is influenced by gender/sex.

Objective 3: The relative ranking of the importance of common determinants of food choices is influenced by health status.

Research question 2:

Objective 1: There are no data available allowing making a valid hypothesis for this objective, therefore it is exploratory.

Objective 2: The sensory proprieties of the five foods are rated higher by women than men.

Objective 3: The ratings of the sensory proprieties of the five foods are not influenced by health status.

Objective 4: There is a positive association between taste ratings and frequency of consumption of the five foods.

Research question 3:

Objective 1: The test meal is associated with a lower postprandial glycemia.

Objective 2: The test meal is associated with higher postprandial serum concentrations of insulin and GLP-1.

Objective 3: The test meal is associated with decreased hunger and desire to eat and increased levels of fullness and satiety.

2.4 SIGNIFICANCE

The first part of this study will allow identifying gender/sex- and health status-related differences, if any, in the perceived importance of common determinants of food choices as well as in the sensory evaluation of almonds, pistachios, avocado, oatmeal, and eggs. It will contribute to better understanding factors that can explain gender/sex-related differences in food choices and intakes and could help in identifying which differences between men and women merit further investigations. This is a key step in developing nutritional interventions that are better suited to men's specific needs.

The second part of the study will allow assessing the metabolic effects of an isocaloric macronutrient-matched meal containing almonds in a sample of men with T2D, which has not been done to date. If significant results are found, it could orient future studies as to the potential physiological mechanisms that could explain the benefits of almonds. In the long run, such studies could contribute to improving clinical nutrition practice for T2D as well as obesity management.

CHAPTER 3

Overview of the methodology

The following figure (**Figure 3.1**) is a schematic representation of the methodologies used in the two parts of this study. Collected data and measures as well as the tools and methods used for their collection are presented for each part of the study, with references to the questionnaires appended to this thesis (*Appendices 4 – 8*).

3.1 PART 1 OF THE STUDY

In the first part of the project, a cross-sectional study design was employed to address the first two research questions and associated specific objectives. A total of 61 middle-aged (40-70 years) adults with or without a diagnosis of prediabetes or T2D were recruited in the Ottawa-Gatineau region between January 2015 and November 2017 using convenience sampling.

All data and measures were collected as part of a 90-minute visit at the Nutrition and Metabolism Laboratory of the Montfort Hospital (Ottawa). Collected data and measures included 1) socio-demographic characteristics (see *Appendix 4*), 2) fasting capillary BG concentrations (using: Bayer™ Contour Next) , 2) anthropometric and body composition measures (using: Health-o-Meter™ stadiometer, Tanita™ BC-418 and flexible measuring tape), 3) relative rankings of common determinants of food choices (see *Appendix 5*), 4) ratings of the sensory attributes of almonds, pistachios, avocados, oatmeal, and eggs (see *Appendix 7*), as well as 5) frequency of their consumption by participants (see *Appendix 7*).

The methodology of this part of the study, measures and data collections tools, as well as statistical analyses used to assess the research objectives are described in further details in the “Methodology” section of the article presented in Chapter 4.

3.2 PART 2 OF THE STUDY

In the second part of the study, a randomised cross-over study design was employed to address the third research question and associated specific objectives. A total of 7 men with a diagnosis of T2D were recruited and completed this part of the study.

Data were collected at the Behavior and Metabolism Research Unit (University of Ottawa, Canada) during two 5-hour experimental sessions, separated by a ≥ 7-day washout period. During the two sessions, the participants received, in a random order, either the control or the test breakfast meals and were given 30 minutes to eat. The test meal contained one of the five foods assessed in part 1 of the study, and its energy (kJ), available carbohydrate (g), protein (g) and lipid (g) content where matched to that of the control meal.

Blood samples were collected in fasting state, as well as 15, 30, 60, 90, 120, and 240 minutes following the consumption of the breakfast meal to quantify BG (method: hexokinase/glucose-6-phosphate dehydrogenase [285]), serum insulin (method: radioimmunoassay [286]) and serum GLP-1 (method: multi-species total GLP-1 ELISA (EDM Millipore Corporation, Etobicoke, ON, Canada)). At the same time points, participants rated their subjective appetite sensations (i.e., hunger, fullness, desire to eat, and prospective food consumption) on 100mm visual analog scales (VASs) [54].

Other collected data and measures included 1) socio-demographic characteristics (see *Appendix 4*), 2) fasting capillary BG concentrations (using: Bayer™ Contour Next), and 3) anthropometric and body composition measures (using: Health-o-Meter™ stadiometer, Tanita™ BC-418 and flexible measuring tape).

The methodology of this part of the study, measures and data collections tools as well as statistical analyses used to assess the research objectives are described in further details in the "Methodology" section of the article presented in Chapter 5.

SENSORY EVALUATION, FREQUENCY OF FOOD CONSUMPTION AND METABOLIC RESPONSES TO A TEST BREAKFAST MEAL IN MIDDLE-AGED ADULTS

Part 1 (one 90-minute visit)

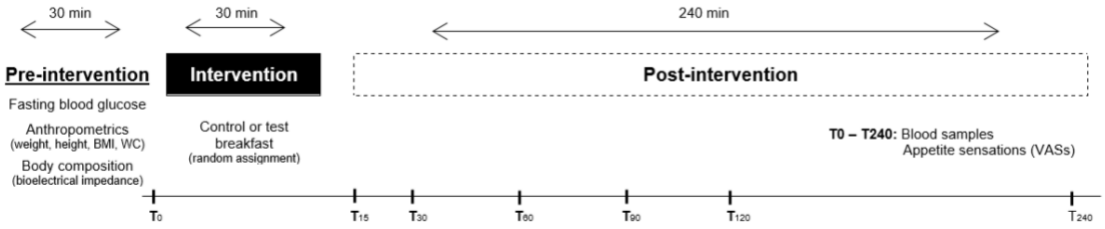
Nutrition and Metabolism Research Laboratory
(Montfort Hospital, Ottawa, Ontario)

- Fasting capillary blood glucose concentrations (Bayer™ Contour Next)
- Anthropometric and body composition measures
  - Height (Health-o-Meter stadiometer)
  - Weight and % body fat (Tanita BC-418)
  - WC (Flexible measuring tape)
- Ranking of common determinants of food choices (see **Appendix 5**)
- Sensory evaluation and frequency of consumption of almonds, pistachios, avocados, oatmeal, and eggs (see **Appendix 7**)
- Socio-demographic questionnaire (see **Appendix 4**) and questionnaire on prediabetes and type 2 diabetes (see **Appendix 5**)

Part 2 (two 5-hour visits)

Behavior and Metabolism Research Unit (University of Ottawa, Ontario)

- Fasting capillary blood glucose concentrations (Bayer™ Contour Next)
- Anthropometric and body composition measures
  - Height (Health-o-Meter stadiometer)
  - Weight and % body fat (Tanita BC-418)
  - WC (Flexible measuring tape)
- Blood samples and subjective appetite sensation ratings on visual analog scales (VASs, see **Appendix 8**) in fasting state and 15, 30, 60, 90, 120, 240 min postprandially
- Socio-demographic questionnaire (see **Appendix 4**) and questionnaire on prediabetes and type 2 diabetes (see **Appendix 5**)



CHAPTER 4

Determinants of food choices, sensory evaluation and frequency of consumption of five health-promoting foods in middle-aged adults

Title:

Determinants of food choices, sensory evaluation and frequency of consumption of five health-promoting foods in middle-aged adults

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ABSTRACT

Aim: This study aimed to assess the influences of gender, sex and health status on the relative ranking of common determinants of food choices, as well as on the sensory evaluation of almonds, pistachios, avocados, oatmeal, and eggs in a sample of middle-aged adults. The association between taste ratings and frequency of consumption of the five foods was also assessed.

Methods: Sixty-one (22 women, 39 men) middle-aged adults were recruited, of which 34 (15 women, 19 men) were cardiometabolically healthy, and 27 (7 women, 20 men) had a diagnosis of prediabetes or type 2 diabetes. Participants were asked to rank-order the importance (i.e., 1 = most important, 10 = least important) of 8 common determinants of food choices. They were also offered, in a random order, 20 g of the five foods (i.e., almonds, pistachios, avocados, oatmeal, and eggs) and were asked to rate their appreciation of appearance, smell, taste, texture, and overall palatability on 100 mm visual analog scales, as well as to report their frequency of consumption of those foods in the past 12 months.

Results: *"Taste and own food preferences"* was ranked as the factor having the greatest influence on participants' food choices. Women accorded more importance to their *"own food-related health beliefs"* ($p = 0.040$), while men reported a higher influence of the *"recommendations of a health professional"* ($p = 0.065$). Women rated the taste ($p = 0.012$), texture ($p = 0.014$) and palatability ($p = 0.031$) of almonds, as well as the taste ($p = 0.044$) and texture ($p = 0.006$) of pistachios significantly higher than men. There were no gender/sex-related differences in the sensory evaluation of avocados, oatmeal, and eggs, nor any health status-related differences in the ranking of factors influencing food choices and for the sensory evaluation of any of the five foods. Moderate-strength and significant associations between taste ratings and frequency of consumption of pistachios ($\beta = 0.323$, $p = 0.018$) and avocados ($\beta = 0.604$, $p < 0.001$) were found.

Conclusion: These results highlight the importance of taste and food preferences in guiding food choices and point to some gender/sex-related differences in the influence exerted by health professionals' recommendations and own health-related food beliefs. As previous work supports these results, the hedonic aspect of food intake, as well as gender/sex-related differences in the determinants of food choices, should be given higher consideration when making dietary recommendations in clinical contexts.

Keywords: Diet, Food choices, Hedonics, Taste, Food preferences, Gender, Sex, Type 2 diabetes.

INTRODUCTION

Eating behaviors include a complex set of interactions between physiological, psychological, social, and environmental factors that influence food choices, the timing of food intake, as well as the quantities of food that are consumed [1]. Given the increasing prevalence of cardiometabolic diseases for which diet can play an essential role in the management of symptoms and the prevention of associated complications [2,3], many studies have focussed on the determinants of food choices. Indeed, acquiring a better understanding of how various factors are driving food choices is important for increasing adherence to current nutrition recommendations, and possibly, for guiding the development of new, more effective dietary evaluation and approaches. Currently, although the beneficial effects of several diets and dietary patterns (e.g., Mediterranean diet, low-glycemic-index diet, etc.) are well supported by the results of randomized controlled trials [4–6], their long-term adherence in real-life situations remains a challenging [7, 8].

The challenges with the implementation and long-time maintenance of dietary changes lie in the complexity of physiological and psychological processes involved in food choices and consumption, as well as the multitude of external factors having the potential to influence them [9–13]. Factors identified as the primary determinants of food choices are generally grouped into three categories: factors related to the food itself (e.g., sensorial attributes, energy and nutrient content, etc.), those related to the individual making the food choices (e.g., expectations, health status, health and nutrition-related knowledge, etc.) as well as external factors (e.g., occasion, availability, cost, etc.) [9–13]. In the absence of external constraints, health conditions influencing dietary needs and intakes, as well as learned food-related beliefs, food choices mainly rely on the sensorial proprieties (e.g., appearance, taste, texture, etc.) of foods [9–13]. Indeed, in controlled laboratory settings, where foods were artificially made to be highly palatable or unpalatable, pleasantness ratings were highly correlated with food intake, with correlation coefficients as high as 0.8-0.9 [14, 15]. In real-life settings, however, the magnitude of these associations is smaller, with correlation coefficients rather ranging between 0.10 and 0.65 [16, 17]. This is explained by

the number of other factors that can come into play, modifying the relationship between the appreciation of a food's sensorial attributes and its consumption [9–13].

Several studies also suggest that gender and sex have an impact on how the above-mentioned factors influence food choices and intakes [18]. For instance, compared to women, men rated their liking of vegetables significantly lower and reported a preference for meat-dominated meals [19, 20]. These differences in food preferences appear to translate into their actual food intakes as some studies have found lower intakes of vegetables and fruit, as well as higher intakes of red and transformed meats in men than in women [19–23]. In some studies, female participants expressed higher levels of awareness of the link between nutrition and health, appeared to have higher levels of nutrition-related knowledge and often reported food choices oriented towards meeting dietary guidelines [24–27]. Male participants, on the other hand, generally described eating as a daily routine and necessary activity to fuel their bodies [24–29]. They also tended to perceive healthy eating as monotonous and unsatisfying, particularly in terms of taste and satiating effect [28, 29]. While these differences are mostly related to gender – the socially constructed roles and behaviors associated with being a man or a woman [30] – some biological differences between men and women can also exert an influence on food choices and intakes. For example, women's appetite and food preferences can be influenced by the normal hormonal variations occurring through the menstrual cycle [31,32]. Some studies also showed that men and women responded to food cue differently due to organizational and structural differences in areas of the brain involved in food reward processing [33, 34]. Therefore, since we cannot distinguish the influence of gender for that of sex, and vice versa, throughout this article, differences between men and women will refer to both gender and sex (the term *"gender/sex"* will be used).

We here used data collected as part of an exploratory study aiming to assess the acceptability of almonds, pistachios, avocados, oatmeal, and eggs prior their inclusion in the standardized breakfast meals of an acute intervention study (results not yet submitted for publication, see Chapter 5). The five foods were selected following a throughout literature search,

for their potential beneficial effects on postprandial glycemia and appetite sensations [35]. In line with the literature presented above, we used available data to specifically assess: 1) the influences of gender/sex on the relative ranking of common determinants of food choices and the sensory evaluation of the five foods, as well as, 2) the association between taste ratings and frequency of consumption of the five foods. Since participants in this study were either cardiometabolically healthy or had a diagnosis of prediabetes or type 2 diabetes (T2D), as a secondary objective, we also assessed the influences of health status on the relative ranking of common determinants of food choices and the sensory evaluation of the five foods. Health status, especially if dietary changes are part of a health condition's management, can be a determinant of food choices itself, as well as influence the relative ranking of other determinants of food choice [13, 18].

METHODS

Study sample

A convenient sample of 61 middle-aged adults with or without a diagnosis of prediabetes or T2D) were recruited and provided all data needed to compute at least one of the analyses described in the statistical analysis section below. Recruitment was done through advertisement posters, during community events, as well as through health professionals from local hospitals, community health centres, and family health teams. All participants self-reported: 1) being non-smokers (i.e., current or in the past 12 months); 2) not having any allergies or intolerances to the tested foods; 3) not having any known chronic (e.g., Parkinson's disease) or acute (e.g., upper respiratory tract infection) disorders affecting taste; 4) not using any pharmacological treatments affecting taste (e.g., chemotherapy); and 5) not having any mastication and/or swallowing difficulties.

The research protocol was approved by the Research Ethics Board of the Montfort Hospital (Ottawa) and by the Office of Research Ethics and Integrity of the University of Ottawa. Written informed consent was obtained from all participants.

Methods and measures

All data were collected during a 90-minute experimental session, which took place between 7am and 10am. Participants were instructed to fast for 12 hours preceding the session.

General characteristics. Participants completed a socio-demographic questionnaire through which age, marital status, ethnicity/racial group, level of education, and household income were assessed. Sex and gender were self-reported orally by participants during the screening process. No discordance between biological sex and gender was mentioned.

Anthropometrics and body composition. Height, weight and waist circumference (WC) were measured at the beginning of the experimental session. Height was measured using a Health-o-Meter™ stadiometer and waist circumference was measured at the mid-point between the iliac crest and the lowest rib using a flexible measuring tape. Body weight (kg) and body composition (i.e., the percentage of body fat and lean body mass) were assessed using hand-to-foot bioelectrical impedance (Tanita™ BC-418). Body mass index (BMI; kg/m^2) was calculated by dividing participants' weight (kg) by their squared height (m^2).

Factors influencing food choices. Participants were asked to rate the importance (i.e., 1 = most important, 10 = least important) 8 common determinants of food choices. The 8 factors being assessed were: 1) taste and own food preferences; 2) taste and food preferences of another member of the household; 3) food availability (e.g., at home, at work, in nearby grocery stores); 4) cost of food; 5) recommendations of a health professional; 6) own food beliefs related to health; 7) social context; 8) emotional state.

Sensory evaluation. Participants were offered, in a random order, 20g of unsalted dry roasted almonds, unsalted raw pistachios, freshly cut avocados, rolled oats cooked with water, and hard-boiled eggs. Participants were asked to rate the appearance, smell, taste, texture, and

overall palatability of the tested foods on 100 mm visual analog scales (VASs). The VASs were anchored with the descriptions *"not at all"* to *"extremely"* for the following questions:

1. How attractive do you find the food?
2. How much do you like the smell of this food?
3. How much do you like the taste of this food?
4. How much do you like the texture of this food?
5. How appetizing do you find the food?

Participants were instructed to mark a vertical line on the VASs at the place corresponding to their feeling at the moment. Quantification of the measurements was made by measuring the distance between the left end of the VASs and the mark. Participants also answered a question about their willingness to buy and include the tested foods in their diets at least once a week (dichotomous answers, yes/no).

Frequency of food consumption. The frequency of consumption of the tested foods over the past 12 months was assessed using the following questions: *"Is this food part of your diet?"* and *"If you answered yes to the previous question, please specify how frequently you ate this food in the last year."*. Participants had the option to report their frequency of consumption as times per day, times per week, times per month, and times per year. All frequency measures were converted to times per year.

Statistical analyses

Unless otherwise specified, data are presented as the mean ± standard error of the mean (SEM) for normally distributed data or as the median ± interquartile range (IQR) for non-normally distributed data. All statistical tests described below were performed after the preliminary verification of the normality of distribution of dependent variables. Relative rankings of factors influencing food choices and frequency of food consumption were found to be not normally distributed. Thus, prior to analyses, the frequency of food consumption was log-transformed for oatmeal, avocados as well as almonds, and square-root-transformed for eggs and pistachios. Since transformation didn't normalize their distribution, differences in the relative rankings of

factors influencing food choices were assessed with a non-parametric statistical test. The level of significance was set at $p < 0.05$. All data were analyzed in with SPSS 24.0 software (Armonk, NY: IBM Corp.).

The influences of gender/sex and health status on the relative rankings of factors influencing food choices were assessed with the Wilcoxon signed-rank test. Differences in mean taste ratings of the five foods were assessed through a one-way ANOVA and Tukey post-hoc tests. Gender/sex- and health status-related differences in ratings of the five sensory characteristics were assessed using independent-sample t-tests. Simple regressions were computed to assess the association between taste ratings and frequency of food consumption.

RESULTS

Among the 61 participants, 22 were women (36.1%) and 39 were men (63.9%). Thirty-four (19 men, 15 women) participants were cardiometabolically healthy (55.7%) and 27 (20 men, 7 women) had a diagnosis of prediabetes or T2D (44.2%). The general socio-demographic and anthropometric characteristics by gender/sex are presented in **Table 4.1**. Participants were aged 58.1 ± 1.0 years and were mostly Caucasian (85.3%). A majority of them had an annual household income ≥ 40 000 $ (68.9%), were married or in a common law union (67.2%) and achieved at least a University degree (63.9%). Men had a mean BMI and WC of 29.4 ± 0.8 kg/m^2 and 99.9 ± 2.3 cm, respectively, and women had a BMI of 29.2 kg/m^2 and a WC of 93.9 ± 3.2 cm.

Except for men being slightly older than women ($p = 0.049$), there were no significant gender/sex-related differences in the socio-demographic and anthropometric characteristics. Participants with prediabetes or T2D were older (61.0 ± 1.2 vs. 55.8 ± 1.5 years, $p = 0.008$), had a higher BMI (32.9 ± 0.9 vs. 27.1 ± 0.9 kg/m^2, $p < 0.001$) and WC (106.3 ± 2.5 vs. 90.9 ± 2.1 cm, $p < 0.001$) than healthy participants.

Since no health status-related differences were found for any of the outcome variables (see sections below), only gender/sex-related differences are presented in tables and figures.

Factors influencing food choices

The factor ranked as having the most influence on food choices was *"taste and own food preferences"* within the whole sample as well as within each sub-group (i.e., men, women, cardiometabolically healthy participants, and participants with prediabetes or T2D only). As shown in **Table 4.2**, the importance of "own food beliefs related to health" was ranked significantly better in women than in men (2.50 (2.75) vs. 3.00 (2.50), W = 531.50, z = -2.05, p = 0.040). Conversely, there was a trend towards a higher influence of the "recommendations of a health professional" in men than in women (4.00 (4.75) vs. 6.50 (4.75), W = 993.00, z = -1.85, p = 0.065). There were no health status-related differences in the ranking of factors influencing food choices (data not shown).

Table 4.1 Socio-demographic and anthropometric characteristics of participants (n=61).

	Men (n=39)	**Women** (n=22)
Age (years)*	59.7 (1.3)[a]	55.3 (1.8)[aa]
Ethnicity**		
Caucasian	84.6 (33)	96.4 (19)
Black or Latino-American	15.4 (6)	13.6 (3)
Annual household income**		
< 20 000 $	2.6 (1)	13.6 (3)
20 000 – 39 999 $	17.9 (7)	13.6 (3)
40 000 – 79 999 $	28.2 (11)	27.3 (6)
≥ 80 000 $	41.0 (16)	40.9 (9)
Preferred not to answer	10.3 (4)	4.5 (1)
Marital status**		
Married or common law	66.7 (26)	68.2 (15)
Single or divorced	33.3 (13)	31.8 (7)
Highest level of education**		
High-school diploma or less	12.8 (5)	13.6 (3)
College diploma	17.9 (7)	31.8 (7)
University degree	69.2 (27)	54.5 (12)
Body mass index (kg/m^2)*	29.4 (0.8)	29.2 (1.5)
Waist circumference (cm)*	99.9 (2.3)	93.9 (3.2)

* Data presented as the **mean (standard error of the mean).**

** Data presented as the **percentage (frequency)**.

[a-aa] : $p < 0.05$ for independent-sample t-test.

Sensory evaluation

Comparison of taste ratings of selected foods. Within the whole sample, there was a significant difference in mean ratings of taste appreciation (F = 29.280, p < 0.001). Post-hoc analyses indicated that the tastes of almonds, pistachios, avocados, and eggs were rated

significantly higher than that of oatmeal (all $p < 0.001$). The taste of almonds ($p = 0.004$) and pistachios ($p = 0.003$) was also rated higher when compared to avocados. When analyses were restricted to a sub-group (i.e., men, women, cardiometabolically healthy participants, and participants with prediabetes or T2D only), post-hoc analyses only indicated a higher appreciation of the taste of almonds, pistachios, avocados, and eggs in comparison to oatmeal (all $p < 0.001$).

Gender/sex-related differences in appearance, smell, taste, texture, and palatability ratings. Women rated the taste (89.6 ± 2.3 mm vs. 78.5 ± 3.3 mm, $t = -2.601$, $p = 0.012$), texture (88.7 ± 2.6 mm vs. 76.6 ± 3.2 mm, $t = -2.555$, $p = 0.014$) and overall palatability (86.3 ± 3.2 mm vs. 76.2 ± 3.2 mm, $t = -2.218$, $p = 0.031$) of almonds significantly higher than men. Similarly, they also rated the taste (88.2 ± 2.8 mm vs. 79.9 ± 2.8 mm, $t = -2.061$, $p = 0.044$) and texture (88.2 ± 2.0 mm vs. 79.0 ± 5.5 mm, $t = -2.872$, $p = 0.006$) of pistachios higher than men. There were no statistically significant gender/sex-related differences in the sensory evaluation of avocados, oats and eggs. Gender/sex-related differences in sensory evaluation of the five foods are presented in **Table 4.3**.

Health status-related differences in appearance, smell, taste, texture, and palatability ratings. There were no statistically significant differences in the ratings of sensory proprieties of the five foods when comparing healthy participants and participants with prediabetes or T2D (data not shown).

Willingness to buy and include in the diet

Except for men's willingness to include oatmeal (i.e., 68.8% were willing) and avocados (i.e., 75.8% were willing) in their diet, over 80.0% of participants reported being willing to buy and include almonds, pistachios, avocados, oatmeal, and eggs in their diet on a weekly basis. Specific percentages and frequencies are presented in **Table 4.3** for men and women separately. There were no statistically significant gender/sex- nor health status-related differences in the willingness to buy and include the five foods in the diet.

Taste ratings and frequency of consumption

The mean annual frequencies of consumption were of 30.4 ± 13.9, 60.6 ± 14.8, 97.2 ± 28.2, and 122.3 ± 22.5 and 138.6 ± 42.0 for pistachios, avocados, oatmeal, eggs, and almonds, respectively. Frequencies of consumption by gender/sex are presented in **Table 4.3**. Except for a higher frequency of consumption of oats in women (131.6 ± 25.0 vs. 76.7 ± 30.2, t = - 2.046, p = 0.046), there were no significant gender/sex- nor health status-related differences.

While only statistically significant for pistachios and avocados, the association between taste appreciation and frequency of consumption was positive for all foods, with correlation coefficients ranging from 0.113 to 0.604. There were moderate-strength and significant associations between pistachios' (β = 0.323, R^2 = 0.086, t = 2.434, p = 0.018; see **Figure 4.1**) and almonds' (β = 0.604, R^2 = 0.353, t = 5.415, p < 0.001; see **Figure 4.2**) taste ratings and their frequency of consumption within this sample of participants.

DISCUSSION

The results of the present study highlight the importance of taste and food preferences in guiding food choices and point to some gender/sex-related differences in the perceived importance of the recommendations of health professionals as well as personal food beliefs related to health. Except for oatmeal, all tested foods seemed well appreciated by both men and women.

Factors influencing food choices

A large body of literature supports the complex and multifaceted nature of food choices [10, 11]. Studies have also quite consistently shown that the level of appreciation of the sensory attributes of foods, mainly taste, is one of the most important determinants of food choices and intakes [5, 7–14, 34]. For instance, analyzes of data from the 2012 Food and Health Survey conducted in the United States revealed that the most important driver of food choices was taste, followed by food's cost, healthfulness, and convenience level [34]. Common to those previous studies, participants of this study ranked *"taste and own food preferences"* as the most influential

factor among the 8 determinants of food intake that were assessed, with no significant differences related to gender/sex, nor health status. While liking a food might increase the likelihood of its inclusion in one's diet, having to give up well-like foods is a common barrier to the adoption of healthier eating habits [5, 26]. In a large cross-sectional study conducted among 15 states members of the European Union investigating, *"giving up well-liked foods"* was the second ("lack of time" was the first) most reported barrier to improving dietary habits and was reported twice as frequently as "not knowing enough about healthy eating" (i.e., 33% vs. 14% of the study sample) [5]. While no gender/sex-related differences were found within this sample of participants, several previous studies suggested that the taste and the pleasurable aspect of eating could be perceived as even more important in men than in women [23–27], and that men might be less willing to compromise on the taste of food for the associated health benefits [35]. The latter aspect could not be addressed with the methodology used in this study, but certainly merits further attention. Quantitative and qualitative studies focussing on factors increasing men's willingness to compromise on the taste of foods and possibly also investigating the level of compromise that they perceive as acceptable in the long run would add to the current available literature and may have interesting clinical implications.

In addition to taste and food preferences, other important factors influencing food choices include their cost, healthfulness and convenience level [7–11]. Convenience is a broad term, including components such as food availability and social context, which were assessed in this study, as well as others, namely time constraints, cooking skills, etc. The perceived healthfulness of foods can be based on personal food-related knowledge and beliefs, recommendations of health professionals and/or general dietary guidelines. Within this sample, we observed no gender/sex- or health status-related differences with regards to the perceived influence of cost, food availability and social context. These findings are not surprising since such factors are most likely influenced by socio-demographic variables such as income and education levels, with no specific rationale for a direct effect of gender/sex or health status [36]. Nonetheless, women's rankings of food choices determinants indicated a higher influence of their "own food beliefs related to health", while the "recommendations of a health professional" tended to have more

influence on men. Possible explanations for these differences between genders/sexes are the levels of concern about healthy eating as well as levels of nutrition-related knowledge. Indeed, studies have constantly shown that women generally express more concern about healthy eating, have higher levels of nutrition-related knowledge, rely less on health professionals to initiate dietary changes, and might be able to learn more about health through their own choice of information sources [17, 22–25]. Conversely, men appear to have lower levels of interest for nutrition and nutrition-practices and reported *"lack of knowledge"* as a barrier to healthy eating more frequently than women [5, 23–27]. In line with our results, in Gough & Conner's (2006) qualitative study, almost all participating men showed skepticism and a certain level of objection towards health promotion messages conveyed through media, due to frequent inconsistencies and conflicting information, and they identified the intervention of a medical authority as being the most likely factor to prompt changes towards a healthier diet [26]. It is likely that a significant part of these gender/sex-related differences in knowledge and interest about nutrition are related to the typical view of food and food-related practices as being feminine. Indeed, in several studies, men did report perceiving nutrition as being a women's domain [23–27, 37], which may lead them to delegate food-related responsibilities to their female partner [37]. Interestingly, we did not find any statistically significant differences in the rankings of common determinants of food choices; as brought up by male participants in Gough & Conner's (2006) study, a diagnosis of prediabetes or T2D could have impacted the relative influence of the "recommendations of a health professional" [26]. It is possible, considering their rather high level of education, that participants in this study already had a sufficient level of basic nutrition-related knowledge [36].

