EFFECTS OF BIOAVAILABILITY OF MACRONUTRIENTS ON OVERALL CONTROL OF PLASMA GLUCOSE: A REVIEW

Mwakalu S[1], Omwenga V[2] and P Ogao[3]

Sidi Mwakalu

*Corresponding author email: mpa.mwakalu@strathmore.edu

[1]Doctoral student, School of Computing and Engineering Sciences, Strathmore University, Kenya

[2]Director of Research and Postgraduate Programmes, School of Computing and Engineering Sciences, Strathmore University, Kenya

[3]Associate Professor, School of Surveying and Spatial Sciences, Technical University of Kenya

https://doi.org/10.18697/ajfand.125.23245

24844

ABSTRACT

Macronutrients play a crucial role in management of type 2 diabetes. This is seen in their ability to modulate plasma glucose concentrations. However, the ideal proportions of macronutrients to be consumed in order to maintain ideal plasma glucose concentrations remains elusive. Therefore, this paper set out to conduct a review to investigate the relationship between macronutrients and plasma glucose concentrations from a physiological perspective. The review was conducted using papers obtained from various databases such as MEDLINE (Pubmed), Open Access Journals Elsevier, Free Medical Journals and Google Scholar. The research papers included general reviews, systemic reviews, meta-analyses, and randomized control trials that examined the effect of macronutrients on plasma glucose concentration as well as papers on mathematical models describing the relationship between macronutrient bioavailability and plasma glucose concentration. The review assessed the effect of various macronutrients on post-prandial plasma glucose concentration, post-prandial plasma insulin, post-prandial glucose-dependent insulinotropic peptide plasma concentration, and post-prandial glucose-like peptide-1 plasma concentration. The results of the review showed that carbohydrates influence plasma glucose concentration in a dose dependant manner but this is dependent on their bioavailability. This bioavailability was shown to be subject to fluctuations determined by food processing techniques, food structure, and food matrix. The results also showed that some specific types of fats and proteins indirectly influence plasma glucose concentration through their effect on incretin hormones. The effect of fats and proteins on incretin hormones was through different mechanisms and pathways. *In-lieu* of the findings, the review concludes that the macronutrient composition of diets designed for type 2 diabetic patients should take into consideration the physiological relationship between the macronutrients and plasma glucose concentrations. In this way, diet proportions can be made in such a manner as to determine the exact amounts that will realize near normal plasma glucose concentrations for a type 2 diabetic patient.

Key words: bioavailability, glucose-insulin system, macronutrients, incretin hormones, type 2 diabetes, glucose absorption models

INTRODUCTION

In the glucose-insulin regulatory system, plasma glucose concentration is maintained within a narrow range of 70-110mg/dL through the action of glucoregulatory hormones such as insulin, glucagon, amylin, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic peptide (GIP) [1]. Insulin and amylin are produced in β-cells, glucagon in the α-cells of the pancreas, and GLP-1 and GIP are secreted in the L-cells of the intestine [1]. In healthy persons, high plasma glucose concentrations stimulate the secretion of insulin, which enables skeletal and adipose tissues to take up glucose [2]. When plasma glucose concentrations reduce below normal range, glucagon causes glycogen to be broken down into glucose [2]. In diabetic patients, this regulatory system is disturbed leading to chronic hyperglycaemia [2]. Diet contributes tremendously to the glucose-insulin regulatory system. In a diabetic patient, the type of food consumed can either worsen glycaemia or help control it. It is for this reason that several guidelines have been published recommending the quantities of carbohydrates, fats and proteins that a patient should consume in order to control plasma glucose levels [3]. These guidelines are generated based on scientific knowledge, clinical experience, expert consensus and evidence from randomized control trials [3]. However, the ideal macronutrient composition of a diet for optimal plasma glucose control remains unclear. The lack of clarity is supported by results from systemic reviews which report either modest results from various carbohydrates diets or inconsistent results [4, 5]. This discrepancy may be due to the fact that such diet compositions recommend fixed percentages of carbohydrates, fats and proteins and do not take into consideration various factors which affect physiological absorption of nutrients from the gut into the circulation system. Such factors, including: chemical composition of foods, food preparation techniques, and inter and intra-subject variabilities affect the fraction of nutrients entering the circulation and thus a "one diet fits all" approach may not be appropriate for diabetic patients. Therefore, this paper investigates the relationship between bioavailability of macronutrients and glycaemic control from a physiological perspective of the glucose-insulin regulatory system. It examines bioavailability and different factors that affect it, relationship between macronutrients and plasma glucose control and the physiological models defining the relationship between macronutrients and plasma glucose concentrations.