Sensory evaluation and frequency of food consumption

Affective responses to the sensorial properties of food play a major role in shaping food preferences, which in turn have a substantial influence on dietary choices [7, 9, 10]. Here, we assessed levels of appreciation of the sensorial attributes of five foods – almonds, pistachios, avocados, oatmeal, and eggs – that have been selected for their potential health benefits. To our knowledge, no previous study specifically assessed the liking of those foods. Except for oatmeal,

all foods seemed well appreciated with mean taste ratings ranging between 66.6 and 83.1 mm. As expected, in concordance with taste ratings, the majority of participants were willing to buy (i.e., 87.0 - 98.1%) and include (i.e., 82.7 - 94.2%) these foods in their diet on a weekly basis, with no difference related to gender/sex or health status. The relatively high incomes and education levels of participants in this study could partly explain their high willingness to buy and include these foods in their diets.

Women rated some sensorial properties of almonds (i.e., taste, texture and palatability) and pistachios (i.e., taste and texture) significantly higher than men, but these differences did not translate into similar differences in the frequency of consumption. Despite significant gender/sex-related differences, both men and women's ratings of the sensorial proprieties of almonds and pistachios were relatively high; perhaps, larger differences are needed to significantly impact the frequency of consumption. The subjectivity of the assessment of sensorial characteristics as well as previous exposure to these foods could also explain the absence of differences in the frequencies of consumption [7–10]. Interestingly, despite no gender-related differences in oatmeal's taste ratings, women reported consuming the food significantly more often than men. As previously suggested by Verbeke et al.'s (2006) study, women might be more willing than men to compromise on the taste of foods for their beneficial health effects [35].

As expected, we found positive associations between taste rating and frequency of consumption for all foods, however statistical significance was reached only for pistachios and avocados. The lack of statistically significant associations between almonds', oatmeal's and eggs' taste ratings and their frequency of consumption could be linked to the fact that the range of taste ratings was narrow, probably due to the rather small sample size. Some authors also suggested that the association between taste and frequency of consumption could vary depending on the type of food, and perhaps their convenience [7, 8].

CONCLUSION

Nutritional education and interventions aimed at improving diet quality tend to primarily focus on the nutritional value and health effects of foods, and may neglect other aspects influencing food choices, such as hedonic appreciation. It is, however, undeniable that, in addition to fulfilling energy and nutrient needs, food has an important hedonic component; physiological mechanisms, namely those involved in reward processing, rely on the positive affective responses to the sensorial attributes of food to promote the intake of well-liked, pleasurable foods.

Our results highlight the importance of taste and food preferences in guiding food choices and point to some gender/sex-related differences in the influence exerted by health professionals' recommendations and own health-related food beliefs. As previous work supports these results, the hedonic aspect of food intake, as well as gender/sex-related differences in the determinants of food choices, should be given higher consideration during dietary evaluations and when making nutrition recommendations in clinical contexts.

Abbreviations: **BMI:** Body mass index; **SEM:** Standard error of the mean; **T2D:** Type 2 diabetes; **VASs:** Visual analog scales; **WC:** Waist circumference

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Table 4.2 Gender/sex-related differences in rankings[¥] of the importance of common determinants of food choices in a sample of middle-aged adults (n=61).

	Men (n=39)	**Women** (n=22)
Taste and own food preferences	2.0 (2.0)	1.0 (1.0)
Taste and food preferences of other household members	3.0 (4.5)	3.5 (6.8)
Food availability (e.g. at home, work, grocery store)	4.0 (4.0)	4.0 (4.8)
Cost of food	5.0 (2.5)	5.5 (6.8)
Recommendations of a health professional	**4.0**[a] (4.8)	**6.5**[a] (4.8)
Own food beliefs related to health	**3.0**[a] (2.5)	**2.5**[aa] (2.8)
Social context	5.0 (5.0)	5.0 (7.8)
Emotional state	7.0 (6.0)	5.0 (6.8)

[¥] Determinants of food intake were ranked on a scale of 1 to 10, with 1 = most important and 10 = least important.

All data are presented as **median (interquartile range).**

[a – aa] : $p < 0.05$; [a – a] : $0.07 \geq p \geq 0.05$ for Wilcoxon signed-rank test.

Table 4.3 Gender/sex-related differences in the sensory evaluation of almonds, pistachios, avocados, oatmeal, and eggs in a sample of middle-aged adults using 100mm visual analog scales (n=54¥).

	Almonds		Pistachios		Avocados		Oats		Eggs	
	Men (n=32)	**Women** (n=21)	**Men** (n=33)	**Women** (n=21)	**Men** (n=32)	**Women** (n=20)	**Men** (n=32)	**Women** (n=20)	**Men** (n=32)	**Women** (n=20)
Appearance (/100 mm)*	76.6 (2.8)	78.8 (4.0)	68.4 (4.4)	72.1 (5.0)	63.9 (5.0)	74.6 (4.9)	47.7 (4.3)	43.5 (5.3)	76.3 (4.1)	78.4 (4.5)
Smell (/100 mm)*	68.3 (3.3)	70.2 (4.6)	65.9 (3.9)	65.5 (4.8)	60.1 (4.33)	60.2 (6.0)	55.2 (3.5)	46.4 (5.0)	66.4 (5.1)	54.8 (6.7)
Taste (/100 mm)*	**78.5[a]** (3.3)	**89.6[aa]** (2.3)	**79.9[a]** (2.8)	**88.2[aa]** (2.8)	63.7 (5.1)	71.3 (7.3)	45.5 (4.3)	41.0 (6.2)	77.9 (3.7)	77.2 (5.2)
Texture (/100àmm)*	**76.6[a]** (3.2)	**88.7[aa]** (2.6)	**79.0[aa]** (5.5)	**88.2[a]** (2.0)	63.1 (4.8)	73.6 (7.1)	54.1 (4.0)	47.4 (6.7)	78.8 (3.4)	77.0 (4.3)
Palatability (/100 mm)*	**76.2[a]** (3.1)	**86.3[aa]** (3.2)	75.8 (3.4)	83.3 (4.0)	64.2 (5.2)	72.5 (7.3)	47.1 (4.2)	41.7 (7.2)	77.3 (3.6)	78.6 (4.7)
Frequency of consumption (times/year)*	140.7 (48.9)	135.3 (31.4)	19.1 (11.0)	48.1 (18.5)	52.1 (12.8)	74.2 (17.9)	**75.7[aa]** (30.2)	**131.6[a]** (25.0)	107.9 (13.0)	145.3 (37.7)
Willingness to buy (yes)**	96.9 (31)	90.5 (19)	84.8 (28)	90.5 (19)	87.9 (29)	90.5 (19)	84.4 (27)	95.0 (19)	96.9 (31)	100.0 (20)
Willingness to include in diet§ (yes)**	96.9 (31)	85.7 (18)	81.8 (27)	90.5 (19)	75.8 (25)	85.7 (18)	68.8 (22)	90.0 (18)	90.6 (29)	95.0 (19)

Almonds and pistachios were dry roasted and unsalted; avocados were raw and freshly cut; oatmeal was cooked with water; eggs were hard-boiled.

¥ The number of participants slightly differs for certain foods because of missing data.

§ Willingness to include in the diet on a regular basis, defined for participants as consuming a portion of the food at least once per week.

* Data presented as the **mean (standard error of the mean).**

** Data presented as the **percentage (frequency).**

[a – aa]: $p < 0.05$ for independent sample t-test.

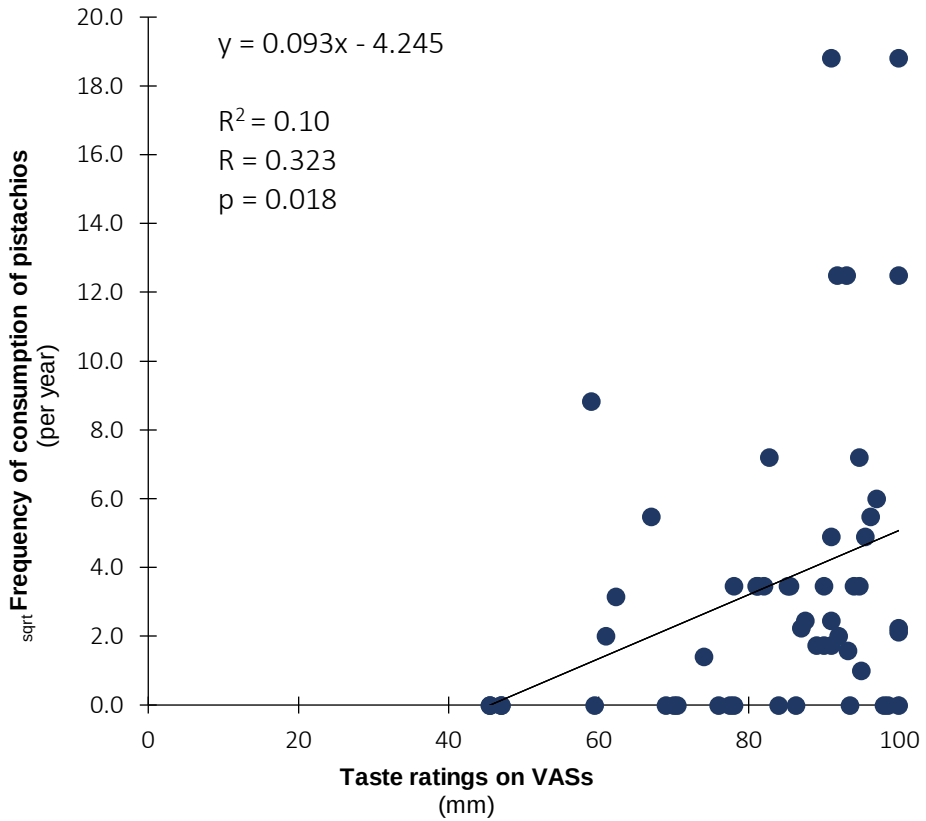

Figure 4.1 Linear regression between taste ratings on 100mm visual analog scales and the square-root of the annual frequencies of consumption of pistachios in a sample of middle-aged adults (n=55).

VASs: Visual analog scales.

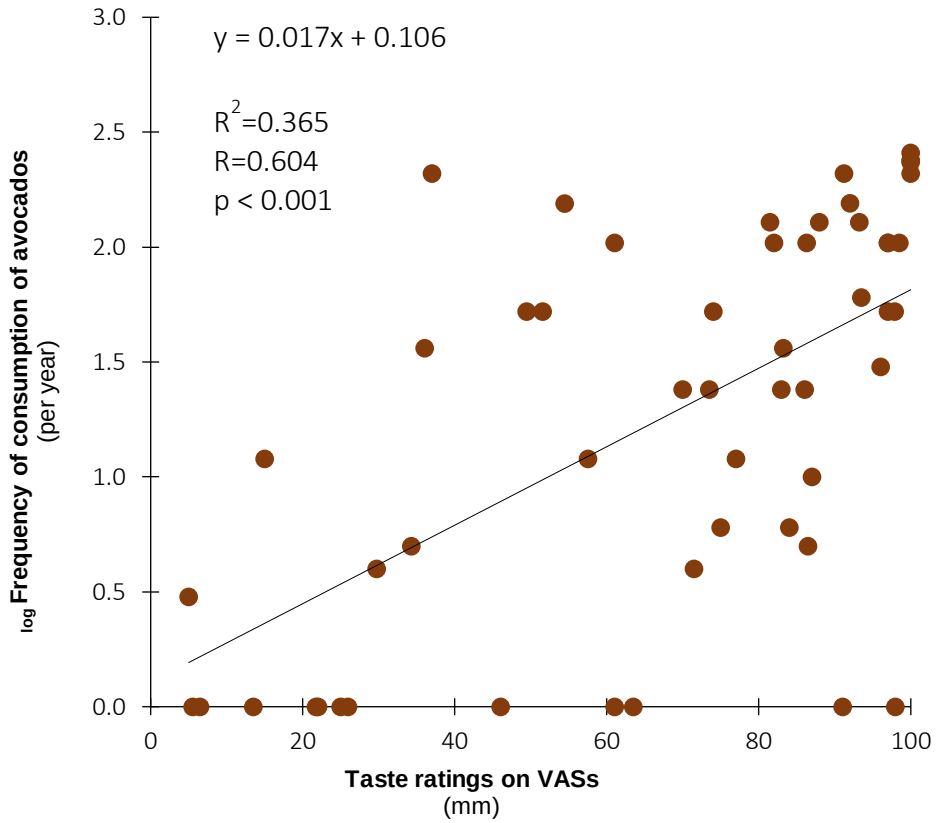

Figure 4.2 Linear regression between taste ratings on 100mm visual analog scales and the logarithmic function of the annual frequencies of consumption of avocados in a sample of middle-aged adults (n=54).

VASs: Visual analog scales.

CHAPTER 5

Acute effects of an isocaloric breakfast meal containing almonds on glycemic, hormonal and appetite responses in men with type 2 diabetes: a randomized cross-over study

Title:

Acute effects of an isocaloric breakfast meal containing almonds on glycemic, hormonal and appetite responses in men with type 2 diabetes: a randomized cross-over study

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ABSTRACT

Aim: This study aimed to assess the effect of almonds on acute postprandial glycemic, hormonal and appetite responses in a sample of men with type 2 diabetes (T2D) using isocaloric macronutrient-matched meals.

Methods: In this randomized crossover study, 7 men with T2D completed two experimental visits during which a control meal (white bread + butter + cheese) and a test meal (white bread + almonds) were ingested. The amounts of energy, available carbohydrates, total lipids, and proteins were the same for both meals. Blood samples were collected in fasting state as well as 15, 30, 60, 90, 120, and 240 minutes postprandially for quantifying serum glucose, insulin, and glucagon-like peptide-1 (GLP-1) concentrations. Subjective appetite sensations were assessed using 100mm visual analog scales at the same time points.

Results: Participants took significantly more time to eat the test meal than the control meal ($p=0.026$). The test meal was associated with lower postprandial glycemia ($p=0.014$), higher GLP-1 serum concentrations ($p=0.044$), decreased hunger ($p=0.032$) and increased fullness ($p=0.014$). The test meal was also associated with increased estimated metabolic clearance rate of glucose ($p=0.005$), a trend towards a higher estimated 1st phase insulin secretion ($p=0.069$), but no meal-related differences in estimated 2nd phase insulin secretion nor postprandial serum insulin concentrations. Desire to eat and prospective food consumption did not differ between meals.

Conclusion: This study documents the acute effects resulting from almond ingestion as part of a meal and suggests that the macronutrient subtypes (i.e., dietary fiber and monounsaturated fatty acids) they contain could have a beneficial impact on glycemic response, insulin sensitivity, postprandial GLP-1 serum concentrations, and appetite sensations in middle-aged men with T2D. Based on the acute effects observed in this study, it is possible that a chronic and regular intake of similar quantities of almonds could improve T2D and weight management, as well as help decrease the risks of cardiometabolic complications.

Keywords: Nuts, Nutrients, Fiber, Monounsaturated fatty acids, Insulin, Glucagon-like peptide-1

INTRODUCTION

Facing the pandemic rise in the prevalence of cardiometabolic diseases, namely type 2 diabetes (T2D), the role of nutrition as part of disease management strategies is being thoroughly emphasized [1]. Nutrients and other food components have direct and indirect influences on key components of cardiometabolic diseases' pathophysiology (e.g., hormone secretion, oxidative stress, inflammation, etc.) as well as their clinical manifestations (e.g., blood lipids and glucose concentrations, insulin sensitivity, etc.) [2–4].

Nuts contain several nutrients and biochemical compounds that have well-supported health benefits, and their consumption has been associated with improved blood lipid profile [5, 6] and blood glucose (BG) control [5, 7] increased satiety and decreased hunger [8], as well as with a decreased risk of developing cardiovascular diseases [9–11] and T2D [9]. Almonds, in particular, are rich in unsaturated fats, fiber, proteins, as well as minerals (e.g., magnesium, potassium), antioxidant vitamins (e.g., vitamin E), and phytochemicals (e.g., polyphenols) [12]. Randomized controlled trials have consistently shown that acutely, when consumed alone, almonds have a minimal impact on BG concentrations in healthy normoglycemic individuals [13, 14] and in individuals with T2D [14]. When added to a carbohydrate-rich meal, almonds appear to decrease the postprandial BG response [13–17] in a dose-dependent manner [14, 15]. The latter effect is likely attributable to a combination of factors, namely a slowdown of the gastric emptying rate associated with almonds' high energy and fat density [18, 19], changes in insulin sensitivity and postprandial insulinemic response [13, 14, 16, 20, 21], increased incretin hormones' secretion [16], and possibly decreased oxidative stress and inflammation [13, 21].

When reviewing currently available knowledge on the acute effects of almonds on glycemic response and associated mechanisms, two main gaps emerge: the scarcity of studies conducted in individuals with T2D, as well as that of studies using isocaloric macronutrient-matched meals. Kendall et al. (2011) conducted the only study comparing the acute glycemic response of healthy individuals and individuals with T2D, following the addition of three different quantities of mixed nuts (almonds, hazelnuts, walnuts, macadamia nuts, and pistachios) to a

carbohydrate-rich meal [14]. Their results suggest that the effects of nuts on postprandial glycemic response might be lesser in individuals with T2D compared to those without, and therefore that higher amounts are needed to reach significant effects [14]. Despite this evidence and the fact that dietary manipulations improving glycemic response are of particular interest for individuals with T2D, the large majority of studies have been conducted in healthy adults [13, 15–17].

To our knowledge, there is also only study assessing the effects of almonds on glycemic response using isocaloric macronutrient-matched meals [13]. The energy and macronutrient content of meals are important considerations; without controlling it, it is difficult to differentiate the effects of almonds and their specific nutrient content from that of increased energy, lipid and/or protein meal content per se. A study by Jenkins et al. (2006) supports that, even in the absence of differences in energy and macronutrient content, almonds improve postprandial glycemic response in healthy normoglycemic individuals [13]. These findings suggest that the subtypes of macronutrients (e.g., unsaturated fats *vs.* saturated fats, amino acid profile, etc.) might also be responsible for the beneficial effects of almonds on glycemic response and BG control.

To validate previous findings and test their reproducibility in individuals with T2D, the present study aimed to assess the effects of almonds on postprandial glycemic and hormonal responses in adults with T2D using isocaloric macronutrient-matched meals. A secondary objective of the study was to assess the effects of almonds on subjective appetite sensations.

METHODS

Study sample

A total of 7 men with a diagnosis of T2D were recruited and completed this study. Previous studies had sample sizes ranging between 9 and 15 participants [13–16, 22]. Despite our small sample size, the power of statistically significant analyses ranged between 0.57 and

0.83. Only men using Metformin (Glucophage®) or a non-pharmacological approach (i.e., diet and physical activity) to manage their T2D were recruited in order to minimize the possible confounding effects of drugs interfering with insulin secretion and glucagon-like peptide-1 (GLP-1) metabolism. Other exclusion criteria were: 1) smoking (current or in the past 12 months), 2) weight loss/gain of ≥ 2 kg in the last 3 months, 3) allergies or intolerances to foods included in the breakfast meals, 3) impaired taste and/or swallowing ability, 4) diagnoses of medical conditions affecting nutrient absorption and/or gastro-intestinal hormone secretion, nutrient and 5) usage of medication affecting BG (other than Metformin), nutrient metabolism and/or appetite.

The research protocol has been approved by the Research Ethics Board of the Montfort Hospital (Ottawa) and by the Office of Research Ethics and Integrity of the University of Ottawa. Written informed consent was obtained from all participants.

Methods and measures

Data were collected during two experimental sessions, separated by a ≥ 7-day washout period (see **Figure 5.1**). All experimental sessions started in the morning, between 7:00 and 9:00. Participants were instructed to fast for 12 hours before each session as well as not to consume alcohol, nor practice moderate to high-intensity physical activities in the previous 72 hours.

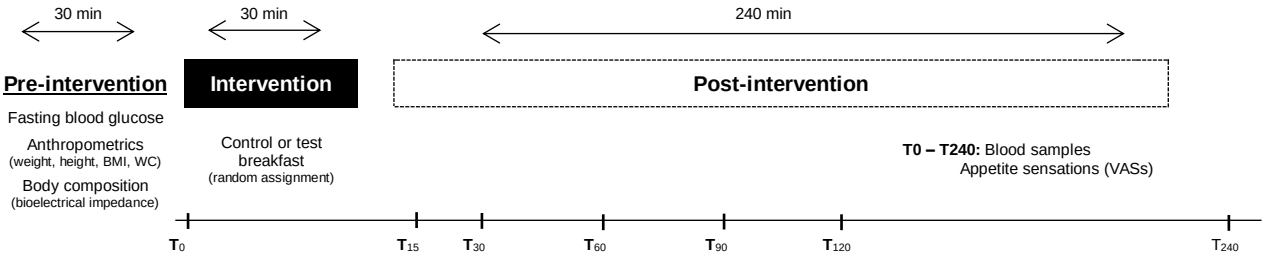

Figure 5.1 Schematic representation of the study protocol

BMI: Body mass index; WC: Waist circumference; VASs: Visual analog scales.

Anthropometrics, body composition and fasting blood glucose. Height, weight, waist circumference (WC), body composition, and capillary fasting BG concentrations were measured at the beginning of each session. Height was measured using a Health-o-Meter™ stadiometer and waist circumference was measured at the mid-point between the iliac crest and the lowest rib

using a flexible measuring tape. Body weight (kg) and body composition (i.e., the percentage of body fat and lean body mass) were assessed using hand-to-foot bioelectrical impedance (Tanita™ BC-418). Fasting capillary BG was measured using a Bayer™ Contour Next glucometer. Body mass index (BMI; kg/m^2) was calculated by dividing participants' weight (kg) by their squared height (m^2).

Breakfast meals. During the two sessions, the participants received, in a random order, either the control or the test breakfast meal and were given 30 minutes to eat. As shown in **Table 5.1A**, the control and the test meal were matched for energy (kJ), available carbohydrate (g), protein (g) and lipid (g) content. Their energy and nutrient content were calculated using nutrition fact tables as well as the Canadian Nutrient File database [23]. The control meal contained white bread, unsalted butter, and cheddar cheese, while the test meal contained white bread and dry roasted unblanched almonds. Participants drank 240mL of decaffeinated coffee (black or with 15mL of 2% milk) or water with their meals. Each participant received the same drink at the first and second data collection session. During the postprandial period, participants were allowed drinking water *ad libitum*.

Blood sampling, glucose and hormone assays. Blood samples were collected through an indwelling catheter installed in a cubital vein in fasting state, as well as 15, 30, 60, 90, 120, and 240 minutes following the consumption of the breakfast meal. Upon collection, blood samples were centrifuged, and serum was frozen at -80°C until analyzes were done. Glucose and insulin serum concentrations were measured by the Biochemistry Laboratory of the Montfort Hospital (Ottawa, ON) using the hexokinase/glucose-6-phosphate dehydrogenase method [24] and radioimmunoassay [25], respectively. GLP-1 was measured using the multi-species total GLP-1 ELISA kit (EDM Millipore Corporation, Etobicoke, ON, Canada). Glucose, insulin, and GLP-1 2- and 4-hour areas under the curves (AUCs) were estimated using the trapezoidal method [26].

Insulin secretion and sensitivity. Fasting serum glucose and insulin concentrations were used to calculate the homeostatic model assessment of insulin resistance (HOMA-IR) index, using the following formula:

$$\mathbf{HOMA-IR} = \frac{\left(\mathbf{Fasting\ glucose}\left(\frac{\mathrm{mmol}}{\mathrm{L}}\right) \times \mathbf{Fasting\ insulin}\left(\frac{\mathrm{pmol}}{\mathrm{L}}\right)\right)}{22.5}$$ [27].

The 1st and 2nd phases of insulin secretion, as well as metabolic clearance rate (MCR) of glucose, an indicator of insulin sensitivity, were estimated using Stumvoll et al.'s (2000) predictive equations [28]:

(a) $\boldsymbol{1st\ phase\ insulin\ secretion}\left(\frac{pmol}{L}\right) = 1283 + (1.829 \times Insulin_{30min}) - (138.7 \times Glucose_{30min}) + (3.772 \times Insulin_{0min})$

(b) $\boldsymbol{2nd\ phase\ insulin\ secretion}\left(\frac{pmol}{L}\right)$
$= 287 + (0.4164 \times Insulin_{30min}) - (26.07 \times Glucose_{30min}) + (0.9226 \times Insulin_{0min})$

(c) $\boldsymbol{MCR}\ (mg \cdot kg^{-1} \cdot min^{-1}) = 18.8 - (0.271 \times BMI) - (0.0052 \times Insulin_{120min}) - (0.27 \times Glucose_{90min})$

Appetite sensations. At the same time points, participants rated their subjective appetite sensations (i.e., hunger, fullness, desire to eat, and prospective food consumption) on 100mm visual analog scales (VASs) adapted from Flint et al. (2000) [29]. Participants were asked to indicate how they felt at the moment they completed the following questions: *"How hungry do you feel?"*; *"How strong is your desire to eat?"*, *"How full do you feel?"*, and *"How much food do you think you could eat?"*. The VASs were anchored with the descriptions *"not hungry at all"* to *"extremely hungry"*, *"very weak"* to *"very strong"*, *"not full at all"* to *"extremely full"*, and *"nothing at all"* to *"a very large amount"*, respectively. The satiety quotient (SQ) was calculated using fasting and 240-minute subjective hunger ratings [30, 31]:

$$\mathbf{SQ}\left(\frac{\mathrm{mm}}{\mathrm{kcal}}\right) = \frac{\mathbf{Fasting\ hunger\ rating}\ (\mathrm{mm}) - \mathbf{240min\ hunger\ ratings}\ (\mathrm{mm})}{\mathbf{Energy\ content\ of\ the\ meal}\ (\mathrm{kcal})} \times 100$$

Statistical analysis

Data are presented as the mean ± standard error of the mean (SEM) unless otherwise specified. All statistical tests described below were performed after the preliminary verification of the normality of distribution of dependent variables. The level of significance was set at $p < 0.05$. All data were analyzed with SPSS 24.0 software (Armonk, NY: IBM Corp.).

Potential differences between the two experimental sessions for body weight, body composition, insulin resistance (HOMA-IR), fasting serum concentrations of glucose, insulin, and GLP-1, as well as fasting subjective ratings of hunger were assessed using paired t-tests. Differences in glucose, insulin, GLP-1, and subjective appetite responses to the control and the test meals were assessed using paired t-tests for overall responses estimated with 2- and/or 4-hour AUC and with the SQ, as well as using 2-way repeated measures ANOVAs for longitudinally-assessed responses. For the later statistical test, the first repeated measure was the meal (2 levels: control and text meals) and the second one was time (7 levels: 0, 15, 30, 60, 90, 120 and 240 minutes). Greenhouse-Geisser (if Greenhouse-Geisser $\varepsilon < 0.75$) or Huynh-Feldt (if Greenhouse-Geisser $\varepsilon > 0.75$) adjusted degrees of freedom were used to correct violations of the assumption of sphericity. When a statistically significant main meal x time interaction was identified through the 2-way repeated measures ANOVAs, multiple paired t-tests with Bonferroni corrections were used to determine the loci of the differences.

RESULTS

Participants were aged 63.9 ± 2.54 years, had been diagnosed with T2D for an average of 9.6 ± 2.4 years and were all using Metformin (Glucophage®). As shown in **Table 5.2**, there were no significant differences in the baseline (fasting (T0) in **Figure 5.1**) measures between the two experimental sessions. Among the 7 participants, 4 received the control meal at their first session followed by the test meal at the second session, and 3 received the test meal at their first session followed by the control meal at the second session. On average, participants took more time to eat the test meal than the control meal (25.4 ± 6.5 min *vs.* 22.4 ± 5.8 min; $t = -2.931$, $p = 0.026$).

Blood glucose

The 4-hour AUC for BG concentrations was significantly lower following the consumption of the test meal than the control meal ($t = 3.085$, $p = 0.022$; **Figure 5.2 A**). When analyses were

restricted to the 2-hour glucose AUC, the difference between meals was not statistically significant, however, still close to the significance level (t = 2.328, p = 0.059; **Figure 5.2 A**). When assessed longitudinally over 4 hours (see **Figure 5.2 B**), BG concentrations were also significantly lower following the consumption of the test meal (F = 11.724, p = 0.014). There was also a significant effect of time (F = 41.585, p < 0.001), but no meal x time interaction (F = 0.305, p = 0.752).

Table 5.2 Baseline measures of participants (n=7) at the two experimental sessions.

	Control meal	Test meal
Body mass index (kg/m^2)	28.9 (1.4)	28.9 (1.5)
Body fat (%)	27.4 (1.6)	28.3 (1.7)
Fasting blood glucose (mmol/L)	6.1 (0.9)	6.0 (0.9)
Fasting serum insulin* (pmol/L)	48.9 (8.4)	49.1 (9.0)
HOMA-IR index**	13.3 (2.2)	12.9 (2.3)
Fasting serum GLP-1 (pmol/L)	66.8 (7.0)	74.8 (9.8)
Fasting subjective hunger (/100mm)	69.4 (7.4)	72.9 (5.9)

*Normal fasting serum insulin concentrations: < 174.0 pmol/L [32]
**Normal HOMA-IR index values: < 2.3 [33]
All data presented as **mean (standard error of the mean).**
***GLP-1**: Glucagon-like peptide-1; **HOMA-IR**: Homeostatic model assessment of insulin resistance.*

Serum insulin, insulin secretion, and insulin sensitivity

There were no significant differences in the 2- and 4-hour insulin AUCs following the consumption of the test meal and the control (p = 0.964 and p = 0.551, respectively; **Figure 5.3 A**). When assesses longitudinally over 4 hours (see **Figure 5.3 B**), there was no effect of the meal (p = 0.254), time (p = 0.079), nor meal x time interaction (p = 0.103).

While not reaching statistical significance, estimated 1st phase insulin secretion tended to be higher following the consumption of the test meal (t = -2.208, p = 0.069; **Figure 5.4 A**). There was no difference in estimated 2nd phase insulin secretion (t = -2.010, p = 0.091; **Figure 5.4 B**). However, insulin sensitivity as assessed with the MCR was significantly higher following the consumption of the test meal (t = -4.408, p = 0.005; **Figure 5.4 C**).

Serum GLP-1 concentrations

The 4-hour AUC for GLP-1 serum concentrations tended to be higher following the consumption of the test meal, however, the difference did not reach statistical significance ($t = -2.340$, $p = 0.059$; **Figure 5.5 A**). When assessed longitudinally over 4 hours (see **Figure 5.5 B**), total GLP-1 serum concentrations were significantly higher when the test meal was ingested ($F = 6.418$, $p = 0.044$). There was also a significant effect of time ($F = 10.443$, $p < 0.001$), but no meal x time interaction ($p = 0.993$).

Subjective appetite sensations

The 4-hour AUC for hunger was significantly lower following the consumption of the test meal ($t = 2.491$, $p = 0.047$; **Figure 5.6 A**). Longitudinal analyses of subjective hunger sensations (see **Figure 5.6 B**) also indicated lower ratings following the consumption of the test meal ($F = 7.708$, $p = 0.032$), as well as a significant effect of time ($F = 37.757$, $p < 0.001$) and a meal x time interaction ($F = 4.377$, $p = 0.010$). Post-hoc analyses for the meal × time interaction effect showed no significant differences between meals at specific time points (significance level set at $p < 0.007$ when applying the Bonferroni correction). The SQ, calculated using hunger ratings, was significantly higher for the test meal than the control meal ($t = -4.741$, $p = 0.003$; **Figure 5.8**).

There was no significant difference between meals for the 4-hour AUC for desire to eat ($t = 2.092$, $p = 0.081$). Longitudinal analyses showed a significant effect of time ($F = 36.905$, $p < 0.001$), as well as a meal × time interaction effect ($F = 4.330$, $p = 0.005$) but no significant effect of the meal alone ($F = 4.659$, $p = 0.074$) on desire to eat ratings. Post-hoc analyses for the meal × time interaction effect showed no significant differences between meals at specific time points (significance level set at $p < 0.007$ when applying the Bonferroni correction).

The 4-hour AUC for fullness was significantly higher following the consumption of the test meal ($t = -2.995$, $p = 0.024$; **Figure 5.7 A**). Longitudinal analyses of fullness levels (see **Figure 6.7 B**) also indicated higher ratings following the consumption of the test meal ($F = 11.754$, $p =$

0.014), as well as a signification effect of time ($F = 41.585$, $p < 0.001$), but no meal x time interaction ($F = 0.305$, $p = 0.752$).

There was no significant difference between meal for the 4-hour AUC for prospective food consumption ($t = 1.569$, $p = 0.169$). When assessed longitudinally, only a significant effect of time was found ($F = 32.283$, $p < 0.001$), but no effect of the meal ($F = 2.590$, $p = 0.159$), nor a meal × time interaction effect ($F = 1.371$, $p = 0.258$).

DISCUSSION

The present study aimed to assess the effects of almonds on postprandial glycemia, potential hormonal mediators (i.e., insulin and GLP-1) and subjective appetite sensations in a sample of middle-aged men with T2D. Almonds were part of a test meal which, to isolate the effects of macronutrient subtypes, had the same energy, available carbohydrate, lipid, and protein contents as the control meal.

Our results show that even when controlling for the effects of energy and macronutrient content, the inclusion of almonds in a meal attenuated glycemic response, decreased hunger and increased fullness levels. These observations were accompanied by an increase in GLP-1 serum concentrations, but no change in the overall insulinemic response. Using predictive equations, we found that almonds were associated with a trend towards an enhanced first-phase insulin release as well as significantly higher postprandial insulin sensitivity.

Glucose metabolism

In healthy individuals, BG concentrations are maintained within narrow ranges through homeostatic mechanisms allowing adjusting glucose entry into the bloodstream (i.e., from food, glycogenolysis, and gluconeogenesis) for its absorption by cells, and vice versa [34, 35]. With the progression from normal BG homeostasis to T2D, a state of insulin resistance develops and insulin production by pancreatic β-cells decreases, resulting in fasting and postprandial

hyperglycemia [34]. Dietary changes are an integral part of T2D management; alone or in combination with antihyperglycemic pharmaceutical agents they can help minimize BG excursions and therefore decrease the risks of developing micro- and macro-vascular complications [1].

Here we showed that isocaloric macronutrient-matched meals elicit different postprandial glycemic responses, depending on the type of food they contain (i.e., in this study, almonds *vs.* cheddar cheese and butter). The postprandial BG concentrations were lower following the consumption of the almonds-containing test meal compares to that of the control meal. Previous studies have already shown that, in meals matched for carbohydrate content only, the inclusion of almonds reduces postprandial BG concentrations in healthy individuals, as well as in individuals with impaired glucose tolerance and T2D [14–16]. Acutely, this effect is likely mostly attributable to the fact that the addition of almonds increases the energy, fat and protein content of the meal, which translates into a slowing down of gastric emptying and luminal nutrient absorption rate [18, 19]. The latter explanation is, however, not applicable to our study since total energy, fat and protein contents did not differ between meals. To our knowledge, the only other study using energy and macronutrient-matched meals reported findings similar to ours with respects to BG, but using a smaller quantity of almonds (i.e., 60g instead of 85g) and in a sample of healthy adults [13].

The reduced glycemic response can theoretically have multiple explanations. One of them is a decreased and slowed-down carbohydrate absorption, which could be related to differences in fiber content of the two meals. As shown in **Table 5.1 A**, the amount of dietary fiber of the test meal was six times that of the control meal (i.e., 10.8g *vs.* 1.8g). Soluble fiber were present in relatively small, but physiologically relevant amounts (i.e., 1.8g), while insoluble fiber constituted the majority of the test meal's fiber content (i.e., 9.0g). Dietary fibers, which in most foods are a combination of soluble and insoluble fiber, can decrease as well as slow-down carbohydrate absorption by 1) increasing the viscosity of the chyme, thus hampering glucose diffusion, 2) reducing carbohydrate availability in the GI tract, and 3) impairing α-amylase activity

by encapsulating starch [36–38]. Some studies also suggested that insoluble fiber may shorten the transit time through the small intestine, thus potentially decreasing net carbohydrate absorption [37, 38].

As major regulators of BG concentrations, changes in insulin secretion and efficiency could also explain the dampened glycemic response. In addition to being closely modulated by elevations in BG concentrations, its secretion is also triggered by the postprandial release of incretin hormones [35, 39]. When in contact with nutrients, incretin hormones, such as GLP-1, are released from enteroendocrine cells and stimulate insulin release by pancreatic β-cells before any changes in BG concentrations have yet occurred [39]. In this study, the test meal was associated with significantly higher postprandial GLP-1 serum concentrations. Only one study assessing almonds' effects on BG metabolism when added to a carbohydrate-rich meal quantified postprandial GLP-1 concentrations and found no significant difference [16]. Another study assessing the effects of pistachios had a design very similar to ours and showed that when added to white bread, both pistachios and cheese + butter induced a more substantial increase in postprandial GLP-1 concentration [22]. Contrary to our results, no significant differences in postprandial GLP-1 concentrations were observed when comparing the pistachio and the cheese + butter meals [22]. In addition to some differences in the nutrient profile of almonds and pistachios, the discrepancy between our results and that of Kendall et al. (2014) could be related to differences in study samples [22]. Indeed, our sample was composed of men with T2D treated with Metformin, while theirs was composed of men and women with obesity and meeting the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) diagnosis criteria for metabolic syndrome [22, 40]. It should also be mentioned that while GLP-1 serum concentrations were significantly different between meals, the magnitude of that difference was quite small (see **Figure 5.5 A and B**).

The increase in GLP-1 concentrations associated with the test meal did not translate into a higher insulinemic response as it would have been expected. Previous studies have shown that, when added to a carbohydrate-rich meal, almonds decrease insulinemic response in

normoglycemic individuals [13] and increase insulinemic response in individuals with impaired glucose tolerance [16]. Additionally, when compared to an isocaloric macronutrient-matched meal containing cheese, butter and mashed potatoes, almonds combined with white bread induced a lower postprandial insulinemic response in healthy individuals [13]. To our best knowledge, there is no previous study assessing the impact of almonds on insulinemic response in individuals with T2D using isocaloric macronutrient-matched meals. When looking at the overall changes in serum insulin concentrations during the 240-minute postprandial period, the test meal appears to have elicited a slightly higher insulinemic response in the first postprandial hour, while the opposite effect is subsequently observed. As illustrated in **Figure 5.3 B**, following the first postprandial hour, serum insulin concentrations decreased at a higher rate following the ingestion of the test meal. As a result, between the second and fourth postprandial hours, serum insulin concentrations were higher following the consumption of the control meal. Using Stumvoll et al.'s (2000) [28] predictive equations, we found a trend towards a higher 1st phase insulin release, while the 2nd phase insulin release did not significantly differ between meals (see **Figure 5.4 A and B**). The insulinotropic effect of GLP-1 could partly explain the enhanced 1st phase insulin release following the consumption of the test meal. The subsequent faster decrease in insulin concentrations is most likely a result of enhanced insulin sensitivity. Indeed, as estimated by the metabolic clearance rate [28], the postprandial insulin sensitivity was significantly higher following the ingestion of the test meal.

This enhanced insulin sensitivity could be associated with the higher fiber content of the test meal, as well as to differences in the type of fats contained in the meals. Indeed, in addition to potentially decreasing or slowing down carbohydrate absorption, dietary fiber, especially the insoluble type, have been associated with increased insulin sensitivity [41]. With regards to fatty acids, both their chain length and the number of double bonds they contain can influence their insulinotropic and insulin-sensitizing potential. In this regard, the prolonged consumption of diets high in monounsaturated fatty acids (MUFAs) as compared to that of diets high in saturated fatty acids (SFAs) has been associated with improved glycemic control in healthy individuals, as well as in those with obesity, metabolic syndrome and T2D [42, 43]. While the results are not as

straightforward in acute intervention studies, several still support a beneficial postprandial effect of MUFAs [44–46]. For instance, Bermudez et al. (2014) showed that individuals with normal and high fasting triglycerides concentrations became more insulin sensitive postprandially as the ratio of MUFAs to SFAs increased [44]. Similarly, Robertson et al. (2002) ranked the acute insulin sensitizing effects of SFAs as being the lowest, followed by omega-6 polyunsaturated fatty acids (PUFAs), omega-3 PUFAs, and MUFAs [45]. The circulating concentrations of non-esterified fatty acids (NEFAs) are a suggested mediating factor between the fatty acid types and insulin sensitivity [46]. When compared to MUFAs and PUFAs, SFAs are associated with higher postprandial NEFAs concentrations, which negative relationship with insulin resistance is well recognized [46, 47].

Appetite sensations

As excess weight is an important risk factor for T2D development, weight maintenance or reduction is often a therapeutic goal for individuals with T2D [48, 49]. In this, regard the satiating proprieties of foods are of particular interest as they influence future food and energy consumption [31].

Many studies support the high satiating value of nuts [17]. Indeed, despite their elevated energy and fat density, the consumption of nuts does not appear to promote weight gain and has in fact even been associated with weight loss in some studies [50, 51]. Here, we showed that a meal containing 85g of almonds suppressed hunger and increased fullness significantly more than an isocaloric macronutrient-matched meal in which almonds were replaced by cheese and butter.

Appetite is physiologically regulated by a well-orchestrated interplay between adipose tissue-derived endocrine mediators, GI peptides and neuronal circuits involving a wide array of neurotransmitters [52]. In addition to its incretin role, GLP-1 is involved in appetite regulation and is currently the most successful gut peptide to be exploited for weight loss and management purposes [53]. In this study, GLP-1 postprandial serum concentrations were higher following the consumption of the test meal, and since GLP-1 is an anorectic peptide, this could partly account

for the observed differences in levels of hunger and fullness. This is contrary to Mori et al.'s (2011) results showing that, while almonds increase fullness, their inclusion in a carbohydrate-rich meal is not associated with higher postprandial GLP-1 serum concentrations [16]. Postprandial changes in GLP-1 concentrations are modulated by the amount and the chemical structure of nutrients reaching the intestinal lumen [4]. For instance, upon digestion, long-chain free fatty acids stimulate GLP-1's secretion by binding to the G-protein-coupled free fatty acid receptors 1 and 4 (FFAR1, FFAR4) [54]. Furthermore, several animal and clinical studies have shown that, in comparison to SFAs, MUFAs [55–57] and omega-3 PUFAs [58, 59] have greater GLP-1 secretory effects. SCFAs, which are products of soluble fiber bacterial fermentation in the colon, are also potent stimulators of GLP-1 secretion [60, 61]. In the long-term, regular soluble fiber consumption appears to promote the proliferation of GLP-1-producing intestinal L-cells [62]. Therefore, it is possible that the high MUFA and fiber content of the test meal has stimulated a greater GLP-1 secretion which translated into higher GLP-1 serum concentrations. Another possible explanation for the decreased hunger and increased fullness levels is the eating pace. Participants of this study took significantly more time to eat the test meal than the control meal, probably due to the fibrous nature of almonds. Indeed, harder solid foods have been consistently associated with slower eating paces when compared to softer solids and semi-liquid textures [63–65]. Slower eating paces have in turn been shown to decrease hunger and increase satiety more than fast eating paces [66, 67]. In healthy individuals slower eating has also been associated with increased postprandial concentrations of anorectic hormones, such as GLP-1 and peptide YY (PYY) [67].

CONCLUSION

This study supports a differential effect of macronutrient subtypes on glycemic response, insulin sensitivity, postprandial serum GLP-1 concentrations, and appetite sensations. Almonds' nutrient profile, in particular, their high fiber and MUFA content, might acutely benefit men with T2D by limiting postprandial BG excursions and by promoting an increased and prolonged level

of satiety. In the long run, such effects may favor glycemic control, weight stability, as well as help decrease the risks of cardiometabolic complications associated with T2D.

Abbreviations: **AUC**: Area under the curve; **BG**: Blood glucose; **BMI**: Body mass index; **FFAR**: Free fatty acids receptor; **GLP-1**: Glucagon-like peptide-1; **HOMA-IR**: Homeostatic model assessment of insulin resistance; **MCR**: Metabolic clearance rate; **MUFAs**: Monounsaturated fatty acids; **NEFAs**: Non-esterified fatty acids; **PYY**: Peptide YY; **SEM**: Standard error of the mean; **SCFAs**: Short-chain fatty acids; **SQ**: Satiety quotient; **T2D**: Type 2 diabetes; **VASs**: Visual analog scales; **WC**: Waist circumference.

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Table 5.1 Meal composition and nutrient content

A. Energy (kJ) and macronutrient (g) composition of the control and the test meal*

Meal	**Quantity** (g)	**Energy** (kJ)	**Energy density** (kJ/g)	**Proteins** (g)	**Total fat** (g)	**SFAs**[a] (g)	*cis* 16:0 *(g)*	*cis* 18:0 *(g)*	**MUFAs**[b] (g)	*cis*Δ[9] 18:1 *(g)*	**PUFAs** (g)	Ω-3 (g)	Ω-6 (g)	**Available CHO** (g)	**Total fiber** (g)	**Insoluble fiber** (g)	**Soluble fiber** (g)
Control	**206.5**	**2,978.5**	**14.4**	**25.1**	**46.8**	**28.9**	11.6	5.1	**12.3**	*9.8*	**3.3**	**0.5**	**2.1**	**50.0**	**1.8**	**0.7**	**1.1**
White bread	114.5	1,119.0	9.8	8.9	2.7	0.9	*0.5*	0.3	1.0	*0.7*	2.0	*0.2*	*1.3*	50.0	1.8	0.7	1.1
Unsalted butter	23.5	714.8	30.4	0.2	19.0	12.0	*5.1*	*2.4*	4.9	*4.0*	0.7	*0.1*	*0.5*	0.0	0.0	0.0	0.0
Cheddar cheese	68.5	1144.7	16.7	16.0	25.1	16.0	*6.0*	*2.4*	6.4	*5.1*	0.6	*0.2*	*0.3*	0.0	0.0	0.0	0.0
Test	**171.5**	**3,071.1**	**17.9**	**25.4**	**47.0**	**4.3**	3.2	0.8	**28.9**	*28.4*	**13.4**	**0.1**	**11.8**	**50.0**	**10.8**	**9.0**	**1.8**
White bread	96.5	945.6	9.8	7.6	2.3	0.8	*0.4*	*0.2*	0.8	*0.6*	1.7	*0.1*	*1.1*	42.3	1.5	0.6	0.9
Dry roasted almonds	85.0	2,125.5	25.0	17.8	44.7	3.5	*2.8*	*0.6*	28.1	*27.8*	11.7	*0.0*	*10.7*	7.7	9.3	8.4	0.9

*Energy and nutrient content of foods were obtained from manufacturers and/or from the Canadian Nutrient File [23].
[a]The control meal also contained butyric acid (4:0), caproic acid (6:0), caprylic acid (8:0), and lauric acid (12:0) from butter and cheddar cheese.
[b]The control and the test meal contained small quantities of palmitoleic acid (cisΔ[9]16:1) from cheddar cheese and almonds.
CHO: *Carbohydrates,* ***MUFAs:*** *Monounsaturated fatty acids,* ***PUFAs:*** *Polyunsaturated fatty acids;* ***SFAs:*** *Saturated fatty acids.*
cis16:0 *: Palmitic acid;* ***cis18:0*** *: Stearic acid;* ***cisΔ[9]18:1*** *: Oleic acid.*

B. Amino acid, vitamin, and mineral content of the control and the test meal

	Control meal	Test meal
Amino acid profile		
Tryptophan (g)	0.508	0.281
Tyrosine (g)	1.087	0.634
Threonine (g)	1.049	0.767
Phenylalanine (g)	1.276	1.388
Proline (g)	1.067	1.199
Isoleucine (g)	1.266	0.980
Leucine (g)	2.117	1.866
Lysine (g)	1.017	0.719
Alanine (g)	0.891	1.149
Arginine (g)	0.791	2.426
Aspartate (g)	1.750	2.663
Glycine (g)	0.762	1.521
Glutamate (g)	6.745	8.088
Cysteine (g)	0.310	0.369
Histidine (g)	0.614	0.645
Serine (g)	1.067	1.199
Methionine (g)	0.571	0.287
Valine (g)	1.455	1.109
Vitamins		
Beta-carotene (µg)	95.36	0.85
Retinol (REA)	333.05	0.00
Vitamin D (IU)	33.78	12.55
Vitamin E (mg)	**1.33**	**20.53**
Vitamin K (µg)	7.18	2.99
Vitamin C (mg)	0.00	0.00
Thiamine (mg)	0.55	0.51
Riboflavin (mg)	0.69	1.34
Niacin (mg)	5.02	7.29
Pantothenic acid (mg)	0.80	0.65
Vitamin B6 (mg)	0.09	0.16
Folacin (µg)	144.45	152.90
Vitamin B12 (µg)	0.69	0.04
Minerals		
Calcium (mg)	558.49	304.04
Phosphorus (mg)	454.45	505.54
Magnesium (mg)	**63.62**	**274.79**
Potassium (mg)	**183.65**	**712.20**
Sodium (mg)	885.70	375.04
Cooper (mg)	0.19	1.06
Zinc (mg)	3.36	3.64
Manganese (mg)	0.45	2.29
Selenium (µg)	55.00	31.52

*Amino acid, vitamin, and mineral content of foods were obtained from the Canadian Nutrient File [23].

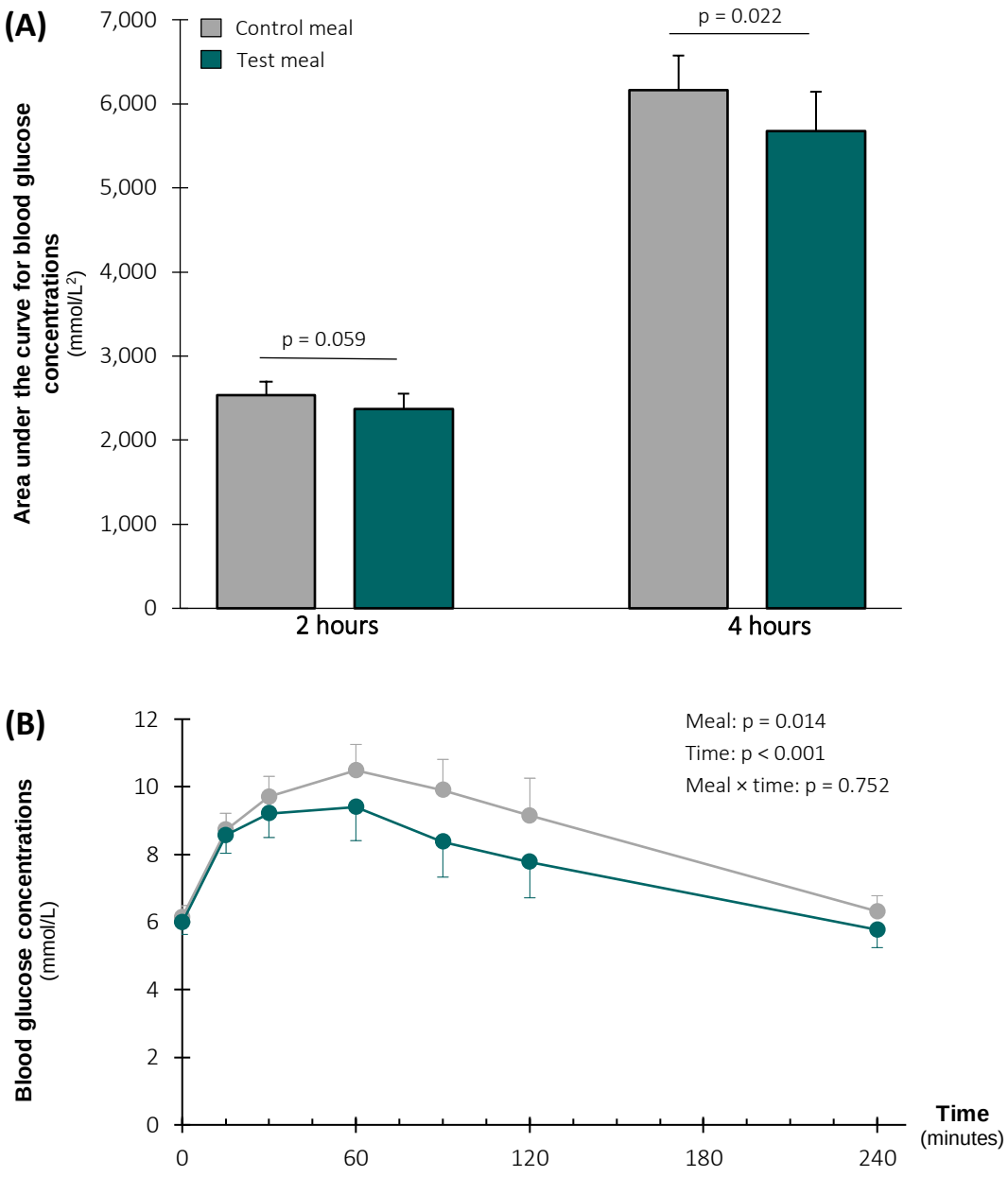

Figure 5.2 Postprandial blood glucose responses presented as areas under the curve **(A)** and individual time-points **(B)** over the 4-hour postprandial period (n=7). Values are means, with vertical bars representing standard error. P-values are presented for paired t-tests (A) and 2-way repeated measures ANOVA (B).

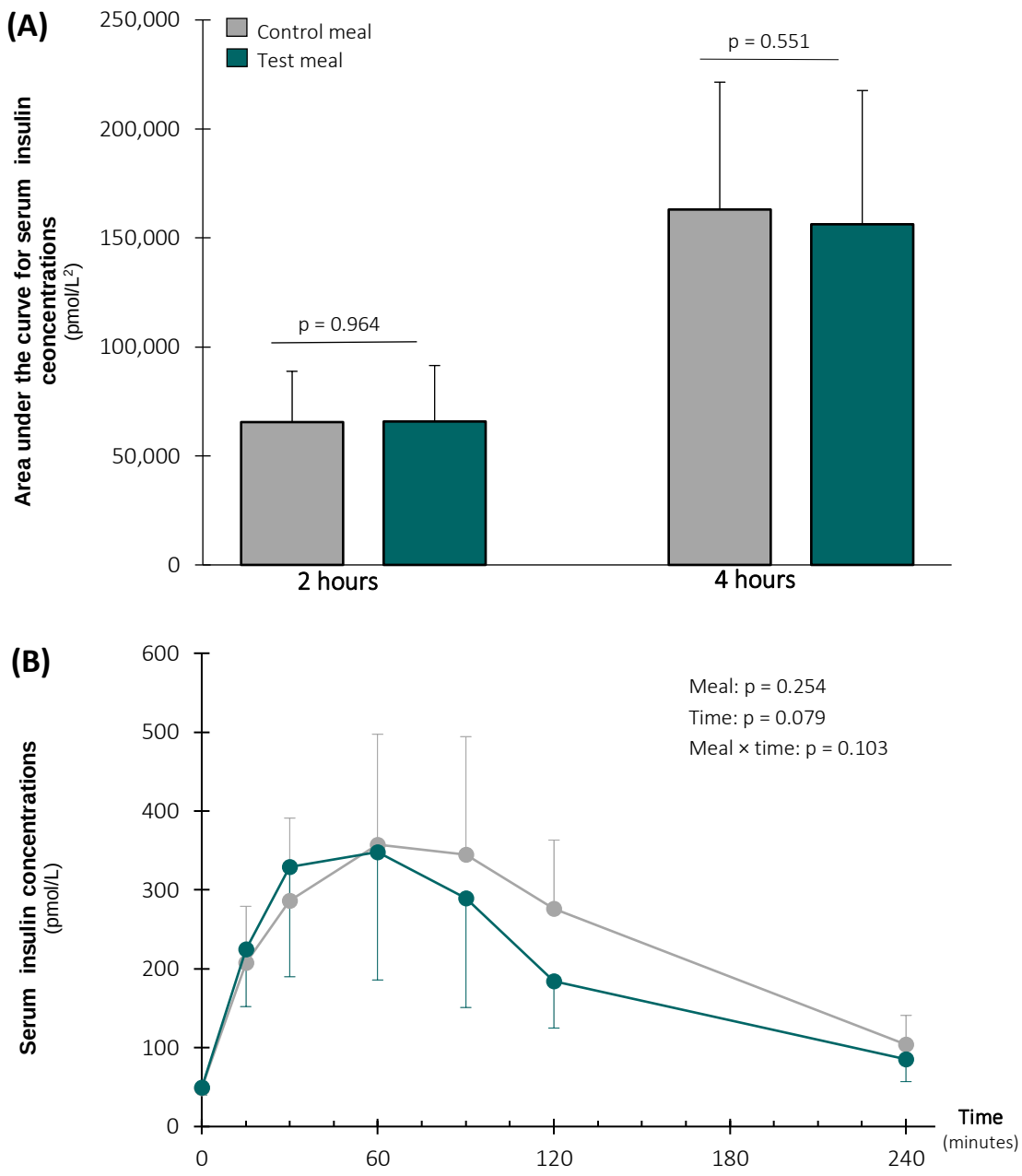

Figure 5.3 Postprandial serum insulin concentrations presented as areas under the curve **(A)** and individual time-points **(B)** over the 4-hour postprandial period (n=7). Values are means, with vertical bars representing standard error. P-values are presented for paired t-tests **(A)** and 2-way repeated measures ANOVAs **(B)**.