METHOD

A comprehensive review was conducted using research papers obtained from several databases: MEDLINE (Pubmed), Open Access Journals Elsevier, Free Medical Journals, Google Scholar, and Google. The reference lists of articles obtained from these databases were also searched and relevant publications were obtained. The search was performed between January and June 2022. The search terms included: "specific macronutrient bioavailability" + "plasma glucose". The outcome assessed was postprandial plasma glucose, insulin, GIP and GLP-1 concentrations. A total of 200 papers were obtained and 40 were selected for use in this review. The papers were selected based on their quality of evidence which was dependent upon the type of study design (randomized control trials were given priority); seriousness of the study limitations; inconsistency of results.

Bioavailability of macronutrients

In nutrition science, bioavailability is defined as the amount of nutrient ingested that is actually digested, absorbed and metabolized in the body [6]. Bioavailability is associated with the efficiency of absorption and metabolic utilization of an ingested nutrient.

There are various factors that affect the bioavailability of macronutrients. These factors include: the food matrix, food processing, and structure of the food. The food matrix regulates the extent and speed at which nutrients are available for absorption [7]. When encapsulated within intact cell walls, starch is digested more slowly because the encapsulation effect of cell walls acts as a physical barrier to the action of digestive enzymes. This has been demonstrated in a study in which subjects with ileostomies were used to investigate digestion of barley to determine whether the physical form of barley affects digestion. The results revealed that 17% of starch from barley was absorbed in the upper intestine when barley was consumed in flake form (3mm in diameter) compared to 2% absorbed from barley in flour form [8].

Various food processing techniques have been reported to affect the bioavailability of starch. Studies report that heating starchy foods in the presence of water results in starch granules absorbing water and swelling [6, 9, 10]. Swelling occurs along the boundary between amylopectin crystalline region and the amorphous amylose region. With increased swelling the crystalline regions are destroyed and the amylose in the amorphous region leaches out. This process is referred to as gelatinization and is observed to increase starch degradation in the digestive tract due to increased viscosity and enzyme action [9]. The effect of food processing

has been illustrated by a study where four different food processing techniques were used to prepare different wheat flour-based products [11]. The study used rotary-moulded biscuits, soft-baked cakes, rusk-type products and extruded products. The results showed that rotary-moulding, which preserved the structure of the starch resulted in products with highest slowly digestible starch content (28g/100g) and significantly lower glycaemic and insulinemic response [11]. The other techniques resulted in very low slowly digestible starch content (below 3g/100g) which was attributed to greater destruction of the starch structure [11].

Another food processing technique that affects bioavailability of carbohydrates especially cereals is milling. Milling destroys the outer layers of grains exposing the endosperm to the action of digestive enzymes [9]. The effect of milling was tested in a randomized crossover trial in which type 2 diabetic patients consumed processed grains for a week and after a washout period received intervention foods consisting of whole-grain products of wheat, oats and brown rice [12]. Results revealed lower postprandial responses following consumption of whole grains compared to processed grains.

The bioavailability of proteins is affected by the presence of antinutritional factors which occur either naturally or form as a result of food processing. Naturally occurring antinutritional factors are mostly found in plant-based proteins. They include: trypsin inhibitors, tannins, phylates, haemagglutinins, glucosinolates, gossypol and uricogenic nucleic acid bases [13]. Typsin inhibitors inhibit the action of nutrient degrading enzyme trypsin, resulting in lower bioavailability [13]. However, the bioactivity of trypsin may be increased through food processing techniques such as milling. For instance, milling of soyabeans, which contain high amounts of trypsin in the cotyledon results in higher levels of trypsin inhibitors of up to 28-65.8mg/g sample [13]. Tannins are water-soluble polyphenolic elements that can form complexes and precipitate in aqueous solutions. They are categorised into condensed and hydrolysable tannins. The hydrolysable tannins readily hydrolyse in acids, alkalis and some enzymes whereas condensed tannins form polymers of flavin-3-ol (catechin) and flavan-4, 4-diol which are resistant to hydrolysis [13]. Condensed tannins are the most abundant form found in food. Among the locally available cereals and legumes, sorghum, millet, beans and peas have some of the largest amounts of tannins with sorghum having as high as 111g/kg [13]. The quantity of tannins in these foods greatly lowers their bioavailability and digestibility. Another important naturally occurring antinutritional factor is phylate. It is usually found in plant tissues in form of salts of mono- and divalent cations such as Mg, Ca, Na, and K. Phylate, which contains an abundance

24848

of negatively charged phosphate groups chelates with several nutrients such as proteins and zinc making them less bioavailable [14].