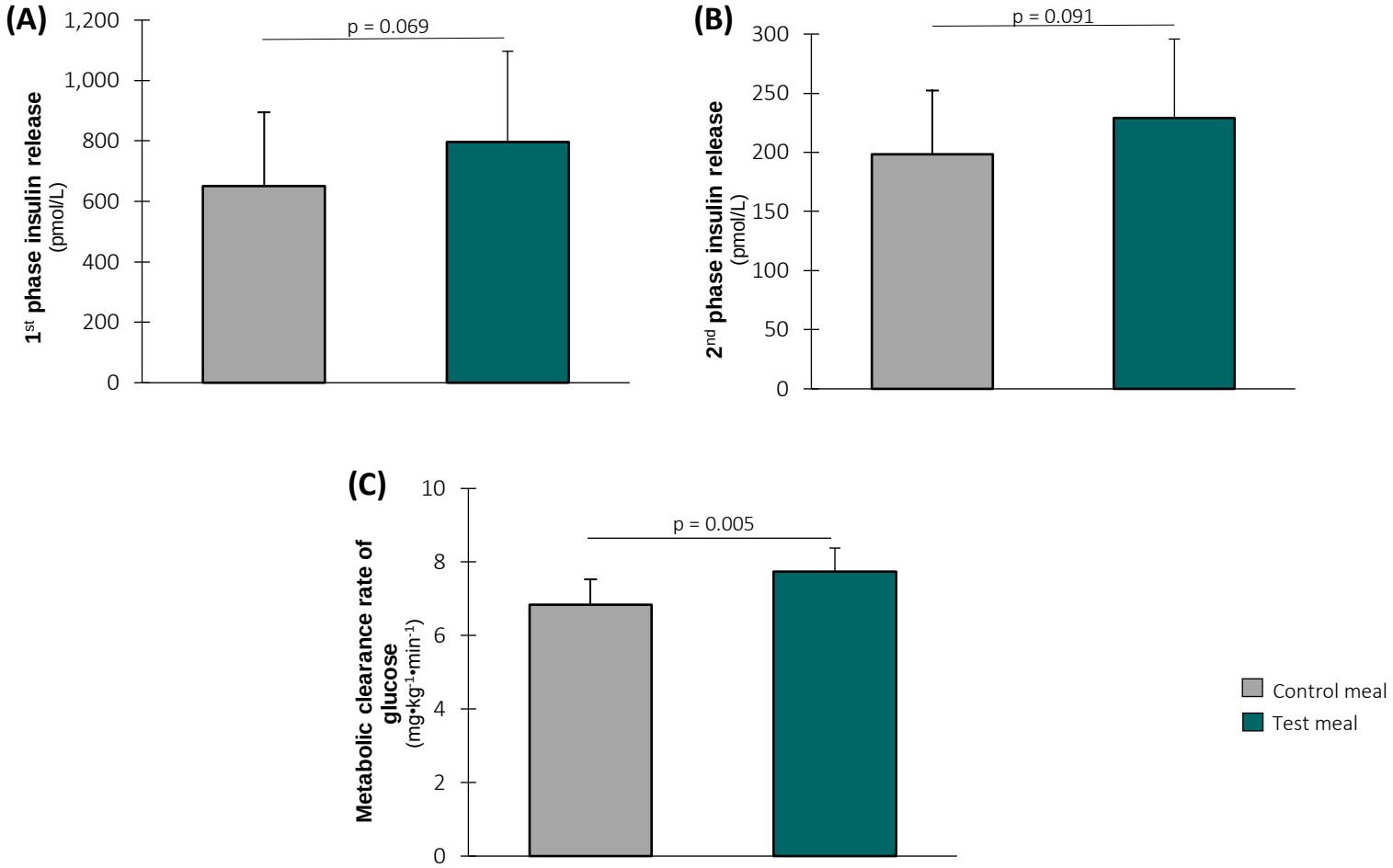

Figure 5.4 Paired comparison between the control and test meals for **(A)** 1st phase insulin release, **(B)** 2nd phase insulin release, and **(C)** metabolic clearance rate of glucose calculated from 2-hour glycemic and insulinemic responses, using Stumvoll et al.'s (2000) [28] predictive equations (n=7). Values are means, with vertical bars representing standard error. All p-values are presented for paired t-tests.

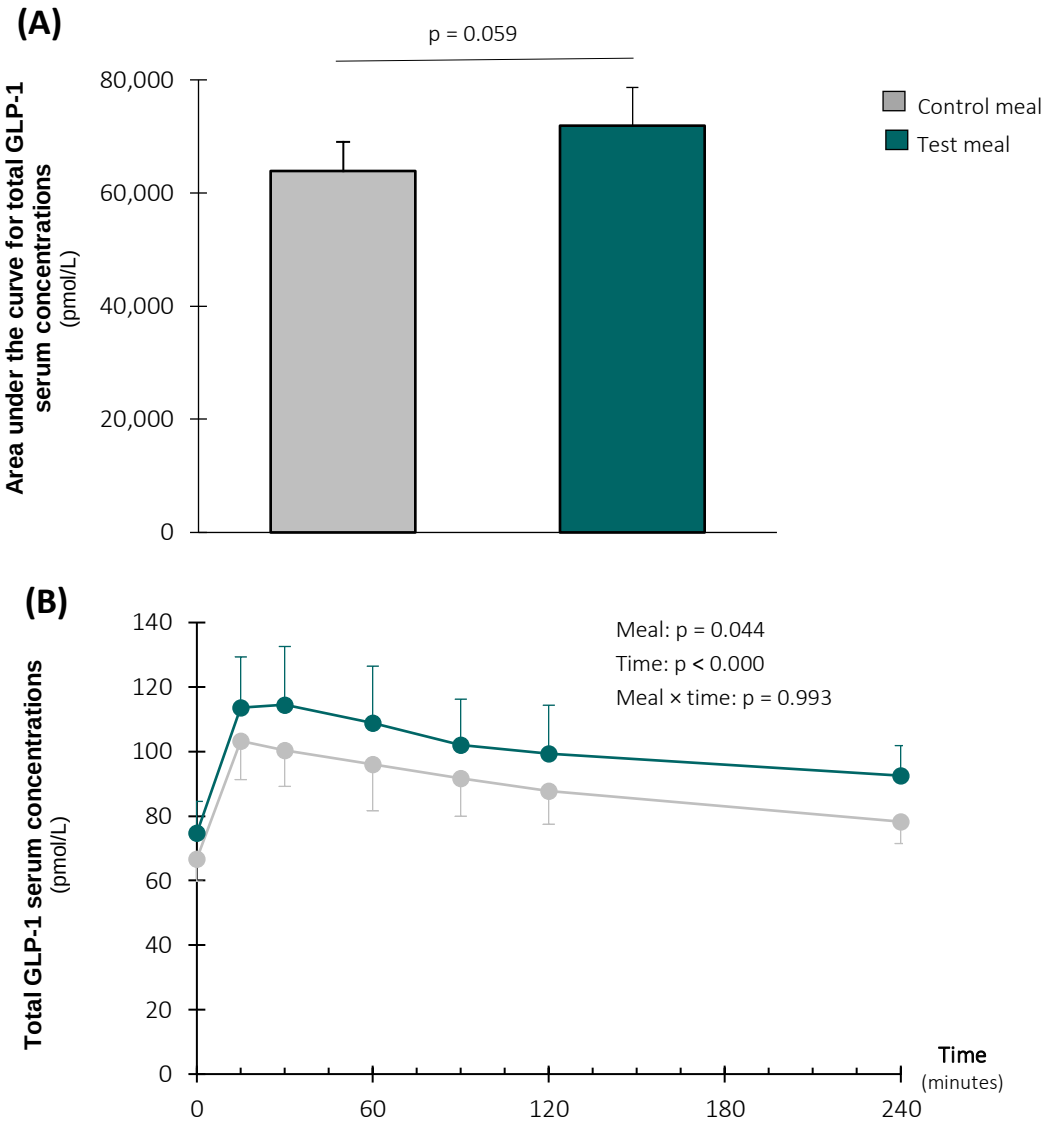

Figure 5.5 Postprandial serum total GLP-1 concentrations presented as areas under the curve **(A)** and individual time-points **(B)** over the 4-hour postprandial period (n=7). Values are means, with vertical bars representing standard error. P-values are presented for paired t-tests **(A)** and 2-way repeated measures ANOVAs **(B)**.

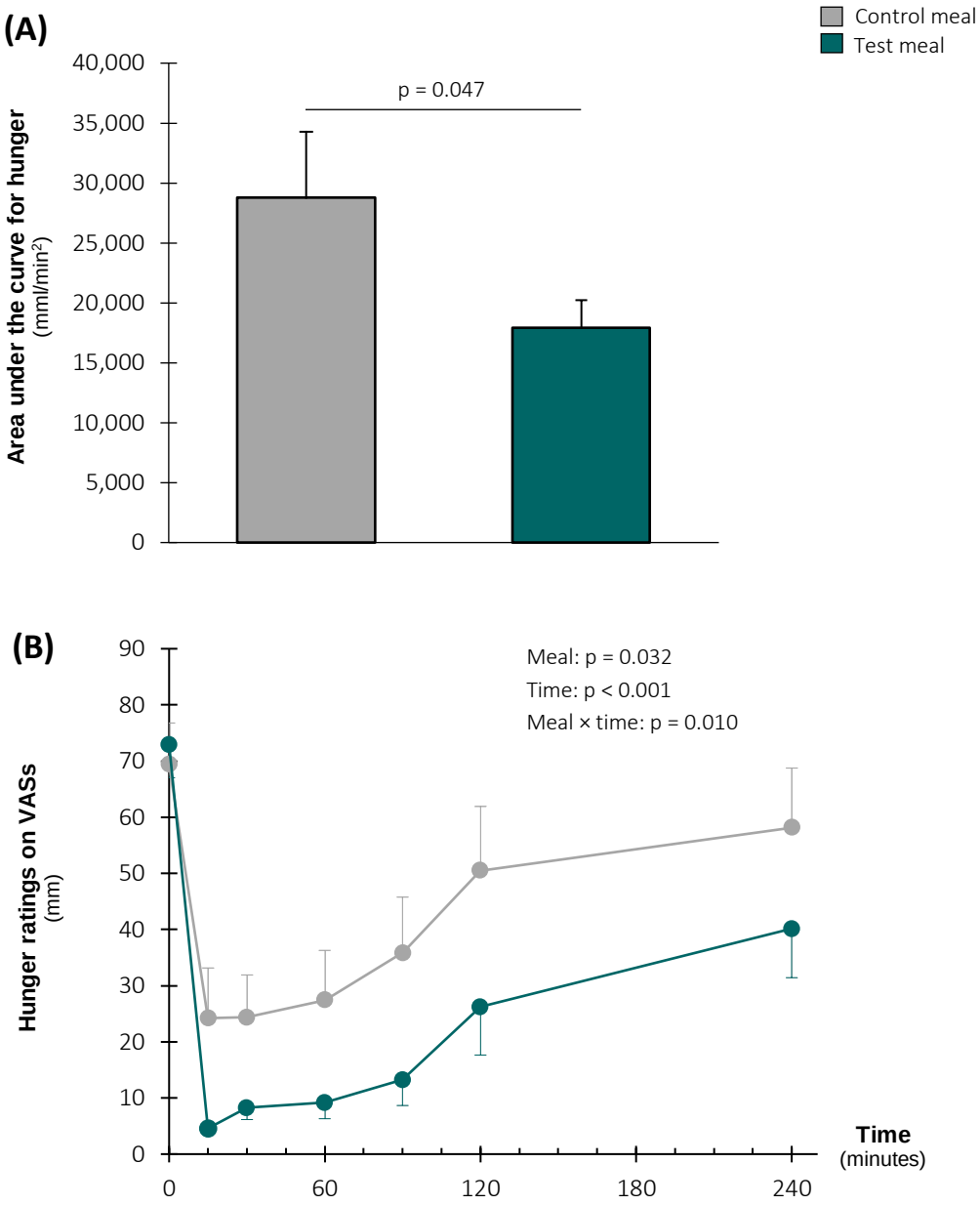

Figure 5.6 Postprandial subjective hunger levels presented as areas under the curve **(A)** and individual time-points **(B)** over the 4-hour postprandial period (n=7). Values are means, with vertical bars representing standard error. P-values are presented for paired t-tests **(A)** and 2-way repeated measures ANOVAs **(B)**.

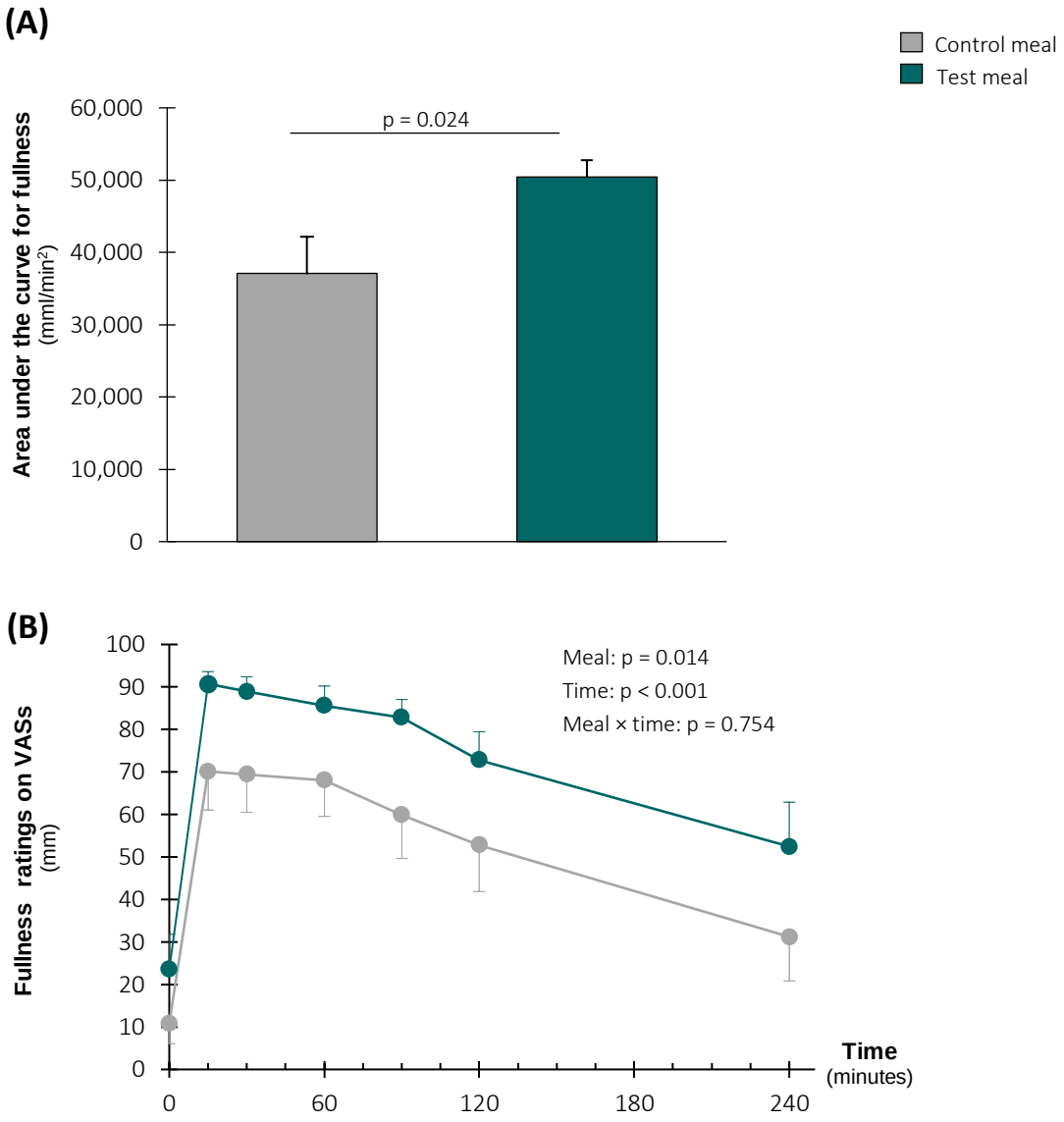

Figure 5.7 Postprandial subjective fullness levels presented as areas under the curve **(A)** and individual time-points **(B)** over the 4-hour postprandial period (n=7). Values are means, with vertical bars representing standard error. P-values are presented for paired t-tests **(A)** and 2-way repeated measures ANOVAs **(B)**.

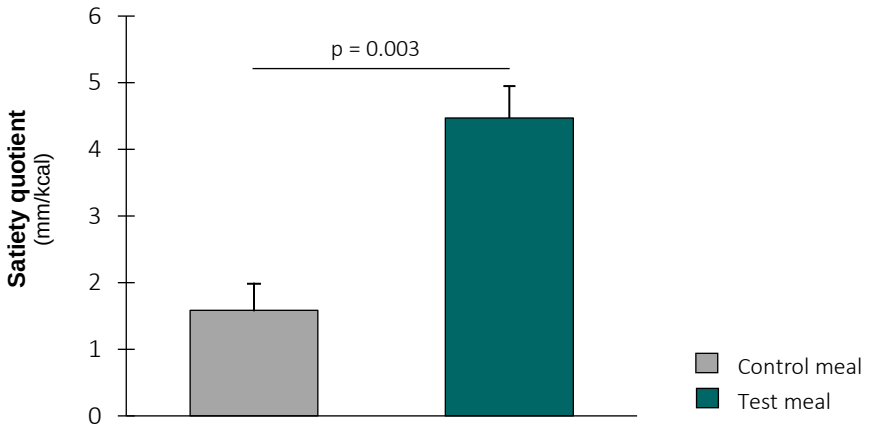

Figure 5.8 Paired comparison between the control and the test meal for the satiety quotient (n=7). Values are means, with vertical bars representing standard error. The p-value is presented for a paired t-test.

CHAPTER 6

General discussion and conclusion

6.1 SUMMARY AND DISCUSSION OF MAIN RESULTS

The burden for individuals with T2D lies, among others factors, in its chronic nature, in the numerous complications associated with its development, as well as in the continuous increase in its worldwide prevalence [287]. Indeed, T2D is associated with a two- to fourfold increase in the risk of developing cardiovascular diseases [287, 288] and is the leading cause of blindness [287, 289, 290], end-stage renal disease [287, 291], and non-traumatic foot amputation [287, 290, 292] in Canadian adults. Individuals with T2D also exhibit higher rates of clinically significant anxiety and depressive symptoms [4, 293, 294], generalized anxiety disorders [293], and major depression [4, 293–295].

According to Wild et al.'s (2004) predictions, the worldwide prevalence of T2D is likely to at least double between 2000 and 2030 [296]. Similarly, in Canada, the prevalence of T2D in adults over 20 years old is expected to increase, from 9.3% in 2015 to 12.1% in 2025 [287]. This emphasizes the need for the development of more effective prevention strategies and also justifies the necessity of continuously improving T2D management strategies, including the nutritional ones.

To hopefully contribute to the process of improving nutritional strategies for the management of T2D, we assessed, in the first part of the study presented in this thesis (see Chapter 4), the influences of gender/sex on the relative ranking of the importance of common determinants of food choices, as well as on the consumption and sensory evaluation of almonds, pistachios, avocados, oatmeal, and eggs in a sample of middle-ages adults. The five foods were selected for their potential beneficial effects on postprandial glycemia and insulinemia, GLP-1 secretion, and subjective appetite sensations. Their macronutrient content and the available literature on their metabolic effects also contributed to the decision of selecting these foods, Furthermore, based on the sensory evaluation and participants' willingness to include these foods in their diet, almonds were included in the test meal of the second part of the study presented in this thesis (see Chapter 5). The second part of the study aimed to assess the effects of the

subtypes of macronutrients contained in isocaloric macronutrient-matched meals on postprandial glycemic, hormonal and appetite responses in middle-aged men with T2D.

6.1.1 DETERMINANTS OF FOOD CHOICES, SENSORY EVALUATION AND CONSUMPTION OF HEALTH-PROMOTING FOODS

The results of the first part of the study showed that, in a sample of middle-aged adults, *"taste and own food preferences"* was the determinant of food choices that participants perceived as having the greatest influence. This result is not surprising, as several previous studies have also shown that the level of appreciation of the sensory attributes of food, particularly the taste, is one of the most important drivers of food choices [297–305]. Furthermore, due to the strong association between food preferences and food intake, food marketing studies frequently use self-reported food preferences and sensory appreciation as predictors of food intake [306].

In this sample of participants, women perceived a significantly higher influence of their *"own food beliefs related to health"* than men, while the perceived influence of the *"recommendations of a health professional"* trended higher in men than women. These results are also in line with those of previous studies which suggested that women were more likely to rely on their own food-related knowledge, while, in men, dietary changes were often prompted by recommendations of a health professional [116–120, 122]. Interestingly, we found no significant differences in the ranking of common determinants of food choices between cardiometabolically healthy participants and those with a diagnosis of prediabetes or T2D, which could be due to our small sample size.

The sensory evaluation of the five foods revealed a higher appreciation of the taste of pistachios, almonds, eggs, and avocados as compared to oatmeal, as well as higher appreciation of the taste of almonds and pistachios as compared to avocados. Women rated some sensorial attributes (i.e., taste, texture and palatability) of almonds and pistachios higher than men, however no gender/sex-related differences were found in the frequency of consumption of these two foods. Interestingly, despite the rather low taste ratings and the absence of gender/sex-

related differences, women reported consuming oatmeal significantly more often than men. This could be explained by women's higher willingness to compromise on the taste of foods for their beneficial health effects [35]. There were positive associations between taste appreciation and frequency for pistachios and avocados.

6.1.2 ACUTE EFFECTS OF AN ISOCALORIC BREAKFAST MEAL CONTAINING ALMONDS ON GLYCEMIC, HORMONAL AND APETITE RESPONSES IN MEN WITH TYPE 2 DIABETES

The results of the second part of the study presented in this thesis showed that even when matching the energy and macronutrient content of the control and the test meals, the inclusion of almonds was associated with lower postprandial glycemia, decreased hunger, and increased fullness. Postprandial GLP-1 serum concentrations were also significantly increased by the test meal, however no changes in serum insulin concentrations were observed. These results partly confirm our initial hypotheses; given the well-known incretin effect on GLP-1, we were expecting to observe an increase in postprandial serum insulin concentrations, especially those of GLP-1 were found to be significantly increased by the test meal. To explore possible explanations for the lower postprandial glycemia despite the absence of increased postprandial insulin serum concentrations, we used Stumvoll et al.'s (2000) [307] predictive equations to assess postprandial insulin sensitivity as well as the 1st and 2nd phases of insulin secretion. We found that postprandial insulin sensitivity was significantly higher following the ingestion of the test meal and that there was trend towards an enhanced 1st phase insulin secretion.

Almonds are a low-glycemic index food containing several nutrients et biochemical compounds with well-supported health benefits [308]. As shown in **Table 5A** of Chapter 5, the main differences in the macronutrient composition of the control and test meals were their fiber content as well as in the types of fatty acids they contained. There were also a few important differences in the micronutrient content of the two meals; the test meal contained more vitamin E, magnesium and potassium, and less sodium than the control meal. Based on previous studies

assessing the metabolic effects of almonds as well as those of individual nutrients contained in almonds, it is almost unequivocal that the observed effects are attributable to a combination of factors. The lower postprandial glycemia associated with the consumption of the test meal could result from a decreased and/or slowed-down carbohydrate absorption as well as the enhanced insulin sensitivity and the slightly higher 1st phase insulin secretion. The mechanisms potentially explaining the lower postprandial glycemia and part of the effect on appetite sensation could have been influenced by fiber and short-chain fatty acids derived from their colonic fermentation [309–311], MUFAs and PUFAs, as well as the ratio of MUFAs to SFAs [312–316].

6.2 STRENGHTS AND LIMITATIONS

A unique aspect and strength of this study is the combination of the two parts; one rather focused on food preferences, and the other on the metabolic effects of food. Despite being one of the most important determinants of food choices and intakes, food preferences are often overlooked in intervention studies. Foods having well-supported health benefits are not always well-liked, and therefore, their inclusion in the diet of the general population or in that of a specific target group of the population, such adults with T2D, can be poor.

An important limitation of both parts of this study is the small sample size and the possible sampling biases. Small sample sizes limit statistical power and increase the risks of type II errors. A type II error is the failure to reject, or the incorrect acceptance of the null hypothesis. Furthermore, as convenience sampling was used, there is an increased likelihood of under- and/or over-representation of certain groups of the population. In the first part of the study which uses a cross-sectional study design, this constitutes a limitation; participants had high education levels and household incomes generally superior to the Canadian mean, which limits the generalizability of the results. In the second part of the study, while still limiting the generalizability of the results, the homogeneity of participants' characteristics can constitute also constitute a strength. Being an acute intervention study, limiting variability in participants' characteristics, in

the second part of the study can help isolate the effects of the independent variable and contribute to increase statistical power.

6.3 SIGNIFICANCE AND CONTRIBUTION TO THE ADVANCEMENT OF KNOWLEDGE

To our knowledge, this is the first study to assess 1) the appreciation of the sensorial attributes of almonds, pistachios, avocados, oatmeal, and eggs in a sample of middle-aged adults with or without a diagnosis of prediabetes or T2D and 2) the acute effects of almonds as part of an isoenergetic macronutrient-matched meal on metabolic markers in middle-aged men with T2D.

Our results show that several health-promoting foods (i.e., almonds, pistachios, avocados, and eggs) are well appreciated by both men and women and could serve as a starting point for future studies in the field of food sciences. Furthermore, with only one previous study using isocaloric macronutrient-matched meals to evaluate almonds' effect on the postprandial glycemic response of healthy adults, the second part of this study contributes to advancing knowledge in this field. Our study is one of the first to assess the acute metabolic effects of almonds in adults with T2D, the population in which dietary manipulations improving glycemic response are of particular interest and especially needed.

In the long run, if the results of this study are replicated and possibly extended to other population groups, evidence-based recommendations on the consumption of almonds could be developed.

6.4 FUTURE RESEARCH DIRECTIONS

Several research avenues resulting from the analysis of the study data of the present theses merit further investigation in the future.

In line with the **first part** of the study presented in this thesis, other topics that would merit further investigation are gender/sex-related differences in the sensory evaluation of foods from all four main food groups (i.e., vegetables and fruit, grain products, milk and alternatives, as well as meat and alternatives), reasons explaining gender/sex-related differences in food preferences, as well as types of nutrition-related messages preferred by men and women. Additionally, as briefly mentioned in Chapter 4, quantitative and qualitative studies aiming to identify factors increasing men's willingness to compromise on the taste of foods for their health benefits, as well as the level of compromise that they perceive as acceptable in the long run could have important clinical implication and serve as a basis a rather new subtopic of research in the area of eating behaviours and food preferences. With regards to sensory evaluation and food preferences, the inclusion of foods with well-supported health effects in other food vehicles as a mean to promote their consumption is another promising and clinically relevant research area. For example, in line with the first part of the study, oatmeal and avocados, which were less appreciated by participants, could be consumed in other forms as well as included in or combined with other foods (e.g., oats could be included in other food products such as bread, crackers, muffins, etc., avocados could be included in smoothies, salad dressings, hummus, desserts, etc.) to increase their acceptability and thus possibly promote their consumption.

To follow-up on the results of the **second part** of the study presented in this thesis, several studies assessing both the acute and the chronic effects of almond ingestion could be conducted. We showed that almonds, as part of an isocaloric macronutrient-matched meal, increase postprandial GLP-1 serum concentrations, decrease hunger, and promote fullness in men with T2D. In addition to assessing the reproducibility of these results in another sample of adults with T2D, a future acute-effect study could assess whether the changes observed in GLP-1 serum concentrations and appetite sensations translate into a diminution of energy intake at the meal. If our results are reproduced or partly reproduced by future studies, another relevant research avenue would be to assess and compare the effects of the consumption of different quantities of almonds. In our study, we used a rather large quantity of almonds (i.e., 90g, which equals to approximately 3 standard portions) to maximize the chances of observing significant

differences and allowing to understand almonds' effects on metabolism, as previous studies [273, 276] reported a dose-depend effect of almonds on postprandial glycemia. However, since almonds are an energy-dense food, the ideal would be to identify the lowest possible amount necessary to observe an effect in individuals with T2D. This amount is likely to vary based on factors such as glycemic control, type of medications used, and possibly sex, which would require reproducing the same study in several homogenous samples of participants. For instance, in our study, participants were all men in a quite narrow age range (i.e., age range: 55 – 70 years), using 500mg of Metformin (Glucophage®) twice a day, and with a rather well-controlled glycemia.

To date, most studies assessing the effect of chronic ingestion of almonds in adults with T2D have focussed on common indicators of glycemic control (i.e., fasting BG and %HbA1C), insulin secretion and sensitivity, as well as inflammatory markers. Given almonds high fiber content and knowing that SCFAs produced through the colonic bacterial fermentation of non-digestible carbohydrates are potent stimulators of GLP-1 secretion, it could be worthwhile assessing whether their chronic ingestion can lead to changes in the composition of the gut microbiota, and if so, whether these changes could further enhance SCFAs production. Indeed, studies have shown that diet composition can have important effects on the composition of the gut microbiota [317–319], and that, in turn, the composition of the gut microbiota influences the production of SCFAs [320]. On another note, since GLP-1R's agonists and DPP-IV inhibitors are increasingly used in the pharmacological management of T2D, it could be of increasing interest to evaluate the influence of diet composition on the efficacy of some antihyperglycemic drugs. In particular, as DPP-IV inhibitors' pharmacological action depends on the bioavailability of GLP-1, combining the use of this drug type with as diet promoting GLP-1 secretions could enhance DPP-IV inhibitors' action and in the long run potentially allow the use of lower doses.

6.5 CONCLUSION

Results presented in this thesis highlight the importance of taste and food preferences and point some gender/sex-related differences in the determinants of food choices. They also

support the beneficial effects of almonds, a food that seems well appreciated by both men and women, on key therapeutic targets of T2D management, namely postprandial glycemia, insulin sensitivity, GLP-1 secretion, and subjective appetite sensations.

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APPENDIX 1 – Nutritional modulation of endogenous glucagon-like peptide-1 secretion: a review

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Nutritional modulation of endogenous glucagon-like peptide-1 secretion: a review

Alexandra M. Bodnaruc[1,2,3], Denis Prud'homme[1,2], Rosanne Blanchet[3] and Isabelle Giroux[2,4*]

Abstract

Background: The positive influences of glucagon-like peptide-1 (GLP-1) on blood glucose homeostasis, appetite sensations, and food intake provide a strong rationale for its therapeutic potential in the nutritional management of obesity and type 2 diabetes.

Aim: To summarize GLP-1 physiology and the nutritional modulation of its secretion in the context of obesity and type 2 diabetes management.

Findings: GLP-1 is mainly synthesized and secreted by enteroendocrine L-cells of the gastrointestinal tract. Its secretion is partly mediated by the direct nutrient sensing by G-protein coupled receptors which specifically bind to monosaccharides, peptides and amino-acids, monounsaturated and polyunsaturated fatty acids as well as to short chain fatty acids. Foods rich in these nutrients, such as high-fiber grain products, nuts, avocados and eggs also seem to influence GLP-1 secretion and may thus promote associated beneficial outcomes in healthy individuals as well as individuals with type 2 diabetes or with other metabolic disturbances.

Conclusion: The stimulation of endogenous GLP-1 secretion by manipulating the composition of the diet may be a relevant strategy for obesity and type 2 diabetes management. A better understanding of the dose-dependent effects as well as the synergistic effects of nutrients and whole foods is needed in order to develop recommendations to appropriately modify the diet to enhance GLP-1 beneficial effects.

Keywords: Diet, Appetite regulation, Blood glucose, Enteroendocrine L-cells, G-protein coupled receptors

Background

Type 2 diabetes (T2D) is a major public health concern due to its pandemic occurrence and its association with several physical and psychological comorbidities [1, 2], as well as with a decreased quality of life [3]. It is widely accepted that obesity, especially excessive fat accumulation in the abdominal area, is the most important predictor of T2D development. Indeed, it is estimated that 60 to 90% of T2D incidence is related to excessive weight gain and obesity [4]. After the onset of T2D, obesity also contributes to increasing the risks of comorbidities and overall mortality rates [5]. The global prevalence of overweight and obesity is expected to reach 57.8% by 2030 [6]. Following a similar trend, the worldwide prevalence of T2D has been projected to double between 2000 (2.2%) and 2030 (4.4%) [7].

Nutrition, along with physical activity and behavioural changes, are cornerstones of obesity and T2D management. Weight loss is induced by a state of sustained negative energy balance, which almost inevitably involves a reduction of energy intake [8]. From a purely thermodynamic perspective, a decrease in energy intake results in weight loss regardless of the type of dietary modifications through which it is achieved. Nonetheless, weight maintenance and improvements in cardiometabolic biomarkers are significantly impacted by the composition of the diet (i.e. macro- and micronutrient contents) [8]. One potential mechanism by which diet composition can influence these outcomes is through its influence on the secretion of gastrointestinal (GI) peptide hormones, including that of glucagon-like peptide-1 (GLP-1) [9]. The latter has been associated with a reduction of appetite and food intake, and appears to

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positively influence blood glucose homeostasis, by acting on the pancreas and the central nervous system [10].

The secretion of GLP-1 is partly mediated by the binding of nutrients to G-protein coupled receptors (GPCRs) expressed by enteroendocrine GI cells [11]. Therefore, manipulating the diet in a way to promote interactions with these receptors could increase GLP-1 secretion and enhance its beneficial effects [11]. This review focuses on GLP-1 physiology and the nutritional modulation of its secretion from enteroendocrine GI cells in the context of obesity and T2D management. It presents recent evidence on possible mechanisms by which specific foods, as well as nutrients and their by-products, could increase GLP-1 secretion, and subsequently influence appetite, food intake, and blood glucose control.

Glucagon-like peptide-1 in the gut-brain-pancreas axis

Synthesis, secretion, and metabolism

The GI tract accomplishes several functions, namely the digestion of food, the absorption of nutrients, and the secretion of digestive juices, mucus, and peptide hormones. The epithelium of the GI wall is composed of several cell types, including enteroendocrine cells which are a key component of the gut-brain-pancreas axis [12]. On their apical surface, enteroendocrine cells possess microvilli expressing several GPCRs that are binding to nutrients and other substrates present in the GI lumen [12]. Enteroendocrine cells can be divided into several subcategories depending on their distribution throughout the GI tract, their GPCRs' expression and their secretory profile. GLP-1 is synthesized and secreted by enteroendocrine L-cells which are expressed over a large portion of the GI tract, starting in the proximal small intestine and progressively increasing in density down to the distal part of the colon. GLP-1 is stored in secretory granules of L-cells until its secretion is triggered, and then uses endocrine and neuronal routes to exert its functions in the pancreas and central nervous system [10]. In addition to L-cells, GLP-1 is synthesized to a lesser extent by neurons of the nucleus tractus solitarius (NTS) of the brainstem [13, 14].

GLP-1 is produced in two major active forms, namely GLP-1 (7-36 amide) and GLP-1 (7-37 amide), and is resulting from the differential processing of its precursor proglucagon [10]. Its synthesis appears to be attributed to tissue-specific expression of pro-hormone convertase 1 and 3 which cleave proglucagon [15]. Proglucagon is a 160-amino acid inactive precursor of several peptide hormones, including glucagon, oxyntomodulin and GLP-1 [16]. Proglucagon encoding gene is expressed in the intestine, the pancreas, as well as the central nervous system [16]. Several studies have confirmed that this gene produces identical messenger ribonucleic acid (mRNA) transcripts in these major expression sites, but is translated and processed differently, thus producing different bioactive peptides depending on the expressing tissue [17–19].

In humans, blood concentrations of GLP-1 generally range between 5 pmol/L and 15 pmol/L in fasting state and increase two- to four-folds after food ingestion [10]. More specifically, GLP-1 blood concentrations rise within 15 minutes after food ingestion and reach a pick after approximately 60 minutes [10]. In the second hour, GLP-1 concentrations start to decrease gradually until the next prandial episode [10]. Postprandial GLP-1 secretion is influenced by both neuroendocrine and nutritional factors, and exhibits a two-phase release profile that is in fact very similar to that of insulin. The initial phase of its secretion, which is detectable 10 to 15 minutes after food ingestion, is thought to be mostly influenced by neuroendocrine factors, and, to a lesser extent, by the interaction of nutrients with L-cells in the proximal small intestine. Conversely, the second phase of GLP-1 secretion, which occurs 30 to 60 minutes postprandially, is mostly influenced by the arrival of nutrients in the distal part of the small intestine and the colon [20]. Nutrients and their by-products bind to GPCRs and activate intracellular pathways that ultimately trigger GLP-1 exocytosis from L-cells' secretory granules [10]. When secreted, GLP-1 can activate vagal afferent neural fibres, as well as diffuse into nearby capillaries and then reach the systemic circulation through the portal vein [10]. In the bloodstream, GLP-1 is highly susceptible to the catalytic activity of the enzyme dipeptidyl-peptidase IV (DPP-IV). The latter cleaves two NH_2-terminal amino acids of the active forms of GLP-1 (i.e. 7-36 amide, 7-37 amide) leading to the production of their biologically inactive forms (i.e. 9-36 amide, 9-37 amide) [21–23]. As a result, GLP-1's half-life is very short – about 1 to 2 min [22, 23]. Animal and *in vitro* studies have shown that less than 25% of the newly secreted bioactive GLP-1 reaches the liver intact [22, 23]. Further catalytic activities take place in the liver, and consequently, only approximately 10-15% of the newly secreted GLP-1 reaches the systemic circulation in its active forms [22, 23].

Action in the pancreas

One of the best-known and probably most important effects of GLP-1 is its ability to stimulate insulin secretion in response to carbohydrate consumption [24–27]. In pancreatic β-cells, GLP-1 activates intracellular pathways that increase intracellular calcium concentrations and subsequently leads to insulin exocytosis from secretory granules [24, 25]. GLP-1 has also been shown to promote insulin gene transcription and biosynthesis [28]. GLP-1 seems to be responsible for nearly half of the total postprandial insulin secretion [29]. This process, known under the name of

"incretin effect", is defined as the differential augmentation in insulin secretion observed after oral glucose intake, compared to intravenous glucose administration resulting in the same blood glucose concentrations [30].

GLP-1 is partly fulfilling its actions in pancreatic β-cells through an endocrine pathway by directly interacting with its receptors (GLP-1Rs). Indeed, competitive inhibition of GLP-1Rs of pancreatic β-cells in rodents and humans resulted in a significant reduction of insulin secretion, as well as in impaired glucose tolerance [26, 27]. Nonetheless, the glucose-lowering effects of GLP-1 are not solely related to its insulinotropic effect, but also to its strong inhibition of glucagon secretion [10, 31]. This effect seems to be partly mediated by the increased insulin and somatostatin secretion from pancreatic islets occurring during the postprandial period, as well as by GLP-1 direct interaction with its receptors on pancreatic α-cells [32–34]. In rodents, prolonged administration of GLP-1 also appears to promote pancreatic β-cell growth by increasing their proliferation and decreasing apoptosis [35–38].

Action in the central nervous system

In addition to its action in the pancreas, GLP-1 plays a role in both homeostatic and non-homeostatic regulations of food intake, which occur in distinct areas of the central nervous system [39, 40]. The homeostatic regulation of food intake, related to short- and long-term energy status, is mainly taking place in the hypothalamus and NTS, areas which convey and integrate numerous peripheral signals [39, 40]. The hypothalamus contains several interconnected nuclei, including the arcuate nucleus (ARC), the paraventricular nucleus (PVN), as well as the dorsomedial nucleus (DMN) [39, 40]. Due to its anatomical position, the ARC plays a critical role in transmitting peripheral information related to energy and nutrient status to other central structures. Indeed, the ARC is situated in the medio-basal area of the hypothalamus, where the blood-brain barrier is highly permeable, and thus likely has a greater exposition to circulating factors [39]. The ARC contains two distinct populations of neurons: 1) the orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) expressing neurons, and 2) the anorexigenic pro-opiomelanocortine (POMC), as well as cocaine and amphetamine-regulated transcript (CART) expressing neurons [39, 40]. Additionally, POMC is a precursor of the α-melanocyte stimulating hormone (α-MSH), a neuropeptide with potent anorexigenic effects [39, 40]. Upon release, POMC and α-MSH activate neurons of the PVN, which inhibits food intake [39, 40]. Conversely, by inhibiting PVN neurons' activation, NPY and AgRP stimulate food intake [39, 40]. Opposite to the PVN, DMN neurons are activated by NPY and AgRP, promoting food intake, and are inhibited by POMC and α-MSH, reducing food intake [39, 40].

GLP-1Rs are widely expressed in the hypothalamus, with the highest expression being described to be in POMC/CART neurons of the ARC, followed by DMN neurons [13, 14, 41–44]. A small quantity of GLP-1 appears to diffuse through the blood-brain barrier and directly bind to its receptors on POMC/CART and NPY/AgRP neurons [45]. In rodents, the peripheral administration of a GLP-1 analogue has been shown to directly activate neurotransmission in POMC/CART neurons, while exerting an inhibitory action in NPY/AgRP neurons [46, 47]. Nonetheless, in reason of its short half-life, endogenous GLP-1 released from L-cells is likely mostly acting on the central nervous system by indirectly stimulating neurons of the NTS and ARC via the activation of vagal afferent neurons [48]. Indeed, GLP-1Rs have been identified on neurons of the nodose ganglion of the vagus nerve [43, 49], and the importance of this pathway in the regulation of food intake has been confirmed in rats, where vagal deafferentation decreased the effects of intraperitoneally administered GLP-1 [50, 51]. While the exact mechanisms and their relative contributions to the observed effects remain to be fully elucidated, the GLP-1's implication in the homeostatic regulation of food intake is well established. In rodents, acute intraperitoneal, subcutaneous or intravenous administration of GLP-1 and GLP-1 analogues have constantly been shown to reduced meal size, as well as cumulative food and energy intakes [51–56]. Similarly, in humans, acute intravenous administration of GLP-1 and GLP-1 analogues decreased appetite, hunger and food intake, and increased fullness and satiety sensations [57–62].

In addition to physiological energy needs, food intake is driven by non-homeostatic central pathways involved in reward processing and reward-motivated behaviours [63, 64]. The palatability of food is a crucial determinant of the decision to eat. As a result, highly palatable food, typically high in energy, lipids, and simple carbohydrates, can trigger food intake in the absence of physiological energy needs [63, 64]. Several central structures, such as the orbitofrontal cortex, insula, amygdala, and striatum play an important role in the processing and evaluation of food cues [65]. Increased activation of these areas of the central nervous system in response to visual and olfactory food cues (referred to as *"anticipatory food reward"*) is associated with increased craving for highly palatable foods [66, 67]. Furthermore, upon food ingestion, dopaminergic neurons send projections from the ventral tegmental area to the nucleus accumbens and other forebrain areas [63, 64]. Dopamine release in these areas of the brain is well correlated with meal pleasantness in healthy individuals with a normal body mass index [68]. Activation of these areas in response to food consumption is referred to as *"consummatory food*

reward". Reduced consummatory food reward is associated with compensatory overeating [65–67, 69, 70]. GLP-1Rs have been identified in areas of the brain involved in anticipatory and consummatory food reward processing, and neurons of the NTS also share dense neuronal connections with these areas [71, 72]. Recent pre-clinical and clinical studies suggest a role of GLP-1 in the modulation of food reward processing. More specifically, the exogenous administration of GLP-1 and GLP-1 analogues appears to influence dopamine neurotransmission in several central areas, and has been associated with decreased anticipatory food reward, increased consummatory food reward and decreased intake of hyperpalatable foods [65, 69, 70, 73–77].

Glucagon-like peptide-1 as a target for obesity and type 2 diabetes management

The positive influences of GLP-1 on many metabolic disturbances associated with T2D, as well as key determinants of weight loss and weight maintenance, make it a therapeutic target with good potential. GLP-1 has been studied in relation to obesity and T2D pathophysiology and treatment. While few studies have shown contradictory results, it is generally well accepted that obesity and metabolic changes occurring with the development of T2D are associated with a decline in the postprandial secretion of GLP-1 from L-cells [78–83]. Overtime, this change in GLP-1's secretion can contribute to further weight gain and adversely impact T2D progression. As a potential strategy to enhance GLP-1actions, several researchers have investigated the metabolic effects of intravenous administration of GLP-1 analogues. Interestingly, when receiving the same dose of a GLP-1 analogue, individuals with obesity and T2D exhibited metabolic and appetite responses that were very similar to their healthy counterparts [57–59, 62, 84, 85]. This finding suggests that sensibility to GLP-1's action is maintained, which is contrary to several other peptide hormones involved in energy and blood glucose homeostasis [86, 87]. Consequently, targeting GLP-1Rs' activation with GLP-1 analogues and increasing GLP-1 half-life in the bloodstream became an area of interest for the management of obesity and T2D. This led to the development of two classes of pharmacologic agents, namely GLP-1Rs agonists and DDP-IV inhibitors [88, 89]. GLP-1Rs agonists are widely used for blood glucose management in individuals with T2D and have recently been approved to use for weight management in the United States [88–90]. Similarly, DDP-IV inhibitors are used alone or in combination with other pharmaceutical agents to inhibit the catabolic deactivation of endogenous GLP-1 [88, 89]. Compared to other commonly used antihyperglycemic drugs such as sulfonylureas and thiazolidinedione, pharmaceutical agents targeting GLP-1's action are associated with lower risks of hypoglycaemia, and have the advantage of promoting weight loss as well as potentially preventing, or at least delaying the progressive decrease in pancreatic β-cell function which generally requires increasing drug dosage [35–38, 89, 91]. Most frequent side effects reported with the use of these agents include GI discomfort, nausea and vomiting [88, 89].

Another relevant, yet less studied, strategy to increase GLP-1's action is to promote its endogenous secretion from L-cells. This could potentially be achieved through pharmacological and dietary approaches. The main critic of dietary approaches is that dietary changes may not lead to a sufficient increase in GLP-1 blood concentration to promote beneficial physiological actions such as improvements in insulin secretion and blood glucose concentrations. Indeed, GLP-1Rs agonist mimic supraphysiological blood concentrations of GLP-1 and have a far longer half-life, varying between 1.5 hours and 5 days depending on the agent [89]. Nonetheless, GLP-1Rs agonists only exert their effects through an endocrine route, while endogenous GLP-1 employs both endocrine and neuronal routes, and therefore such high concentrations may not be needed. In fact, changes in GLP-1 blood concentrations after bariatric surgery suggest that a rise within physiologically normal blood concentrations may be sufficient to promote beneficial metabolic effects. Several studies have shown that Roux-en-Y gastric bypass increases GLP-1 blood concentrations up to fourfold 6 months to 1 year after the procedure [92, 93]. This increase in GLP-1 concentrations is associated with improvements in dietary choices and intake, further excess weight loss, improved glycaemic control, and often T2D resolution [92, 94]. Le Roux et al. [92] showed that individuals who underwent Roux-en-Y gastric bypass within 36 months had significantly higher GLP-1 blood concentrations 30 minutes following a meal ingestion (47.4 ± 11.4 pmol/L) compared to subjects with morbid obesity (13.5 ± 6.9 pmol/L). Postprandial GLP-1 concentrations observed in subjects who underwent Roux-en-Y gastric bypass were within physiologically normal GLP-1 concentration ranges, and therefore it is plausible that promoting a similar increase in GLP-1 postprandial secretion with dietary approaches would promote similar beneficial actions on food intake, glycaemic control and weight management over time.

Nutritional modulation of glucagon-like peptide-1 secretion

The nutrient composition of ingested food and meals varies considerably between individuals and within the same individual over the course of the day. In this regard, macronutrient composition of the diet has been shown to influence appetite and metabolic responses, including glycaemia and insulinemia [95, 96]. One possible mechanism to explain the differential effects of macronutrients on these parameters is the modulation of GLP-1 secretion by their catabolic by-products. As described

above, L-cells' GPCRs bind several products of food and macronutrients' breakdown, including monosaccharides [97–102], short-chain fatty acids (SCFAs) [103–109], medium and long-chain fatty acids [110, 111] , as well as amino acids and peptides [112–116], leading to GLP-1 secretion.

Nutrients and single-nutrient foods

Monosaccharides

Upon ingestion, digestible carbohydrates undergo enzymatic degradation and are absorbed in the form of glucose, and to a lesser extent in the form of galactose and fructose. Glucose absorption by enterocytes as well as glucose-mediated GLP-1 secretion from L-cells appear to be mediated by the sodium glucose transporter-1 (SGLT-1), a membrane transport protein expressed in the small intestine [97–102]. Moriya and colleagues [98] investigated the mechanisms underlying glucose-stimulated GLP-1 secretion by administering glucose and Phloritzine, a competitive inhibitor of SGLT-1, in the small intestine of mice. While glucose administration alone acutely increased circulating GLP-1, co-administration of glucose and Phloritzine blocked first-phase glucose-induced GLP-1 secretion [98]. Similarly, compared to controls, SGLT-1 knockout mice had decreased first-phase GLP-1 secretion and developed glucose and galactose malabsorption [99]. This is explained by the fact that glucose binding to SGLT-1 induces the closure of ATP-sensitive potassium channels, leading to membrane depolarization and to a rise in intracellular calcium concentrations [117]. Collectively, this work outlines the importance of SGLT-1 in luminal monosaccharide absorption, as well as glucose-mediated GLP-1 secretion in the proximal small intestine. The characterization of GLP-1's secretion as being biphasic led researchers to investigate the prolonged effect the pharmacological inhibition of SGLT-1 in rodents and humans [100–102]. While also confirming an inhibition of first-phase GLP-1 secretion and an increase in luminal glucose concentrations, Powell and al. [100] found an increase in second-phase GLP-1 secretion and a decrease in blood glucose excursions over a 6-hour postprandial period in mice. These results were confirmed in two clinical studies conducted in healthy adults, as well as in adults with T2D [101, 102]. The increase in second-phase GLP-1 secretion observed in these studies suggests that SGLT-1 inhibition enhances other mechanisms promoting GLP-1 secretion from the distal part of GI tract. As proposed by the authors, possible explanations include an enhanced opportunity for interactions with L-cells as carbohydrates move down the GI tract during digestion, as well as an increased fermentation of undigested carbohydrates in the colon which could raise the production of SCFAs [100–102]. Concordant with the latter hypothesis, Powell and al. [100] observed a decrease in the pH of the caecum – which could indeed be an indicator of increased bacterial fermentation – in SGLT-1 knockout mice as well as mice that received a SGLT-1 inhibitor.

Non-digestible carbohydrates and short-chain fatty acids

In the colon, non-digestible carbohydrates undergo fermentation, leading, depending on their type, to the production of various amounts of SCFAs [118–121]. SCFAs are carboxylic acids that contain fewer than 6 carbons, the most abundant ones being acetate, butyrate and propionate [122]. In humans, SCFAs concentrations range from ~130 mmol/L in the caecum to ~80 mmol/L in the descending colon [122, 123]. Acetate appears to be the most abundant SCFA in the colon, followed by propionate and butyrate, with an overall colonic molar ratio of 50-60:15-20:10-20, respectively [122, 123].

Fermentable dietary fiber and their metabolites, the SCFAs, seem to promote GLP-1 secretion from L-cells by interacting with the free fatty acid receptors 2 and 3 (FFAR2, FFAR3) [103–109]. An *in vitro* study showed that propionate was the most potent agonist of both FFAR2 and FFAR3, that acetate was more active and selective on FFAR2, and that butyrate was more active on FFAR3 than FFAR2 [105]. In colonic cell cultures, physiological concentrations of acetate, butyrate and propionate have been shown to stimulate GLP-1 secretion [124]. The role played by FFAR2 and FFAR3 in the SCFA-induced GLP-1 secretion was confirmed by demonstrating the loss of postprandial GLP-1 secretion in FFAR2 and FFAR3 knockout intestinal cells [124]. Similar results were found *in vivo*, where propionate-induced GLP-1 secretion was lost in FFAR2 knockout rodents [125]. Additionally, Chambers and colleagues [126] recently showed that acute targeted delivery of propionate in the colon through an inulin-propionate ester supplement acutely stimulated GLP-1 secretion following a standard breakfast meal and reduced energy intake at a buffet-style lunch in adults with overweight or obesity. Concordant with the acute effects of GLP-1 on appetite sensations and food intake, daily delivery of propionate in the colon over 6 months also reduced body weight, abdominal fat and hepatic lipid accumulation as assessed with magnetic resonance imagery and spectroscopy [126].

The effects of diets rich in fermentable fiber on GLP-1 secretion have also been investigated in animal models and humans [127, 128]. Indeed, the main way to increase colonic SCFA concentrations in humans is through non-digestible carbohydrate consumption. The results from six experimental studies assessing the impact of fiber on GLP-1 secretion in animal models and humans are summarized in Table 1. Compared to a standard control diet, the consumption of a diet enriched in fermentable fiber for 50 days increased GLP-1 concentrations in the proximal colon, which was associated with an increased

Table 1 Chronic[a] effects of non-digestible carbohydrates on glucagon-like peptide-1 (GLP-1) secretion and associated outcomes

Studies	Experimental model	Dietary intervention	Main outcomes measured
Cani 2005a [129]	) Male Wistar rats	Oligofructose (10% of diet[b])	↑ GLP-1 concentrations in the proximal and medial colon ↑ Proglucagon mRNA concentrations in the caecum and proximal colon ↓ Triglyceride blood and hepatic concentrations ↓ Food and energy intake ↓ Body weight gain
Cani 2005b [132]	) Streptozotocin-treated diabetic rats	Oligofructose (10% of diet[b])	↑ Proglucagon mRNA concentrations in the proximal colon ↑ Pro-hormone convertase 1 mRNA concentrations in the proximal colon ↑ GLP-1 concentrations in the portal vein ↑ Glucose tolerance ↑ Insulin and C-peptide blood concentrations ↑ Pancreatic β-cell mass ↓ Food and energy intake
Cani 2005c [131]	) Healthy men and women	Oligofructose (16 g/day)	↓ Energy intake over 24 hours ↑ Satiety ↓ Hunger ↓ Prospective food consumption
Cani 2006 [133]	) Male C57BL/6 J mice with high-fat feeding-induced diabetes	Oligofructose (10% of diet[b])	↑ GLP-1 concentrations in the proximal colon ↑ GLP-1 concentrations in the portal vein ↑ Proglucagon mRNA concentrations in the proximal colon ↑ Blood and pancreatic insulin concentrations ↓ Fasting and postprandial blood glucose concentrations
Cani 2007 [134]	) Male Wistar rats	Oligofructose (10% of diet[b])	↑ GLP-1 concentrations in the portal vein and proximal colon ↑ Proglucagon mRNA concentrations in the proximal colon ↑ L-cell number in the proximal colon ↑ Neurogenin-3 and Neuro-D mRNA concentrations in the proximal colon ↓ Food and energy intake ↓ Body weight gain
Zhou 2008 [130]	) Sprague-Dawley rats) Streptozotocin-treated C57BL/6 J mice	Resistant starch (53% of diet[b])	↑ GLP-1 blood concentrations ↑ PYY blood concentrations ↓ Variation in blood glucose and insulin concentrations ↑ Proglucagon and PYY colonic mRNA concentrations ↑ Glucose tolerance in diabetic mice

GLP-1 Glucagon-like peptide-1, *mRNA* Messenger ribonucleic acid, *PYY* Peptide tyrosine-tyrosine
[a] 10 days - 1 year interventions
[b] weight : weight proportion

expression of proglucagon in colonic L-cells [129]. Fermentable fiber also decreased food intake, weight gain, as well as blood triglyceride concentrations and triglyceride accumulation in the liver [129]. Similarly, while also increasing GLP-1 blood concentrations and proglucagon expression in the colon, consumption of a diet rich in resistant starch for 10 days increased peptide tyrosine-tyrosine (PYY) blood concentrations and colonic expression in rats [130]. This result is not surprising as the anorectic PYY is also synthesized and released from L-cells, and its secretion could be stimulated by similar mechanisms as that of GLP-1. In healthy humans, a crossover pilot study showed that the daily supplementation with 16 g of fermentable fiber for a two-week period increased postprandial satiety, and decreased hunger, prospective food consumption as well as energy intake over 24 hours following the intake of a standard breakfast meal [131]. As GLP-1 blood concentrations were not assessed in this study, it is not known whether these effects were mediated by an increase in its secretion or through other mechanisms [131]. The effects of fermentable fiber in rodent models of diabetes were comparable to those found in healthy animals. Indeed, consumption of a diet enriched with fermentable fiber for 4 to 6 weeks increased GLP-1 concentrations in the proximal colon and portal vein, as well proglucagon expression in the proximal colon [132, 133]. In streptozotocin-treated diabetic rats, the fiber-enriched diet also up-regulated pro-hormone convertase 1 expression in the proximal colon and increased pancreatic β-cell mass which potentially mediated the improvement in glucose tolerance and the observed increase in insulin and C-peptide blood concentrations [132]. In mice with high-fat diet-induced diabetes, these effects were diminished with the use of a GLP-1R antagonist and were completely lost in a GLP-1R knockout group of rats, therefore confirming the importance of GLP-1 interaction with its receptors for exerting its beneficial effects [133].

Overall, results from these studies suggest some pathways linking fermentable fiber to its positive effects on food intake, body weight gain and blood glucose

homeostasis via an increased secretion of GLP-1. Fermentable fiber and SCFAs produced by their colonic fermentation appear to increase GLP-1 synthesis by upregulating the expression of proglucagon [129, 132–134], as well as that of pro-hormone convertase 1 [132], which, as discussed above, is responsible for its cleavage [15]. Cani and colleagues [134] also found an increased proximal colon's L-cell number with fermentable fiber consumption, which could be another possible explanation for the increased GLP-1 synthesis and secretion. The increase in L-cell number was also associated with an enhanced expression of transcription factors that are critical for the differentiation of intestinal stem cells into enteroendocrine cells, namely neuregenin-3 and neuro-D [134].

Free fatty acids

The majority of dietary lipids are triglycerides, which are composed of a glycerol molecule and three fatty acids [135]. Upon ingestion, triglycerides undergo emulsification by bile salts in the duodenum, hydrolysis by lipases, and are absorbed by enterocytes in the form of glycerol and free fatty acids [135].

Free fatty acids, such as unsaturated long-chain fatty acids, are potent stimulators of GLP-1 release through interactions with free fatty acid receptors 1 and 4 (FFAR1, FFAR4) [110, 111]. Substrate binding to FFAR1 and FFAR4 activate phospholipase C, leading to inositol triphosphate mediated calcium release from the endoplasmic reticulum into the cytosol [136]. The secretion of GLP-1 has been shown to be increased by unsaturated long-chain fatty acids. The main outcomes of nine experimental studies assessing the impact of lipid consumption on GLP-1 secretion and blood concentrations are summarized in Table 2. Thomsen and colleagues (1999, 2003) were the first ones to assess GLP-1 responses following a meal containing olive oil in healthy adults or adults with T2D [137, 138]. Compared with a meal containing butter, which is high in saturated fatty acids (SFAs), the ingestion of the olive oil containing meal resulted in higher postprandial GLP-1 blood concentrations [137, 138]. However, no significant acute difference in blood glucose, nor insulin blood concentrations was observed [137, 138]. In a subsequent study conducted in rodents, the prolonged consumption of an olive oil-enriched diet resulted in an increased GLP-1 secretion, which coincided with a higher glucose-stimulated insulin secretion, as well as an improved glucose tolerance at the 36th day of the intervention [139]. Comparable results were found in Streptozotocin-treated diabetic rats, where the intake of a diet rich in monounsaturated fatty acids (MUFAs) from olive oil for 50 days increased GLP-1 blood concentrations, decreased weight gain and improved insulin sensitivity [140]. In humans with abdominal obesity and insulin resistance, Paniagua and colleagues [141] showed that ingestion of a Mediterranean diet rich in olive oil for 28 days resulted in significantly higher postprandial GLP-1 blood concentrations. Compared to a diet high in SFAs, consumption of the Mediterranean diet also improved insulin sensitivity, an effect which could have mediated the observed decrease in insulin secretion as well as fasting and postprandial blood glucose concentrations [141].

In addition to the beneficial effects of MUFAs, some studies showed that the colonic administration of the polyunsaturated α-linolenic acid acutely increased GLP-1 and insulin blood concentrations, and decreased blood glucose concentrations in healthy and diabetic rat models [142]. Similarly, while also resulting in increased GLP-1 blood concentrations, long-term administration of α-linolenic acid has been shown to increase β-cell proliferation in rodents [143]. As GLP-1 has been shown to decrease apoptosis, as well as to increase neogenesis of pancreatic β-cells, the authors hypothesized that the increased β-cell proliferation was mediated by the increase in GLP-1 concentrations induced by α-linolenic acid ingestion [143]. A recent study showed that fish oil and flax seed oil, which are a source of α-linolenic acid, increased FFAR4 expression in rodents' colon and decreased the expression of the pro-inflammatory tumour necrosis factor α (TNFα) [144].

Taken together, these studies suggest that, with similar energy contents, diets that are richer in MUFAs or omega-3 polyunsaturated fatty acids (PUFAs) than in SFAs, could increase GLP-1 secretion from L-cells, which may be a mediator for the increase in insulin secretion, insulin sensitivity, β-cell proliferation, as well as the improved glucose tolerance observed in animal models and in humans.

Peptides and amino acids

Dietary proteins are generally described as the most satiating nutrient, an effect which may be partly mediated by the stimulation of anorexigenic GI peptides secretion, including that of GLP-1 [145–147]. Upon ingestion, proteins are broken down by acid hydrolysis and proteases to produce peptones, tripeptides, dipeptides and single amino acids. Specifics mechanisms responsible for protein-induced GLP-1 secretion are relatively poorly understood, and the optimal profile of proteins' breakdown products remains to be elucidated. Nonetheless, two pathways by which products of protein breakdown seem to stimulate GLP-1 secretion is through their binding to the calcium-sensing receptors (CaSR) and the class C, group 6, subtype A GPCR (GPCR-C6A) which are expressed on L-cells. CaSR binds to a variety of amino acids including phenylalanine, tryptophan, asparagine, arginine, glutamine and histidine, as well as to peptones, tri- and dipeptides [112–116]. *In vitro*, their binding to CaSR stimulated GLP-1 secretion, and this effect was abolished with the use of a CaSR inhibitor

Table 2 Acute[a] and chronic[b] effects of monounsaturated fatty acids (MUFAs) and omega-3 polyunsaturated fatty acids (PUFAs) on glucagon-like peptide-1 (GLP-1) secretion and associated outcomes

Studies	Experimental model	Dietary intervention	Main outcomes measured
Thomsen 1999 [137]	) Healthy men and women	MUFAs from olive oil[a] (80 g)	↑ GLP-1 blood concentrations ↑ Glucose-insulinotropic peptide blood concentrations
Thomsen 2003 [138]	) Men and women with T2D	MUFAs from olive oil[a] (80 g)	↑ GLP-1 blood concentrations ↓ Triglyceride blood concentrations ↑ High-density lipoprotein cholesterol blood concentrations
Hirasawa 2005 [136]	) Male C57/B6 rats	α-linolenic acid (0.1 μmol)[a]	↑ GLP-1 blood concentrations ↑ Insulin blood concentrations
Prieto 2005 [139]	) Wistar rats	MUFAs from olive oil[b,c]	↑ GLP-1 blood concentrations ↑ Glucose-stimulated insulin secretion ↑ Glucose tolerance
Cancelas 2006 [140]	) Streptozotocin-treated diabetic rats	MUFAs from olive oil[b,c]	↑ GLP-1 postprandial secretion ↑ Insulin sensitivity ↓ Weight gain
Adachi 2006 [142]	) Male C57BL/6 J mice) Diabetic male NSY mice) C3H/He mice	α-linolenic acid (0.3 μmol)[a]	↑ GLP-1 blood concentrations ↑ Insulin blood concentrations ↓ Blood glucose concentrations
Paniagua 2007 [141]	) Insulin resistant men and women	MUFAs from an olive-oil containing Mediterranean diet (23% of total energy intake)[b]	↑ Postprandial GLP-1 concentrations ↑ Insulin sensitivity ↓ Postprandial insulin secretion ↓ Fasting and postprandial blood glucose concentrations
Tanaka 2008 [143]	) Male Wistar rats	α-linolenic acid (3 μmol)[a,b]	↑ GLP-1 blood concentrations ↑ pancreatic β-cell number and mass
Cheshmehkani 2015 [144]	) Male Sprague-Dawley rats	Fish or flaxseed oil[b,d] (10% of diet)	↑ FFAR4 expression in the colon ↓ TNFα blood concentrations

FFAR4: Free fatty acid receptor 4; GLP-1: Glucagon-like peptide-1; MUFAs: Monounsaturated fatty acids; SCFAs: Short-chain fatty acids; TNFα: Tumour necrosis factor α

[a] Acute effect (5 minutes post-consumption)

[b] Chronic effect (28 to 50 days of consumption)

[c] Specific MUFA content not known

[d] weight : weight proportion

[112–116]. Oya and colleagues [148] have shown that GPCR-C6A binds to the basic amino acids arginine, lysine and ornithine. The stimulatory effect of these amino acids on GLP-1 secretion was abolished in GPCR-C6A knockout intestinal cells [148].

Mixed-nutrient foods

In contrast with single nutrients and single-nutrient foods (e.g. oil), more complex foods containing a mix of nutrients are more representative of what humans consume and could allow targeting a combination of enteroendocrine pathways that would synergistically enhance GLP-1 secretion. In regards to T2D management, clinical guidelines recommend carbohydrate intake from high-fiber foods such as vegetables, fruit, legumes and whole grains, while limiting SFAs intake and promoting that of MUFAs and omega-3 PUFAs [149, 150], all of which have been associated to different extents with an increased GLP-1 secretion.

Some experimental studies conducted with healthy individuals have examined the effects of several specific foods on glycemic response, subjective appetite sensations as well as energy intake at a subsequent meal [151–168]. The main findings of these studies are summarized in Table 3. Several researchers have investigated the effects of high-fiber grain products, which could enhance GLP-1 secretion by binding to SGLT-1, FFAR2 and FFAR3. In this regard, two recent studies compared appetite responses after isoenergetic breakfast meals containing ready-to-eat breakfast cereals (low-fiber) or oatmeal (high-fiber) among healthy young adults [151, 152]. Compared to ready-to-eat breakfast cereals, oatmeal (66.8 g) increased fullness, and reduced hunger, desire to eat, as well as subjective prospective food intake [151, 152]. Furthermore, oatmeal decreased energy intake at the following meal [152]. Likewise, in adults with insulin resistance, daily consumption of a high wheat-fiber breakfast cereal (test group, 24 g/day of fiber from the cereal) for one year, significantly increased colonic SCFAs production, as well as GLP-1 blood concentrations compared to low-fiber breakfast cereals (control group, 0.5 g/day of fiber from the cereal) [165]. More

Table 3 Summary of experimental studies assessing the effects of mixed-nutrient foods on glucagon-like peptide-1 (GLP-1) secretion and associated outcomes

Studies	Subjects		Dietary intervention		Main outcomes measured
	N	Characteristics	Food	Duration	
Rebello 2013 [151]	48	) Healthy[a]	Oatmeal[b] (66.8 g)	4 h	↑ Fullness ↓ Hunger ↓ Desire to eat ↓ Prospective food consumption
Rebello 2016 [152]	48	) Healthy	Oatmeal[b] (66.8 g)	4 h	↑ Fullness ↓ Hunger ↓ Desire to eat ↓ Prospective food consumption ↓ Energy intake at the next meal
Freeland 2010 [165]	28	) Hyperinsulinemia	High-fiber cereal (24 g/day)	1 year	↑ Acetate and butyrate blood concentrations ↑ GLP-1 blood concentrations
Nilsson 2015 [166]	20	) Healthy	Barley kernel-based bread[c] (100 g of available starch per day)	3 days	↑ PYY postprandial blood concentrations ↑ GLP-1 fasting blood concentrations ↑ Fasting and postprandial breath hydrogen concentrations ↑ Total SCFAs and acetate fasting blood concentrations ↓ Blood glucose postprandial concentrations ↓ Insulin postprandial blood concentrations
Jenkins 2006 [156]	15	) Healthy	Raw almonds[b] (60.0 g)	4 h	↓ Blood glucose postprandial concentrations ↓ Insulin postprandial blood concentrations ↓ Oxydative damage to proteins measured in blood serum
Josse 2007 [167]	9	) Healthy	Raw almonds[c] (30, 60 and 90 g)	4 h	↓ Blood glucose postprandial concentrations[d]
Jenkins 2008 [157]	27	) Hyperlipidemia	Raw almonds- (37.0 and 73.0 g)	1 month	↓ 24-hour insulin secretion
Mori 2011 [159]	14	) Impaired glucose tolerance	Raw almonds[c] (42.5 g)	8 h	↓ Blood glucose concentrations ↑ Insulin blood concentrations ↓ Non esterified fatty acid blood concentrations after a second meal ↑ Fullness
Kendall 2011 [153]	10	) Healthy	Pistachios[b] (28.0, 56.0 and 84.0 g)	2 h	↓ Blood glucose concentrations[d]
Kendall 2014 [154]	20	) Metabolic syndrome	Pistachios[c] (85.0 g)	3 h	↑ GLP-1 postprandial blood concentrations ↑ Glucose-insulinotropic peptide postprandial blood concentrations ↓ Blood glucose postprandial concentrations ↑ Insulin postprandial blood concentrations
Reis 2013 [168]	30	) Obese women	(a) Whole peanuts[c] (42.5 g) (b) Peanut butter[c] (42.5 g)	8 h	↓ Blood glucose concentrations after second standard isocaloric meal (b) ↑ Insulin postprandial blood concentrations (a,b) ↓ Non esterified fatty acid blood concentrations after second meal (b) ↑ PYY postprandial blood concentrations (b) ↓ Desire to eat following the second meal (a,b)
Parham 2014 [155]	48	) Type 2 diabetes	Pistachio[d] (50.0 g per day)	12 weeks	↓ Fasting blood glucose concentrations ↓ Percentage of glycated blood haemoglobin ↓ Systolic blood pressure ↓ Body mass index ↓ C-reactive protein blood concentrations
Ratliff 2010 [160]	21	) Healthy men	Whole egg[b] (3)	24 h	↓ Blood glucose postprandial concentrations ↓ Ghrelin postprandial blood concentrations ↓ Insulin postprandial blood concentrations ↓ Hunger ↑ Satisfaction ↓ Energy intake at lunch and over 24 hours
	31	) Healthy	Whole eggs[b] (2)	4 h	↑ Fullness

Table 3 Summary of experimental studies assessing the effects of mixed-nutrient foods on glucagon-like peptide-1 (GLP-1) secretion and associated outcomes *(Continued)*

Pombo-Rodrigues 2011 [162]				↓ Desire to eat ↓ Prospective food consumption
Vander Wal 2005 [161]	30) Overweight women	Whole eggs[b] (2)	36 h	↑ Satiety ↓ Energy intake at the next meal and over 24 and 36 hours
Liu 2015 [163]	28) Healthy children and adolescents	Eggs[b]	3 h	↑ PYY postprandial blood concentrations
Wien 2013 [164]	26) Overweight	Fresh avocado[b] (50.0 to 90.0 g)	3 h	↓ Insulin postprandial blood concentrations ↓ Desire to eat ↑ Satisfaction

GLP-1 Glucagon-like peptide-1, *PYY* Peptide tyrosine-tyrosine, *SCFAs* Short-chain fatty acids
[a] Unless otherwise mentioned, study samples include adults of both sexes
[b] Isocaloric test and control meals, however, not marched for macronutrient contents
[c] Test and control meals matched for carbohydrate content only
[d] In a dose-dependent matter

specifically, at 9 months into the intervention, acetate and butyrate plasma concentrations were already significantly higher in the test group [165]. Along the same lines, Nilsson and colleagues [166] showed that consumption of high-fiber barley kernel-based bread for 3 days was associated with increased fasting GLP-1 blood concentrations, as well as increased postprandial PYY blood concentrations in healthy adults. These changes in GI peptides concentrations were associated with improved insulin sensitivity and decreased postprandial blood glucose concentrations in healthy individuals [166]. The fact that the authors found an increase in breath hydrogen and SCFAs blood concentrations, suggests that the positive effects of the barley kernel-based bread were mediated by an increased SCFAs production triggered by the colonic of dietary fiber [166].

The addition of foods with a high protein, MUFAs and fiber content, such as almonds (30.0 to 90.0 g) or pistachios (28.0 to 85.0 g) to a high-carbohydrate meal has also been shown to improve postprandial glycemic responses in a dose-dependent manner [153–159, 167]. Jenkins and colleagues [156] also found a decrease in insulin secretion in healthy adults and in adults with hyperlipidemia following acute and prolonged almond consumption. Similarly, daily intake of 50.0 g of pistachios for 12 weeks decreased C-reactive protein blood concentrations, systolic blood pressure, and body mass index in adults with T2D [155]. In women with obesity, consumption of peanuts (42.5 g) or peanut butter (42.5 g) as part of a standard breakfast meal increased postprandial insulin blood concentrations and decreased desire to eat following a standard lunch meal [166]. Additionally, peanut butter significantly increased postprandial PYY blood concentrations and decreased postprandial blood glucose concentrations following the standard lunch meal [166]. Since GLP-1 and PYY are co-released from L-cells [12], it is plausible that peanut butter may also promote postprandial GLP-1 secretion. Only three of these studies assessed GLP-1 blood concentrations [154, 159, 168]. Mori et al. [159] found no significant differences in GLP-1 blood concentrations following the addition of 42.5 g of almonds to a carbohydrate-containing meal, which could be due to the small sample size of the study. Indeed, with a larger sample size, Kendall et al. [154] found higher GLP-1 and glucose insulinotropic peptide blood concentrations following the addition of 85.0 g of pistachios to a carbohydrate-containing meal in adults with metabolic syndrome. As Reis et al. [168] showed no statistically significant difference in GLP-1 blood concentrations with the addition of 42.5 g of peanuts or peanut butter to a carbohydrate-containing meal, it is also possible that higher quantities of nuts are necessary to induce a sufficient rise in GI hormone secretion.

Consumption of eggs (2 to 3), which are high in protein and also contain MUFAs, for breakfast or lunch, has been shown to improve subjective postprandial appetite sensations [160–163]. Furthermore, when compared to a bagel breakfast, consumption of a breakfast containing eggs (3) in adult men was associated with a lower postprandial blood glucose concentrations, decreased hunger, and reduced energy intake in the next 24 hours [160]. Men also reported higher subjective satisfaction after eating eggs [160]. While GLP-1 blood concentrations were not measured in these studies, Li and al. [163] found a significant increase in postprandial blood concentrations of PYY in adolescents following ingestion of an egg-containing breakfast compared to an isocaloric bagel breakfast. One study also showed that adding avocado (50 to 90 g), which is high in fiber and MUFAs, to a high-carbohydrate isocaloric meal improved subjective satiety sensation and satisfaction [164].

Discussion and Conclusion

In light of this literature review, it is evident that manipulating the composition of the diet in order to

promote GLP-1 secretion represents a promising lifestyle strategy for obesity and T2D management. The therapeutic potential of GLP-1 has already been established as several pharmaceutical agents promoting its effects are successfully used for blood glucose management in individuals with T2D, and for body weight management in individuals with obesity [87, 89]. In comparison with the use of GLP-1Rs agonists and DPP-IV inhibitors, targeting endogenous pathways through dietary modifications has the added benefits of potentially stimulating the release of other anorexigenic gut peptides (e.g. PYY), promoting beneficial changes in several markers of cardiometabolic health such as helping normalize blood lipid profile and blood pressure, as well as avoiding side effects associated with medication. Furthermore, as DPP-IV pharmacological action depends on the bioavailability of endogenous GLP-1 into the blood-stream, combining the use of this drug type with a diet promoting GLP-1 secretion could promote DPP-IV inhibitors' action and potentially allow the use of lower doses. Therefore, it would be worthwhile to investigate the relationship between diet composition and DPP-IV inhibitors' efficacy in future studies.

When summarizing existing studies on the modulation of endogenous GLP-1 secretion from enteroendocrine L-cells by single nutrients and their by-products (e.g. non digestible carbohydrates and SCFAs), single-nutrient foods (e.g. olive oil, fish oil) as well as mixed-nutrient foods, it appears that the nutritional modulation of GLP-1 secretion involves several GPCRs expressed on L-cells. Furthermore, specific mechanisms for the increase in GLP-1 synthesis and secretion in L-cells include the up-regulation of proglucagon expression [129, 132–134], as well as that of post-transcriptional factors (e.g. pro-hormone convertase 1) [132]. The synthesis and secretion of GLP-1 may also be enhanced by promoting the differentiation of intestinal stem cells into L-cells [134].

In comparison with single nutrients, mixed-nutrient foods theoretically constitute a more promising and practical treatment option as they can allow targeting several enteroendocrine pathways. The main limitation of existing studies assessing the effects of specific foods is that it is impossible to distinguish the specific impact of macronutrient types (e.g. MUFAs versus SFAs) from the impact of the amount of the intake *per se* because none of the experimental meals were matched for macronutrient content. Furthermore, several studies [154, 156, 161, 167, 168] did not use isocaloric test and control meals. In these studies, the test meal was contained more calories which leads to question whether the observed effects is to be attributed to the tested foods or the energy content of the meal. These limitations call for more rigorous experimental designs to confirm the effects of these foods on GLP-1's and other gut hormone's secretion. Future studies should also aim to gain a better understanding of dose-specific effects of single nutrients, mixed nutrients, specific foods and food combinations in humans. There is also a need to compare the effects of food ingestion on GLP-1 secretion in healthy adults versus adults with metabolic disturbances such as metabolic syndrome, impaired glucose tolerance, and T2D. Well-designed randomised control trials should be planned to evaluate the impact of foods promoting GLP-1 secretion on the progression from impaired glucose tolerance to frank T2D. Lastly, efforts should be made to identify ranges of postprandial GLP-1 concentrations that are associated with beneficial metabolic effects acutely and in the long-term. Such knowledge advances could help individuals modify their dietary habits in a way that obesity and T2D could be better managed and maybe prevented.

Abbreviations

AgRP: Agouti-related peptide; ARC: Arcuate nucleus; CART: Cocaine and amphetamine-regulated transcript; CaSR: Calcium-sensing receptor; DMN: Dorso-medial nucleus; DPP-IV: Dipeptidyl-peptidase IV; FFAR1-4: Free fatty acid receptor 1-4; GI: Gastrointestinal; GLP-1: Glucagon-like peptide-1; GLP-1R(s): Glucagon-like peptide-1 receptor(s); GPCR(s): G-protein coupled receptor(s); GPCR-C6A: Class C group 6, subtype A G-protein coupled receptor; mRNA: Messenger ribonucleic acid; MUFA(s): Monounsaturated fatty acid(s); NPY: Neuropeptide Y; NTS: Nucleus tractus solitarius; POMC: Pro-opiomelanocortine; PUFA(s): Polyunsaturated fatty acid(s); PVN: Paraventricular nucleus; PYY: Peptide tyrosine-tyrosine; SFA(s): Saturated fatty acid(s); SGLT-1: Sodium glucose transporter-1; T2D: Type 2 diabetes; TNFα: Tumour necrosis factor α; α-MSH: α-melanocyte stimulating hormone

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Authors' contribution

AMB, DP and IG formulated the aim of this review. AMB conducted the bibliographical search, critically reviewed articles included in this paper and took primary responsibility in its redaction. DP, RB and IG participated in the critical review of selected articles and revised this paper for important intellectual content. All co-authors read and approved the final version of this manuscript.

Competing interests

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APPENDIX 2 – Research ethics boards' approval certificates

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Avis d'approbation éthique
Comité d'éthique de la recherche de l'Hôpital Montfort

Le 9 novembre 2015

Chercheuse principale :

Isabelle Giroux
École des Sciences de l'activité physique,
Université d'Ottawa
Institut de Recherche de l'Hôpital Montfort (IRHM)
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Chercheur principal du site Hôpital Montfort:

Dr Denis Prud'homme
Vice-président associé à la recherche et
Directeur scientifique
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Collaboratrices

Dre Lyne Pitre
Unité de médecine familiale académique
Hôpital Montfort

Alexandra Bodnaruc
Assistante de recherche, coordonnatrice du projet
Université d'Ottawa
Institut de Recherche de l'Hôpital Montfort (IRHM)

Titre du projet : « Les effets de la composition des déjeuners sur la réponse glycémique et la sécrétion d'hormones gastro-intestinales chez les hommes d'âge moyen avec le diabète de type 2 – **Volet 1** »

Numéro du dossier : IG-02-09-15

Date de début : 9 novembre 2015

Date de fin : 8 novembre 2016

En conformité avec l'Énoncé de politique des trois conseils — Éthique de la recherche avec des êtres humains (ÉPTC 2), décembre 2014, le Conseil canadien des normes, les bonnes pratiques cliniques : directives consolidées, Conférence internationale sur l'harmonisation des exigences techniques relatives à l'homologation des produits pharmaceutiques à usage humain (ICH-GCP E6), la Loi de 2004 sur la protection des renseignements personnels sur la santé, les lois et règlements applicables en Ontario, je confirme que le Comité d'éthique de la recherche (CÉR) de l'Hôpital Montfort a étudié et approuvé les documents suivants :

- Annexe 1 : Principaux questionnaires et mesures recueillies à chaque visite, soumis le 2 sept. 2015
- Annexe 2 : Feuille de cueillette des données (FR et EN), soumise le 2 sept. 2015
- Annexe 3 : Rappel de 24 heures de l'alimentation (FR et EN), soumis le 2 sept. 2015
- Annexe 4 : Protocole pour rappel de 24 heures des enquêtes sur la santé des collectivités canadiennes de Statistiques Canada, soumis le 2 sept. 2015
- Annexe 5 : Liste des aliments oubliés (FR et EN)

- Annexe 6 : Questionnaire sur l'appréciation des aliments (FR et EN)
- Annexe 7 : Questionnaire démographique (FR et EN) version datée du 22 oct. 2015
- Annexe 8 : Questionnaire sur la santé et les habitudes de vie (FR et EN) version datée du 8 oct. 2015
- Annexe 9 : Questionnaire sur les comportements alimentaires (FR et EN), soumis le 2 sept. 2015
- Annexe 10 : Questionnaire canadien sur le risque de diabète (CANRISK) / FR et EN, soumis le 2 sept. 2015
- Annexe 11 : Questionnaire sur le diabète et prédiabète (FR et EN) version datée du 22 oct. 2015
- Annexe 12 : Questionnaire sur les sensations subjectives d'appétit (FR et EN), soumis le 2 sept. 2015
- Annexe 13 : Budget de l'étude, soumis le 2 sept. 2015
- Annexe 14 : Feuillet d'information (FR et EN), soumis le 30 oct.2015
- Annexe 15 : Affiche de recrutement (bilingue), version datée du 8 oct. 2015
- Annexe 16 : Cartes de visite, soumis le 2 sept. 2015
- Annexe 17 : Formulaire de renseignements et de consentement au volet 1 du projet, version datée du 6 nov. 2015
- Annexe 18: Information sheet and consent form, Part 1 of the research project, version datée du 6 nov. 2015
- Annexe 19 : Grille de présélection du volet 1, soumis le 2 sept. 2015
- Annexe 20 : Algorithme des valeurs de glycémie capillaire pour la prévention des complications associées à l'hypoglycémie et l'Hyperglycémie, soumis le 30 oct. 2015.

Le CÉR de l'Hôpital Montfort est constitué et exerce ses activités d'une manière conforme à la Loi sur les aliments et les drogues, la Partie C, Titre 5, du Règlement sur les aliments et drogues et aux règlements applicables, la partie 4 du Règlement sur les produits de santé naturels; partie 3 du Règlement sur les instruments médicaux ainsi qu'au « Codes of Federal Regulations » des États-Unis.

Le protocole de l'étude ne peut être modifié sans une approbation préalable du CÉR sauf s'il est question de la sécurité immédiate des participants ou de logistique administrative comme un changement de numéro de téléphone. Vous devez aviser le CÉR immédiatement de tout changement, événement indésirable ou nouvelle information pouvant augmenter le risque de l'étude, modifier le cours de l'étude ou atteindre la sécurité des participants. Les modifications au projet et aux outils de recrutement doivent être soumises au CÉR.

Veuillez nous acheminer **quatre semaines avant la date d'échéance de cet avis d'approbation**, un rapport final afin de fermer le dossier ou de faire une demande de renouvellement du certificat d'approbation éthique de l'étude.

Si vous avez des questions, vous pouvez communiquer avec le bureau du CÉR de l'Hôpital Montfort au 613-746-4621, poste 2221 ou par courriel à ethique@montfort.on.ca.

Lynn Casimiro, Pht., Ph. D.
Présidente du Comité d'éthique de la recherche — Hôpital Montfort

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

Certificat d'approbation déontologique

CÉR Sciences et science de la santé

Chercheur principal / Superviseur / Co-chercheur(s) / Étudiant(s)

Prénom	Nom de famille	Affiliation	Rôle
Isabelle	Giroux	Sciences de la santé / Autres	Chercheur principal
Denis	Prud'homme	Sciences de la santé / Activité physique	Chercheur principal
Lyne	Pitre		co-Chercheur
Alexandra	Bodnaruc		Coordinateur de projet

Numéro du dossier: H11-15-25

Type du projet: Professeur

Titre: Les effets de la composition des déjeuners sur la réponse glycémique et la sécrétion d'hormones gastro-intestinales chez les hommes d'âge moyen avec le diabète de type 2

Date d'approbation (mm/jj/aaaa)	Date d'expiration (mm/jj/aaaa)	Approbation
12/07/2015	12/06/2016	Ia

(Ia: Approbation complète, Ib: Autorisation préliminaire de libération de fonds de recherche)

Conditions Spéciales / Commentaires:

Approbation partielle octroyée le 7 décembre 2015 : Ce certificat d'approbation partielle est seulement valide pour le volet 1 de l'étude.

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Numéro de dossier: H11-15-25 **Date (mm/jj/aaaa):** 12/07/2015

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

La présente confirme que le Comité d'éthique de la recherche (CER) de l'Université d'Ottawa identifié ci-dessus, opérant conformément à l'Énoncé de politique des Trois conseils et toutes autres lois et tous règlements applicables de l'Ontario, a examiné et approuvé la demande d'approbation éthique du projet de recherche ci-nommé. L'approbation est valide pour la durée indiquée plus haut et est sujette aux conditions énumérées dans la section intitulée "Conditions Spéciales / Commentaires".

Lors de l'étude, le protocole ne peut être modifié sans approbation préalable écrite du CER sauf si le participant doit être retiré en raison d'un danger immédiat ou s'il s'agit d'un changement ayant trait à des éléments administratifs ou logistiques de l'étude comme par exemple un changement de numéro de téléphone. Les chercheurs doivent aviser le CER dans les plus brefs délais de tout changement pouvant augmenter le niveau de risque aux participants ou affecter considérablement le déroulement du projet. Ils devront aussi rapporter tout évènement imprévu et / ou dommageable et devront soumettre toutes les nouvelles informations pouvant nuire à la conduite du projet et/ou à la sécurité des participants. Toutes modifications apportées au projet, aux lettres d'information / formulaires de consentement ainsi qu'aux documents de recrutement doivent être soumises pour approbation en utilisant le document intitulé "Modification au projet de recherche" au: http://recherche.uottawa.ca/deontologie/submissions-and-reviews.

Veuillez soumettre un rapport annuel au Bureau d'éthique quatre semaines avant la date d'échéance indiquée afin de renouveler de l'approbation éthique. Afin de fermer le dossier, un rapport final doit être soumis. Ces documents sont disponibles en ligne au: http://recherche.uottawa.ca/deontologie/submissions-and-reviews.

Pour toutes questions, vous pouvez communiquer avec le Bureau d'éthique en composant le poste 5387 ou par écrit à: ethique@uOttawa.ca.

Riana Marcotte
Responsable d'éthique en recherche
Pour Daniel Lagarec, Président du CÉR en Sciences de la santé et sciences

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Avis d'approbation éthique
Comité d'éthique de la recherche (CÉR) de l'Hôpital Montfort

Le 6 octobre 2016

Chercheure principale

Alexandra Maria Bodnaruc
Institut de recherche de l'Hôpital Montfort (IRHM)

Collaboratrice

Dre Lyne Pitre
Équipe de santé familiale académique Montfort

Superviseurs :

Professeure Isabelle Giroux
Université d'Ottawa
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Dr Denis Prud'homme
Institut de recherche de l'Hôpital Montfort (IRHM)
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Titre du projet : « Les effets de la composition des déjeuners sur la réponse glycémique et la sécrétion d'hormones gastro-intestinales chez les hommes d'âge moyen avec le diabète de type 2_Volet 2 »

Numéro du dossier : IG-03-08-16

Date de début : 6 octobre 2016

Date de fin : 5 octobre 2017

En conformité avec la dernière édition de l'Énoncé de politique des trois conseils — Éthique de la recherche avec des êtres humains (ÉPTC 2), je confirme que le Comité d'éthique de la recherche (CÉR) de l'Hôpital Montfort a **évalué** et **approuvé votre projet de recherche** et les documents suivants pour les dates de début et de fin mentionnées ci-dessus :

- Annexe 1 : Principaux questionnaires et mesures recueillies à chaque visite _EN
- Annexe 2 : Fiche de cueillette des données _FR et EN
- Annexe 3 : Fiche de rappel alimentaire de 24 heures _FR et EN
- Annexe 4 : Protocole de rappel alimentaire de 24 heures _FR
- Annexe 5 : Liste des aliments oubliés _FR et EN
- Annexe 6 : Questionnaire sur l'appréciation des aliments _FR et EN
- Annexe 7 : Questionnaire démographique _FR et EN
- Annexe 8 : Questionnaire sur le comportement alimentaire _FR et EN
- Annexe 9 : Questionnaires sur la santé et les habitudes de vie _FR et EN
- Annexe 10 : Questionnaire canadien sur le risque de diabète _FR et EN
- Annexe 11 : Questionnaire sur le pré-diabète et le diabète _FR et EN
- Annexe 12 : Questionnaire sur les sensations subjectives d'appétit _FR et EN
- Annexe 13 : Budget de l'étude

- Annexe 14 : Affiche de recrutement Partie 2_FR et EN
- Annexe 15 : Dépliants de recrutement Partie 2_FR et EN
- Annexe 16 : Carte de visite _FR et EN, version datée du 21 sept. 2016
- Annexe 17 : Formulaire de renseignement et de consentement Partie 2_FR et EN, version datée du 30 sept. 2016
- Annexe 18 : Script téléphonique Partie 2_FR et EN, version datée du 21 sept. 2016
- Annexe 18 : Script téléphonique pour permission à être contacté
- Annexe 19 : Grille de pré-sélection du volet 2_FR et EN
- Annexe 20 : Liste de médicaments _FR et EN
- Annexe 21 : Algorithme des valeurs de glycémie capillaire
- Annexe 23 : Preuve de financement datée du 4 juillet 2015
- Protocole de recherche soumis pour la demande subvention, du 1er mai 2015, révisé et soumis le 21 sept. 2016

Le CÉR a également reçu le document suivant :

- Rapport sur la proposition de thèse de maîtrise datée du 20 juin 2016

Le CÉR de l'Hôpital Montfort est constitué et exerce ses activités d'une manière conforme à la Norme nationale du Canada visant la surveillance de l'éthique de recherches comportant des essais cliniques biomédicaux de l'Office des normes générales du Canada, aux Bonnes pratiques cliniques : directives consolidées, du Conseil international sur l'harmonisation des exigences techniques relatives à l'homologation des produits pharmaceutiques à usage humain (CIH-BPC E6), à la Partie C, Titre 5, du Règlement sur les aliments et drogues et aux règlements applicables, à la partie 4 du Règlement sur les produits de santé naturels; à la partie 3 du Règlement sur les instruments médicaux, au « *Code of Federal Regulations* » des États-Unis, à la Loi ontarienne de 2004 sur la protection des renseignements personnels sur la santé, de même qu'aux lois et règlements applicables en Ontario.

Le protocole de l'étude ne peut être modifié sans une approbation préalable du CÉR sauf s'il est question de la sécurité immédiate des participants. Le chercheur doit, avant toute utilisation, soumettre pour évaluation et approbation toutes les modifications au protocole et à la documentation destinée aux participants, par exemple, formulaire de consentement et aux outils de recrutement. Vous devez aussi aviser le CÉR immédiatement de tout événement indésirable ou nouvelle information pouvant augmenter le risque ou modifier le cours du projet de recherche.

Veuillez-nous acheminer **quatre semaines avant la date d'échéance de cet avis d'approbation**, un rapport d'étape annuel et le cas échéant une demande de renouvellement du certificat d'approbation éthique de l'étude. Vous pouvez en tout temps soumettre un formulaire de fin d'étude et y joindre un rapport final.

Si vous avez des questions, vous pouvez communiquer avec le bureau d'éthique de la recherche (BÉR) de l'Hôpital Montfort au 613-746-4621 poste 2221 ou par courriel à ethique@montfort.on.ca.

Richard Carpentier, Ph. D.
Président du Comité d'éthique de la recherche — Hôpital Montfort

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

Certificat d'approbation déontologique

CÉR Sciences et science de la santé

Chercheur principal / Superviseur / Co-chercheur(s) / Étudiant(s)

Prénom	Nom de famille	Affiliation	Rôle
Isabelle	Giroux	Sciences de la santé / Autres	Superviseur
Denis	Prud'homme	Sciences de la santé / Activité physique	Co-Superviseur
Alexandra Maria	Bodnaruc	Sciences de la santé / Activité physique	Étudiant-chercheur
Lyne	Pitre	Équipe de santé familiale académique Montfort	Autre collaborateur

Numéro du dossier: H10-16-22

Type du projet: Thèse de maîtrise

Titre: Les effets de la composition des déjeuners sur la réponse glycémique et la sécrétion d'hormones gastro-intestinales chez les hommes d'âge moyen avec le diabète de type 2_Volet2

Date d'approbation (mm/jj/aaaa)	Date d'expiration (mm/jj/aaaa)	Approbation
11/22/2016	10/05/2017	Approbation

Conditions Spéciales / Commentaires:
N/A

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APPENDIX 3 – Consent forms

Information Sheet and Consent Form

Part 1 of Research Project

1. GENERAL INFORMATION

Project Name: Assessment of organoleptic characteristics appreciation by middle-aged adults with or without diabetes

Project Coordinator and Research Assistant's name and contact information:

Alexandra Bodnaruc, DtP, BSc, MSc (candidate)
Institut du Savoir Montfort – Recherche

Principal Researcher's name and contact information:

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Name and contact information of Co-researchers:

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Name of collaborators:

Lyne Pitre, MD, CCMF, FCMF, MMedEd
Montfort Academic Family Health Team

Emergency Contacts*:* Isabelle Giroux, 613-562-5800 ext. 2398, Denis Prud'homme, 613-746-4621, ext. 6044

Funding Source: This project is founded by l'Institut du Savoir Montfort (ISM) - Recherche.

Conflict of Interests: There are no apparent or potential conflicts of interest in this project and no disclosure of the likelihood of marketing the results.

2. INTRODUCTION

Before agreeing to participate in this research project, please take the time to read and carefully consider the following information. This document explains the purpose of the research project, its procedures, benefits, risks and drawbacks. Please ask the person who gave you this document any questions you consider relevant.

3. INVITATION TO PARTICIPATE

I am being asked to participate in the above-named research project conducted by Isabelle Giroux, member of the Institut du Savoir Montfort. I am free to participate in this optional study or not. My decision to participate or withdraw from the study will not affect the quality of service provided to me now or in the future in any way.

4. PURPOSE

The purpose of the study is to assess the appreciation of organoleptic characteristics of almonds, pistachios, avocados, eggs and oats by adults aged between 40 and 70 years old with or without a diagnosis of prediabetes or type 2 diabetes. Those five foods have been selected for their potential beneficial effects on appetite and blood sugar concentrations after a meal. Studies show that the appreciation of food characteristics has a significant impact on food choices and satisfaction after a meal.

5. INCLUSION/EXCLUSION CRITERIA

To be eligible to this study, I must:

- Be an adult aged between 40 and 70 years old;
- Understand French or English enough to be able to answer questionnaires follow instructions and interact with the research team.

I am not eligible to this study if:

- I have an allergy or an intolerance to the tested foods;
- I smoke;
- I suffer from a medical condition affecting taste such as an oral, nasal, pharyngeal or nasal infection, cancer (treated or not with chemotherapy and/or radiotherapy) or Parkinson disease;
- I have trouble chewing or swallowing;
- I have a cognitive impairment that prevents participation to this study.

6. PARTICIPATION

My participation to the will consist in on visit to the Nutrition and Metabolism laboratory of Montfort Hospital that will last about 90 minutes. The visit will be planned in the morning, between 7am and 10am, either during week or during the weekend, depending on my own availabilities. I will be ask to come to the laboratory following a 12-hours fasting (not consuming any food or beverage except water) period. My visit will unfold as follows:

1. **Welcoming** to the Nutrition and Metabolism laboratory (room 1E109) by the research assistant of the project.

2. **Blood sugar and glycated hemoglobin measures** – The research assistant will measure my blood sugar level in the small blood vessels of the finger using a glucometer and my percentage of glycated hemoglobin (%HbA1C) using a small portable device. If I prefer, I can do the measure myself.

3. **Anthropometric measures –** My height, my weight and my waist circumference will be measure by the research assistant in a private place, the room 1E107 of the Nutrition and Metabolism laboratory.

4. **Body composition measures** – My body composition will be measured using a bioelectrical impedance device that will analyse my body fat mass with a non-evasive current. Before this procedure, I will have to remove all metal and electronic devices from my clothing and body. I will then step on a platform (without shoes and socks) and stand on it for one minute without moving.

5. **24-hours dietary recall** – The 24-hours dietary recall is a tool that is commonly used to assess food intake. The research assistant will ask me questions on the foods that I ate the day before my visit to the Nutrition and Metabolism laboratory.

6. **Tasting and organoleptic characteristic evaluation** – During this part, I will taste the five selected food and answer questions on my appreciation of several characteristics and my willingness to include those foods in my diet on a regular basis.

7. **Other questionnaires** – I will be asked to answer several other questionnaires. The estimated time needed to fill out those questionnaires is 45 minutes.

- **Demographic questionnaire:** In this questionnaire, I will answer questions on general information such as age, education level, employment status, income, etc.

- **Health and lifestyle questionnaire:** In this questionnaire, I will answer questions on my health status, my weight history and my lifestyle, including my eating habits and practice of physical activity.

- **Canadian diabetes risk questionnaire (CANRISK):** This questionnaire contains 10 questions that will help me identify my level of risk for developing prediabetes or type 2 diabetes.

- **Food behavior questionnaire:** In this questionnaire, I will answer 18 questions on my eating behaviours (i.e., restriction, uncontrollable eating and emotional eating).

- **Prediabetes and diabetes questionnaire (if applicable):** In this questionnaire, I will answer basic questions on health care received, self-management practices for prediabetes and type 2 diabetes, as well as type 2 diabetes complications.

7. BENEFITS

My participation in this research will provide information on middle-aged adults' food preferences and will contribute to the advancement of knowledge in diabetes research area. The data collected in this study, as well as in future studies, could contribute to the development of nutritional approaches for prediabetes, type 2 diabetes and other chronic diseases management strategies that are better suited for middle-aged adults specific needs.

Following my participation to the study, I will also receive an individualised health assessment sheet including information on my diet, my weight, my body composition and my blood sugar levels. I will also receive several resources on healthy eating and physical activity such as the *"Eating Well with Canada's Food Guide"* guide and the Canadian Physical Activity Guidelines for Adults. If my blood sugar level is above threshold values for prediabetes or diabetes diagnosis, the research team will inform me and ensure that appropriate follow-up will be done my family doctor or another qualified health professional. Early detection of diabetes and prediabetes in order to initiate blood sugar management is very important and helps reduce, or at least delay, the onset of associated complications (e.g., eye diseases, kidney diseases, erectile dysfunction, etc.).

8. RISKS

The risks associated with my participation in this study are minimal. A well-trained registered nurse will be present at the research laboratory during the visits and an emergency chart will be readily available if needed. I understand that my participation in this study involves doing a blood sugar and glycated hemoglobin (A1C) test using small portable devices. Those devices are very safe and are commonly used by individual with diabetes for autosurveillance purposes. I might feel a slight pinch on the tip of my finger when the small needle of the device is inserted, but it usually only last a few seconds. I understand that my participation in this study also involves providing personal information and that this poses little risk for me or my family. I have received assurance from the researchers that every measure will be taken to minimise any risks including ensuring the confidentiality of my personal information.

9. CONFIDENTIALITY AND ANONYMITY

I have the researchers' assurance that every measure will be taken to minimise all risks of personal information confidentiality breach. I expect that the content will be used only for the purposes of this study and with respect for confidentiality. To protect the confidentiality of the information I share with the researcher, all data will be identified with a code that will be assigned to my name at the beginning of the study. The list linking names to the identification codes will be stored in the responsible site researcher office, separately from the paper and electronic data. Moreover, my name will not appear on any publication related to this research project.

However, there is some possibility that research records identifying me will be examined in the presence of the researcher by a representative of the organization funding the research (Institut du Savoir Montfort – Recherche), Health Canada, and the Research Ethics Board for research control purposes. However, I have been given assurances that no record identifying me, by name or initials, for example, will be permitted to leave the Nutrition and Metabolism Laboratory of Montfort Hospital.

If any other persons (e.g., interns, students) than those mentioned in this document participate in the research activities of this project, they will have to sign a confidentiality agreement before being authorised to access collected data or to be in contact with the participants. Those persons will be supervised by a researcher or a co-researcher of this study.

10. DATA CONSERVATION

The data gathered will be kept in a secure manner. All paper data will be kept at the Nutrition and Metabolism laboratory of the Montfort Hospital in a closed file. Electronic data will also be saved on a secured network for data bases and questionnaires. Only those mentioned in this document,

as well as students and interns that have completed the confidentiality agreement will have access to those data. I have been given assurances that no record identifying me will be permitted to leave the research laboratory. The data collected in this study will be kept i for a period of 25 years post-publication. Data will subsequently be destroyed following the secured protocol for confidential documents in place at Montfort Hospital (paper data) or deleted (electronic data). After 10 years, the list linking names to the identification codes will be destroyed and data will become anonymous.

11. VOLUNTARY PARTICIPATION

My participation in the study is voluntary. I am free to withdraw at any time or to refuse to answer certain questions without exposing myself to any negative consequences. If I choose to withdraw from the present study, I wish that the collected data are

□ Conserved

□ Destroyed

12. REMBOURSEMENT/INDEMNISATION

I will receive a parking pass to cover my parking fees. If I came to the research laboratory by bus, the OC Transpo or STO bus tickets will be reimbursed. Moreover, I will receive a ticket for the Montfort Hospital cafeteria so I can get a breakfast after my visit to the research laboratory.

13. NOTIFICATION OF RESULTS

At the end of the study, I will be invited to a data dissemination session. Throughout the study, and after, I can contact the research team to discuss my results and/or the progression of the study. Data collected during this study will be published in research articles and abstract that will be submitted to scientific journals and conferences. Moreover, the study results will be presented to Montfort Hospital health professionals. Results from this study will also be published in graduate student thesis.

14. CIVIL LIABILITY

My consent to participate in this study does not affect my right to seek legal recourse in any manner whatsoever. If my participation causes me any prejudice, I reserve the right to take any available legal recourse against the various research partners

This information is mine.

CONSENT

1. I had in my possession a copy of the letter of information and consent form, which I have had a chance to read.

2. The nature, the objectives and the methodology of this study were explained to me verbally.

3. I was informed of the advantages and that there are few known risks associated with my participation.

4. I understand that my participation is voluntary and that I can withdraw at any time without consequences. If I chose to drop from the study, I understand that the data collected can be kept or destroyed as I wish.

5. I understand that all of the data from this study will be used in all confidentiality and that it will only be used for scientific purposes. I understand that my name will never be revealed.

6. I had the opportunity to ask all of the questions I wanted in link with this study and I have obtained satisfactory answers.

7. After my visit at the research laboratory on nutrition and metabolism, I will receive by mail an individualized health summary about my diet, my weight, body composition and my blood sugar level, according to information I gave.

8. Throughout the study, as well as after, I can contact research team members to discuss my results and/or obtain information on the progress of the study.

DISSEMINATION OF RESULTS

Would you like to receive a summary of the study's results?
□ Yes □ No Initials : _____

If applicable, would you like to receive educational resources that have been developed following this study?
□ Yes □ No Initials : _____

If yes, please indicate the mode of communication that you prefer:
□ E-mail: _____
□ Phone: _____
□ Address: _____
_____

Acceptance:

I, _____, agree to participate in this research project conducted by _____. For any further information concerning this study, please contact the researcher.

For information concerning ethical aspects of this research, I may contact the Montfort Hospital Research Ethics Board, 745-A Montreal Road, Suite 102, Ottawa, Ontario by telephone at 613-746-4621, extension 2221, or by email at ethique@montfort.on.ca.

There are two copies of the consent form, one of which I may keep.

Participant's Signature: _____ Date: _____

Researcher's Signature: _____ Date: _____

Information Sheet and Consent Form

Part 2 of Research Project

1. GENERAL INFORMATION

Project Name: The effects of breakfast composition on glycemic response and gastrointestinal hormone secretion in middle-ages adults with type 2 diabetes mellitus – Part 2

Name of the principal investigator:
Alexandra Bodnaruc, DtP, BSc, MSc (candidate)
School of Human Kinetics, Faculty of Health Sciences, University of Ottawa
Institut du Savoir Montfort – Recherche

Name of the supervisor:

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Full Professor
School of Human Kinetics, Faculty of Health Sciences, University of Ottawa
Associate vice-president Research and the Scientific director, Institut du Savoir Montfort – Recherche
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Name of the co-supervisor:

Isabelle Giroux, PhD, RD, BÉd, PHEc
Associate Professor
School of Nutrition Sciences, Faculty of Health Sciences, University of Ottawa
Institut du Savoir Montfort – Recherche
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Name of collaborators:

Lyne Pitre, MD, CCMF, FCMF, MMedEd
Montfort Academic Family Health Team

Emergency Contact*:* Isabelle Giroux, 613-562-5800 ext. 2398, Denis Prud'homme, 613-746-4621, ext. 6044

Funding Source: This project is founded by a Pilot Study grant from the Institut du Savoir Montfort – Recherche.

Conflict of Interests: There are no apparent or potential conflicts of interest in this project and there is no possibility of commercializing the results.

2. INTRODUCTION

Before agreeing to participate in this research project, please take the time to read and carefully consider the following information. This document explains the purpose of the research project, its procedures, benefits, risks and drawbacks. Please ask the person who gave you this document any questions that you consider relevant.

3. INVITATION TO PARTICIPATE

You are invited to participate in the above-named research project conducted by Alexandra Bodnaruc (RD, BSc), master of science candidate at the School of Human Kinetics, Faculty of Health Sciences, under the supervision of Denis Prud'homme (MD, MSc) and the co-supervision of Isabelle Giroux (RD, PhD) from the Faculty of Health Sciences and Institut du Savoir Montfort.

You are free to participate in this study or not. Your decision to participate or withdraw from the study will not affect the quality of service provided to you currently or in the future in any way.

4. PURPOSE

The purpose of this study is to evaluate the effects of meals' composition on glycemic responses (blood sugar concentrations after a meal), hormonal responses (blood concentrations of some hormones such as insulin), appetite, and food intake.

5. INCLUSION AND EXCLUSION CRITERIA

To be eligible for this study, you must:

- Be an adult between the ages of 40 and 70 years old;
- Understand French or English enough to be able to answer questionnaires, follow instructions and interact with the research team;
- Have a diagnosis of type 2 diabetes managed with lifestyle modification and/or Metformin (Glucophage™).

You are not eligible to participate to this study if you:

- Have an allergy or an intolerance to the foods included in the test and/or control breakfast meal;
- Smoke;
- Suffer from a medical condition affecting taste such as an oral, nasal or pharyngeal, cancer (treated or not with chemotherapy and/or radiotherapy) or Parkinson disease;

- Suffer from a medical condition (other than diabetes) and/or take any medication (other than metformin) affecting metabolism, nutrition absorption, gastrointestinal secretion and/or appetite.
- Have trouble chewing or swallowing;
- Have lost ≥ 2kg (4.4lbs) in the last 3 months;
- Have a high physical activity level;
- Do not regularly eat a breakfast.
- Have a cognitive disability preventing full participation in this study.

6. PARTICIPATION

Your participation in this study consists of two visits lasting 5 hours and 30 minutes each. Moreover, a 24-hours dietary recall will be done by telephone the day following the two visits. These two visits will take place at the Behavior and Metabolism Research Unit (BMRU) laboratory of the University of Ottawa. The two visits will be separated by at least seven days and will take place between 7:00am and 12:30pm on a week day, according to your availability.

We will ask you to present yourself at the research laboratory following a 12-hour fasting period (not consuming any food or beverage, except water). We will also ask you not to consume any alcoholic beverage and not to do any moderate or high intensity physical activity in the 72 hours preceding your visit.

The two visits will unfold as follows:

1. **Welcoming** at the BMRU (200, Lees Avenue, Block E, Ottawa, K1S 5L5).

2. **Capillary blood glucose measure** – The researcher will measure your blood sugar level in the small blood vessels of one of your fingers using a glucometer. If you prefer, you can do this measurement yourself**.**

3. **Anthropometric measures** – Your height, weight, waist circumference and body composition (i.e., your body fat and lean body mass percentage) will be measured by the researcher in a private room of the Nutrition and Metabolism laboratory. Your body composition will be measured using a bioelectrical impedance device that uses a non-evasive electric current to measure your body fat mass. Before this procedure, you will have to remove all metal and electronic devices from your clothing and body. Without

shoes and socks, you will then step on a platform and stand on it for one minute without moving.

4. **24-hour dietary recall** – The 24-hour dietary recall is a tool that is commonly used to assess food intake. The researcher will ask you questions about the foods and beverages that you consumed the day before your visit to the laboratory.

5. **Blood samples** – A catheter will be inserted in a forearm vein by a registered nurse and a fasting blood sample will be taken. Six other blood samples will be taken 15, 30, 60, 90, 120 and 240 minutes following the consumption of the standardized breakfast meal (**point 8**). A total blood volume of 126mL, which equals to 8 tablespoons, will be taken. The catheter will be removed immediately after the last blood sample is taken.

6. **Appetite sensations** – You will be asked to evaluate your appetite sensations on visual analog scales. You will have to indicate your level of each sensation on a 0 to 100mm scale in fasting state, as well as 15, 30, 60, 90, 120 and 240 minutes following the consumption of the standardized breakfast meal (**point 8**).

7. **Standardized breakfast** – Following the fasting blood sample, a standardized breakfast meal will be served. The meal will contain white bread and either almonds or butter and cheddar cheese. You will have thirty minutes to eat the breakfast.

8. **Varied questionnaires** – If you have not participated in the first part of this study, you will be asked to answer a few questionnaires (described below) during the waiting time. The estimated time needed to fill out these questionnaires is approximately 45 minutes.

    - **Demographic questionnaire:** In this questionnaire, you will answer general questions about your age, education, employment status, income, etc.

    - **Health and lifestyle questionnaire:** In this questionnaire, you will answer basic questions about your health status, weight history and lifestyle, including your eating habits and current physical activity.

    - **Food behavior questionnaire:** In this questionnaire, you will answer questions about your eating behaviours (i.e., restriction, uncontrollable eating and emotional eating).

- **Diabetes questionnaire:** In this questionnaire, you will answer basic questions about health care services that you have received, as well as your diabetes self-management practices and any complications associated with diabetes.

9. **24-hour dietary recall (next day)** – A 24-hour dietary recall will be completed by telephone the day following your visit. The researcher will ask questions about the foods and beverages that you consumed after you left the laboratory on the day of your visit. The estimated time for this phone call is 15 minutes.

7. BENEFITS

Your participation in this research will allow clinical data on the effects of meal composition on glycemic responses (blood sugar concentrations after a meal), hormonal responses (blood concentrations of some hormones such as insulin), appetite and food intake. Data collected in this study, as well as results from future studies, could contribute to the development of nutritional approaches for prediabetes, type 2 diabetes and other chronic diseases management that are better suited for individual's needs.

Following your participation to the study, you will receive an individualised health assessment sheet including information on your diet, weight, body composition and blood tests. You will also receive several resources on healthy eating, physical activity and diabetes management. If you wish, at the end of the study, you will be offered a 90 minutes session with a registered dietitian in order to do a complete nutrition assessment and to address your questions regarding diabetes management. An assessment session with a registered dietitian has an estimated value of 150.00$. Blood sugar management is very important in order to prevent, or at least delay, the development of several complications associated with diabetes (e.g., eye diseases, kidney diseases, erectile dysfunction, etc.).

8. RISKS

The risks associated with your participation in this study are minimal.

Capillary blood glucose measurements – The glucometers used for these measures are very safe devices and are commonly used by individual with diabetes for auto-surveillance purposes. You might feel a slight pinch on the tip of my finger when the small needle of the device is inserted, but it usually only last a few seconds.

Blood samples – Blood samples entail very few risks and will be done by a registered nurse. You might feel a slight pinch when the catheter is inserted and removed from your forearm. A

small local hematoma (i.e., a bruise at the location where the catheter was inserted) could appear for a few days following the blood sample.

All measurements will be explained in details by the researcher. A well-trained registered nurse will be present at the research laboratory during the visits and an emergency chart will be readily available, if needed. All measures will be taken to minimize any risks including ensuring the confidentiality of my personal information.

9. CONFIDENTIALITY AND ANONYMITY

All measures will be taken to minimise all risks of personal information confidentiality breach. All data and samples collected will be used only for the purposes of this study and with respect to this confidentiality agreement. To protect the confidentiality of the data and samples collected, participants' names will be coded with an identification code on all paper and electronic documents, as well as on all tubes containing the blood samples. The list linking names to the identification codes will be stored in the office of the principal investigator, separately from the paper and electronic data. Your name will not appear on any publication related to this research project.

There is some possibility that research records identifying you will be examined in the presence of the researcher by a representative of the organization funding the research (Institut du Savoir Montfort) and the Research Ethics Board for research control purposes. However, you have the researchers' assurances that no record identifying you (e.g., by name or initials), will be permitted to leave the Nutrition and Metabolism Laboratory of the Montfort Hospital.

If anyone other than those mentioned in this document (e.g., interns, students) participate in the research activities of this project, they will have to sign a confidentiality agreement before being authorised to access collected data or be in contact with the participants. These individuals will be supervised by the researcher or the co-researcher of this study.

10. DATA CONSERVATION

All data and blood samples collected will be kept in a confidential and secure manner. All paper data and blood samples will be kept at the Nutrition and Metabolism laboratory of the Montfort Hospital in closed files and freezers. Electronic data will also be saved on a secured network for databases and questionnaires. Only those mentioned in this document, as well as students and interns that have completed the confidentiality agreement will have access to the data. You receive researchers' assurance that no record identifying you will be permitted to leave the research laboratory.

All data and blood samples collected in this study will be kept for a period of 25 years post-publication. Data and blood samples will subsequently be destroyed following a secured protocol for confidential documents and biological samples, and deleted in the case of electronic data. After 10 years, the list linking names to the identification codes will be destroyed and data will become anonymous.

11. VOLUNTARY PARTICIPATION

Your participation in the study is entirely voluntary. You are free to withdraw at any time, without any negative consequences. You are also free to refuse to answer certain questions without exposing yourself to any negative consequences. If you choose to withdraw from the present study, you wish that:

- All data collected up to that point are:
  - ☐ Conserved
  - ☐ Destroyed

- All blood samples collected up to that point are:
  - ☐ Conserved
  - ☐ Destroyed

Please note that it will be impossible to remove your data from the study once they are made anonymous, namely 10 years after the completion of the study.

12. REMBOURSEMENT/INDEMNISATION

Parking fees will be covered for each visit at the BMRU. If you came to the research laboratory by bus, the OC Transpo or STO bus tickets will be reimbursed. You will also receive a financial compensation of $40.00 per visit for the first two visits, as well as a $20.00 financial compensation for the optional part of the study. If you decide to withdraw from the study during participation, you will receive financial compensation for the visits that you have attended.

13. NOTIFICATION OF RESULTS

Throughout the study, and after, you can contact the research team to discuss your results and/or the progression of the study. Data collected during this study will be published in research articles and abstract that will be submitted to scientific journals and conferences. Moreover, the study results will be presented to health professionals at the Montfort Hospital. Results from this study will also be published in a graduate student's thesis.

14. CIVIL LIABILITY

Your consent to participate in this study does not affect your right to seek legal recourse in any manner whatsoever. If your participation causes you any prejudice, you reserve the right to take any available legal recourse against the various research partners.

This information is yours.

CONSENT

1. I had in my possession a copy of the letter of information and consent form, which I have had a chance to read.

2. The nature, the objectives and the methodology of this study were explained to me verbally.

3. I was informed of the advantages and that there are few known risks associated with my participation.

4. I understand that my participation is voluntary and that I can withdraw at any time without consequences. If I chose to leave the study, I understand that the data collected can be kept or destroyed as I wish. I understand that it will be impossible to remove my data from the study once they are made anonymous, namely 10 years after the completion of the study.

5. I understand that all of the data from this study will be used in a confidential manner and that it will only be used for scientific purposes. I understand that my name will never be revealed.

6. I had the opportunity to ask all of my questions concerning this study and I have obtained satisfactory answers.

7. Throughout the study, as well as after, I can contact research team members to discuss my results and/or obtain information on the progress of the study.

OPTIONAL PART

This study has an optional part that consists in a 2 hours and 30 minutes visit that can take place, according to your preference, at the BMRU laboratory or at your domicile.

The optional visit will take place in the three weeks following the second visit at the research laboratory. The visit will unfold as follows:

1. **Welcoming** to the BMRU laboratory by the researcher or **arrival to your domicile**.
2. **Capillary blood glucose measure** – The researcher will measure your blood sugar concentrations in the small blood vessels of the finger using a glucometer. Blood sugar measures will be taken in fasting state as well as 15, 30, 60 and 120 minutes following the consumption of the standardized breakfast (**point 3**). If you prefer, you can do this measurement yourself**.**
3. **Standardized breakfast** – Following the fasting blood sugar measure, a standardized breakfast meal will be served. The meal will contain white bread. You will have thirty minutes to eat the breakfast.

It is not necessary to consent to this optional part to participate in the present study.

□ I agree to participate in the optional part
□ I refuse to participate in the optional part

Acceptance:

I, _____, agree to participate in this research project conducted by _____. For any further information concerning this study, please contact the researcher.

For information concerning ethical aspects of this research, I may contact the Montfort Hospital Research Ethics Board, 745-A Montreal Road, Suite 102, Ottawa, Ontario by telephone at 613-746-4621, extension 2221, or by email at ethique@montfort.on.ca.

There are two copies of the consent form, one of which I may keep.

Participant's Signature: _____ Date: _____

Researcher's Signature: _____ Date: _____

APPENDIX 4 – Socio-demographic questionnaire

Participant code: _ _ -_ _

Socio-demographic questionnaire

Please answer the following questions. This personal information will be held in strict confidence.

1. What is your age? _____ years old

2. What is your current marital status?

□ Single □ Married □ Common-Law

□ Separated □ Divorced □ Widowed

3. With which ethnic or racial group do you identify? You may identify with more than one group.

□ Caucasian/White

□ Black

□ Latino-American

□ Arab

□ Chinese

□ Korean

□ West Asian (ex. Saudi Arabia, Iran, Turkey, Egypt, etc.)

□ South East Asian (ex. Singapore, Indonesia, Malaysia, Vietnam, etc.)

□ South Asian (ex. India, Bangladesh, Nepal, Afghanistan, etc.)

□ Filipino

□ Japanese

□ Hispanic

□ Aboriginal

□ Other, specify : _____

4. What is your country of origin? _____

If you are born abroad, please indicate your arrival date (month/year) in Canada:

_____

5. What is the highest level of education you have completed? Please check only one answer.

□ Less than high school diploma or its equivalent

□ High school diploma or a high school equivalency certificate

□ Trade certificate or diploma

□ College, CEGEP or other non-university certificate or diploma (other than trades

certificates or diplomas)

□ University certificate or diploma below the bachelor level

□ Bachelor's degree (e.g., B.A., B.Sc., LL.B.)

□ First cycle doctoral degree (ex. MD, Pharm. D)

□ University certificate above bachelor level

□ Master degree

□ Doctoral degree (Ph.D)

□ Post-doctoral degree

□ Other, specify: _____

6. What is the gross (before taxes) annual income of your household in Canadian dollars?

□ Less than 5 000 $

□ 5 000 $ to less than 10 000 $

□ 10 000 $ to less than 15 000 $

□ 15 000 $ to less than 20 000 $

□ 20 000 $ to less than 25 000 $

□ 25 000 $ to less than 30 000 $

□ 30 000 $ to less than 40 000 $

□ 40 000 $ to less than 50 000 $

□ 50 000 $ to less than 60 000 $

□ 60 000 $ to less than 70 000 $

□ 70 000 $ to less than 80 000 $

□ 80 000 $ to less than 90 000 $

□ 90 000 $ to less than 100 000 $

□ 100 000$ and over

□ Would prefer not to answer

7. How many adults are supported by this household income (including you)? ____ adult(s)

8. How many children are supported by this household income? ____ child(ren)

End of questionnaire. Thank you for your time!

APPENDIX 5 – Health and lifestyle questionnaire

Participant code: _ _ -_ _

Health and lifestyle questionnaire

Please answer the following questions. This personal information will be held in strict confidence.

A) General health and chronic diseases

1. In general, would you say your health is …?

□ Excellent
□ Very good
□ Good
□ Fair
□ Poor

2. Compared to one year ago, how would you say your health is now? Is it …?

□ Much better now than 1 year ago
□ Somewhat better now than one year ago
□ About the same as one year ago
□ Somewhat worse than one year ago
□ Much worse now than one year ago

3. Do you have a diagnosis of …

a) Hypertension? Yes □ No □

b) Diabetes? Yes □ No □
Type 1? Yes □ No □
Type 2? Yes □ No □

c) Prediabetes or high blood sugar (hyperglycemia/glucose intolerance)? Yes □ No □

d) High cholesterol (hypercholesterolemia)? Yes □ No □

e) Kidney disease? Yes □ No □

f) Heart disease (cardiac disease) or a stroke? Yes □ No □

g) Hypothyroidism? Yes □ No □

h) Depression or mood disorder? Yes □ No □

i) Anxiety disorder? Yes □ No □

j) Other (please specify) : Yes □ No □

_____
_____
_____
_____

4. Do you take any medication on regular basis? Yes □ No □
If yes, what medication(s) are you taking: _____
_____
_____
_____
_____

5. Do you take any nutrition supplements (e.g., glucosamine, calcium, vitamin D, etc.) on a regular basis? Yes □ No □

If yes, what supplement(s) are you taking: _____
_____
_____
_____
_____

6. Do you have a regular doctor? Yes □ No □ **(go to the next section)**

7. Do you and this doctor usually speak in French, English or another language?
□ French □ English
□ Other (please specify) : _____

8. Have you ever seen or talked to a registered dietitian? Yes □ No □

B) <u>Day-to-day stress level</u>

1. Thinking about the amount of stress in your life, would you say that most days are …?

□ Not at all stressful
□ Not very stressful
□ A bit stressful
□ Quite a bit stressful
□ Extremely stressful

2. Thinking about stress in your day-to-day life, what is the **<u>most important</u>** thing contributing to feeling of stress that you may have?

□ Time pressures / not enough time

□ Own physical health problem or condition

□ Own emotional or mental health problem or condition

□ Financial situation (e.g., not enough money, debt)

□ Own work situation (e.g., hours of work, working conditions)

□ Employment status (e.g., unemployment)

□ Caring for own children or others

□ Personal relationships

□ Discrimination

□ Health of family members

□ Other, specify: _____

3. When faced to this source of stress, how strongly do you agree with the following statements :

a) I can count on people that I know to help me deal with the situation.

□ Strongly agree
□ Agree
□ Neither agree nor disagree
□ Disagree
□ Strongly disagree

b) I have the personal ability to deal with the situation.

□ Strongly agree
□ Agree
□ Neither agree nor disagree
□ Disagree
□ Strongly disagree

C) <u>Weight history</u>

1. Throughout your adulthood, what has been :

a) Your highest weight : _____ kg or _____ lbs
b) Your lowest weight: _____ kg or _____ lbs
c) Your most stable weight: _____ kg or _____ lbs

□ my weight has never been stable

d) Ideally, how much would you like to weight: _____ kg or _____ lbs

2. In general, how satisfied are you with your **<u>current body weight</u>**?

□ Very satisfied
□ Satisfied
□ Moderately satisfied
□ Not very satisfied
□ Not at all satisfied

3. In general, how satisfied are you with your **current body appearance**?

□ Very satisfied
□ Satisfied
□ Moderately satisfied
□ Not very satisfied
□ Not at all satisfied

4. Have you ever followed a diet in order to lose weight?
Yes □ No □ **(go to question 8)**

5. In the last ten years, how many times have you followed a diet in order to lose weight?

□ Only once
□ Two to three times
□ Four to five times
□ More than five times

6. What is the highest amount of weight that you have lost following a diet?
_____ kg or _____ lbs

7. How much time have you maintained that weight loss?

□ Less than one month
□ One month to six months
□ Six months to one year
□ More than one year
□ I am still maintaining that weight loss

Specify for how much time : _____

8. How often do you weight yourself?

□ Several times every day
□ Once every day
□ Once every two to three days
□ Once every week
□ Occasionally

D) Lifestyle

Sleep habits

1. How long do you usually spend sleeping each night?

□ Less than 4 hours
□ 4 hours to less than 5 hours
□ 5 hours to less than 6 hours
□ 6 hours to less than 7 hours
□ 7 hours to less than 8 hours
□ 8 hours to less than 9 hours
□ 9 hours to less than 10 hours
□ 10 hours to less than 11 hours
□ 11 hours to less than 12 hours
□ 12 hours or more

□ Other, please specify :

_____

2. How often do you find your sleep refreshing?

□ Never
□ Rarely
□ Sometimes
□ Most of the time
□ All of the time

Food choices

1. Please rate the importance of the influence of the following factors on your food choices. 1 represents the factors that has the largest influence on you food choices and 10 represents the factor that has the least influence on your food choices:

___ The cost of food

___ Taste and own food preferences

___ Taste and food preferences of another member of my household

___ My own food beliefs related to health (what I perceived as being good or bad for my health)

___ The food beliefs related to health of another member of my household (what he/she perceives as being good or bad for health)

___ My other beliefs (for e.g., religious beliefs, concerns for environment, etc.)

___ The other beliefs of another member of my household (e.g., religious beliefs, concerns for environment, etc.)

___ Food availability (e.g., food available at home, at work, in the grocery stores of your neighbourhood, etc.)

___ The recommendations of a health professional (e.g., doctor, dietitian, nurse, etc.)

___ The social context in which I am finding myself (e.g., with colleagues at work, during a family party, etc.)

___ My emotional state (e.g., culpability, stress, sadness, joy etc.)

___ Other (please specify): _____

2. Do you choose certain foods or avoid others:

a) Because you are concerned about your body weight?
Yes □ No □

b) Because you are concerned about chronic diseases (e.g., diabetes, heart diseases)?
Yes □ No □

3. Do you choose certain foods because of :

a) The lower fat content?
Yes □ No □

b) The fiber content?
Yes □ No □

4. Do you avoid certain foods because of :

a) The calorie content?
Yes □ No □

b) The fat content?
Yes □ No □

c) The type of fat they contain?
Yes □ No □

d) The sugar content?
Yes □ No □

e) The salt content?
Yes □ No □

f) The gluten content
Yes □ No □

Physical activity

1. Please indicate the type of physical activity involved in your current work.

I am not in employment (e.g., retired, retired for health reasons, unemployed, full-time career etc.) □

I spend most of my time at work sitting (such as in an office) □

I spend most of my time at work standing or walking. However, my work does not require much intense physical effort (e.g., security guard, hairdresser, cashier in a store, etc.) □

My work involves definite physical effort including handling of heavy objects and use of tools (e.g., plumber, electrician, carpenter, hospital nurse, etc.) □

My work involves vigorous physical activity including handling of very heavy objects (e.g., construction worker, refuse collector, etc.) □

2. During the last week, how many hours did you spend on each of the following activities. Please mark one box only on each row.

	None	Less than 1 hour	More than 1 hour but less than 3 hours	3 hours or more
Physical exercise such as swimming, jogging, aerobics, football, tennis, gym workout, etc.				
Cycling, including cycling to work and during leisure time.				
Walking, including walking to work, shopping, for pleasure, etc.				
Housework				
Gardening				

3. How would you describe your usual walking pace? Please mark one box only.

□ Slow pace (less than 4 km per hour)
□ Average pace (4 to 5 km per hour)
□ Brisk pace (5 to 6 km per hour))
□ Fast pace (more than 6 km per hour)

E) Food skills

1. In general, would you say that your eating habits are:

□ Excellent
□ Very good
□ Good
□ Fair
□ Poor

2. When preparing the main meal at home, which of the following choices you do the most often? By main meal we mean the meal of the day that requires the most preparation.

□ You use mostly whole basic foods such as vegetables, fruits, pasta, legumes and meat

□ You use mostly easy to prepare foods such as frozen lasagna

□ You use a mix of whole basic foods and easy to prepare foods

□ You buy ready-to eat food or order takeout or delivery

3. How would you describe your ability to cook from basic ingredients?

□ I don't know where to start when it comes to cooking

□ I can do things such as boil an egg or cook a frilled cheese sandwich but nothing more advanced

□ I can prepare simple meals but nothing too complicated

□ I can cook most dishes if I have a recipe to follow

□ I can prepare most dishes

□ I frequently prepare sophisticated dishes

4. How would you rate your skills:

a) In using a kitchen knife safely?

□ Very good □ Good
□ Basic □ Very limited/No skills

b) In peeling, chopping or slicing vegetables or fruit?

□ Very good □ Good
□ Basic □ Very limited/No skills

c) In freezing vegetables or fruit, from raw to bagged in your home freezer?

□ Very good □ Good
□ Basic □ Very limited/No skills

d) In canning from raw ingredients to finished products in sealed glass jars?

□ Very good □ Good
□ Basic □ Very limited/No skills

e) In cooking a piece of raw meat/chicken/fish?

□ Very good □ Good
□ Basic □ Very limited/No skills

f) In cooking a soup, stew or casserole from scratch?

□ Very good □ Good
□ Basic □ Very limited/No skills

g) In baking muffins or cake using a pre-packaged mix?

□ Very good □ Good
□ Basic □ Very limited/No skills

h) In baking muffins or cake from scratch with a recipe?

□ Very good □ Good
□ Basic □ Very limited/No skills

5. Have you ever adjusted a recipe to make it healthier?
Yes □ No □ **(go to question 7)**

6. How did you make it healthier? Chose all answers that apply.

□ Reduced fat content
□ Reduced salt content
□ Reduced sugar content
□ Added more vegetables or fruit
□ Chose whole grain options
□ Other

7. When season permits, do you grow vegetables, herbs, or fruits at home or in a community garden?
Yes □ No □

End of questionnaire. Thank you for your time!

APPENDIX 6 – Questionnaire on prediabetes and type 2 diabetes

Participant code: _ _ -_ _

Questionnaire on prediabetes and type 2 diabetes

Please answer the following questions. This personal information will be held in strict confidence.

Use of health care services

1. How old were you when you were first diagnosed with type 2 diabetes or prediabetes?
_____ years old

2. Which of the following health professionals or practitioners do you consider **most responsible** for treating you diabetes or prediabetes?

□ Family doctor or general practitioner

□ Pharmacist

□ Other medical doctor or specialist, specify: _____

□ Other health professional, specify: _____

□ Diabetes educator

□ Nurse or nurse practitioner

□ No health professional responsible for treating my diabetes or prediabetes

3. In the past 12 months:

a) Have you seen or talked to a diabetes specialist or endocrinologist?
Yes □ No □

b) Have you seen or talked to a kidney specialist or nephrologist?
Yes □ No □

c) Have you seen or talked to a podiatrist or foot specialist?
Yes □ No □

d) Have you seen or talked to a dietitian or nutritionist?
Yes □ No □

4. In the past 12 months, has a doctor or other health professional discussed:

a) Taking prescription medication to help control you blood sugar?
Yes □ No □

b) Changing the type or amount of food you eat to help control your blood sugar?
Yes □ No □

c) Participation in physical activity or exercise to help control your blood sugar?
Yes □ No □

d) Controlling or losing weight to help control your blood sugar?
Yes □ No □

e) Diabetes and/or prediabetes complications?
Yes □ No □

f) Stress management?
Yes □ No □

5. Has a doctor or other health professional ever recommended monitoring your blood sugar at home? Yes □ No □

Diabetes and prediabetes self-management practices

1. As a result of being diagnosed with diabetes or prediabetes, did you ever changed the type or amount of food you eat to help control you blood sugar?
Yes □ No □ **(go to question 3)**

2. If you answered yes to the previous question, are you still doing this?

□ Yes, all the time **(go to question 4)**

□ Some of the time

□ Yes, most of the time **(go to question 4)**

□ None of the time

3. What are the reasons why you never changed or are not maintaining the changes in the type or the amount of food you eat to help control you blood sugar?

□ Lack of will power

□ Too costly/financial constraints

□ I do not like to eat healthier foods

□ I do not know how to change my diet

□ Time constraints (too busy, work schedule, etc.)

□ I do not think that changing my diet is important/recommended

□ Already changed diet for other reasons, specify: _____ _____

□ Other, specify: _____ _____

4. As a result of being diagnosed with diabetes or prediabetes, did you ever changed the amount of exercise you do or participated in physical activities to help control you blood sugar? Yes □ No □ **(go to question 6)**

5. If you answered yes to the previous question, are you still doing this?

□ Yes, all the time **(go to question 7)**

□ Some of the time

□ Yes, most of the time
(go to question 7)

□ None of the time

6. What are the reasons why you never changed or do not maintained changes in the amount of exercise you do or participate in physical activities to help control your blood sugar?

□ Lack of will power

□ I do not like to exercise

□ Time constraints (too busy, work schedule, etc.)

□ Already doing physical activities and exercise for other reasons, specify:
_____

□ Too costly/financial constraints

□ Not available in area

□ I do not think that exercise is important/recommended

□ Other, specify:
_____

7. As a result of being diagnosed with diabetes or prediabetes, did you ever try to control your weigh or lose weight to help control your blood sugar?
Yes □ No □ **(go to question 9)**

8. Have you been able to maintain or achieve you goal weight?
Yes □ **(go to question 10)** No □

9. What are the reasons you did not try or been able to lose weight to help control your blood glucose?

□ I do not need to lose weight/ already have a healthy weight

□ Still trying to lose weight

□ Lack of will-power

□ I do not want to lose weight

□ Time constraints (too busy, work schedule, etc.)

□ Already losing weight for other reasons, specify:_____
_____

□ Disability/ health problem other than diabetes makes it hard to lose weight

□ Too costly/ financial constraints

□ I do not know what to do to lose weight

□ I do not think that weight loss is important/recommended

□ Other, specify: _____
_____

10. In the last 12 months, have you used any of the following services or programs to help manage your diabetes or prediabetes?

□ Diabetes Centre

□ Fitness facilities or programs

□ Smoking cessation programs

□ Support groups

□ Educational programs

□ Self-help groups

□ Stress management programs

□ Walking programs (e.g., mall walking)

□ Did not use any services or programs to help manage diabetes or prediabetes

Diabetes complications

Please fill out this section only if you have a diagnosis of diabetes (not prediabetes).

1. In the past 12 months, did you ever have to visit an emergency room because of low blood sugar (hypoglycemia) or very high blood sugar (hyperglycemia)?
Yes □ No □

2. Have you ever had any of the following conditions diagnosed by a health professional:

a) Diabetic eye disease or diabetic retinopathy?
Yes □ No □

b) Cataracts?
Yes □ No □

c) Glaucoma?
Yes □ No □

d) Protein in your urine?
Yes □ No □

e) Kidney failure?
Yes □ No □

f) Nerve damage or neuropathy?
Yes □ No □

g) Heart disease (e.g., angina, heart attack)?
Yes □ No □

h) High blood pressure (hypertension)?
Yes □ No □

i) Stroke or mini-stroke?
Yes □ No □

j) Erectile dysfunction?
Yes □ No □

k) Poor circulation in the feet or legs?
Yes □ No □

l) Foot or leg ulcers or infections?
Yes □ No □

m) Problem with your gums?
Yes □ No □

End of questionnaire. Thank you for your time!

APPENDIX 7 – Sensory evaluation of food

Savoir Montfort
A Knowledge Institute

Participant code: _ _ -_ _

Food *(to be checked by the research assistant)*:

□ Oats □ Egg □ Avocado □ Almonds □ Pistachios

Instructions (questions 1 to 5): Please draw a vertical line on the five scales below at the place that best represents your impression for the aspect mentioned in each question. Consider the extremities of the scale as being the two extremes of that impression.

1. How attractive do you find the food?

Not at all — Extremely

2. How much do you like the smell of this food?

Not at all — Extremely

3. How much do you like the taste of this food?

Not at all — Extremely

4. How much do you like the texture of this food?

Not at all — Extremely

5. How appetizing do you find this food?

Not at all — Extremely

APPENDIX 8 – Subjective appetite sensations questionnaire

Savoir Montfort
A Knowledge Institute

Participant code: _ _ -_ _

Subjective appetite sensations questionnaire

Time: _____

Instructions: Please quantify on the five scales below your sensation for the feelings mentioned in the question preceding the scale. Consider the extremities of the scales as the two extremes of the sensation. On each scale, draw a vertical line that best represents your sensation at this moment in time.

1. **How hungry do you feel?**

Not hungry at all — Extremely hungry

2. **How strong is your desire to eat?**

Very weak — Very strong

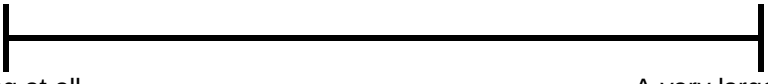
3. **How satiated do you feel?**

Not satiated at all — Satiated

4. **How full do you feel?**

Not full at all — Extremely full

5. **How much food do you think you could eat?**



Nothing at all — A very large amount

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