Food processing also affects the bioavailability of proteins. Thermal processing and storage of proteins result in chemical changes that adversely impact the nutritional value of proteins. One such chemical process is the Maillard reaction which occurs between a carbonyl group of a reducing sugar and a free amino acid group [13]. An example is the reaction between lysine and a reducing sugar which has been observed in various products including dairy foods, eggs and cereals. In this reaction, lysine is changed to fructose or lactuloselysine in dairy products which results in both being unavailable [13]. The Maillard effect was studied in a cross-over trial conducted on adolescent males who were grouped into two and assigned a diet rich in Maillard reaction products and one without the products [15]. The results showed that the diet rich in Maillard reaction products resulted in 47% higher nitrogen faecal excretion and 12% lower apparent nitrogen absorption compared to the diet devoid of Maillard reaction products [15].

The bioavailability of lipids is affected by their structure, physical state (solid or liquid) and food matrix [16]. Fatty acids (FA) on a triacylglycerol (TAG) can either be on the internal *sn-2* position or external *sn-1* and *sn-3* positions [16]. The bioavailability and metabolism of TAG largely depends on the position of FAs on the glycerol backbone. For instance, in an animal model, it was observed that after administration of cocoa butter, palm oil and lard, the fraction of absorption was lower in cocoa butter and palm oil which have saturated FAs at position *sn-1,3* compared to lard which has saturated FA at position *sn-2* [16]. The effect of the structure of lipids on bioavailability has also been observed in human subjects where consumption of fish oil results in faster absorption of Docosahexaenoic acid (DHA) compared to Eicosapentaenoic acid (EPA) in plasma TAG. This is attributed to DHA having *sn-2* while EPA takes *sn-1,3* positions on the glycerol backbone [16].

The physical state of dietary lipids also determines their bioavailability. The melting points of FAs is dependent on the length of the carbon chains and degree of saturation. Long-chain saturated FA have higher melting points [16]. The implication of this has been observed in human studies where high melting points of TAGs rich in palmitic and stearic acids result in their low absorption rates [16]. Further, the postprandial activity of plasma TAG is observed to be higher after ingestion of sunflower oil which is liquid at room temperature compared to shea butter which is mostly solid at room temperature [16].

The food matrix, where lipids are bonded to proteins, sugars, starch and fibres impedes accessibility of lipases to TAGs [16]. This has been observed in foods like almonds, where the cell walls limit the release of lipids and thus their absorption and bioavailability [16]. The viscosity of food may also affect the degree of bioavailability of lipids in foods. For instance, fresh milk is more bioavailable compared to fermented milk [16]. This is attributed to high viscosity which increases duration of gastric emptying and delays time of peak of plasma TAG postprandially [16].

Common macronutrients that influence plasma glucose concentrations
Carbohydrates elicit different effects on plasma glucose concentration depending on their type, chemical structure, food processing techniques and presence of other nutrients in a meal. Starch is the most digestible carbohydrate, made up of amylose, a linear unbranched α-1, 4-linked glucose unit, and amylopectin which is a branched-chain polymer of α-1,6-linked glucose units [17]. The amylose-amylopectin ratio of starches greatly influences their bioavailability with a high amylose content being associated with low digestibility of starch [18]. Mechanisms advanced to explain this include: the linear unbranched nature of amylose which makes it relatively insoluble in water; formation of amylose-lipid complexes, which reduces enzymatic action; and encapsulation of gelatinized starch in layers of resistant starch [10]. This ratio has been shown to affect the physical properties of starches. A study demonstrated that maize starches containing low amylose content compared with medium and high amylose content varieties, largely retained its structure after processing [18]. Maize varieties with normal amylose content were found to have greater absorption than low amylose content maize starches [18].

Another type of carbohydrate that is reported to have implications on glycaemic control is dietary fibre. Several studies report health benefits of fibre-rich diets key among them being the ability to lower plasma glucose and insulin responses after a meal. A study investigated the effect of purified insoluble fibres on glucose response, insulin, GIP and GLP-1 [19]. Subjects were fed oat fibre, wheat fibre, and resistant starch followed by a control [19]. The results indicated that fibre enrichment accelerated early insulin response. There was also early postprandial GIP response after consumption of oat fibre. Furthermore, increased fibre intake over a period of 24 hours resulted in reduced postprandial glucose response on the following day [19]. Similarly, another study conducted a randomized, controlled, single-blind, cross-over experiment to assess the effect of cereal fibre on whole-body insulin sensitivity in obese women [20]. The results showed a remarkable improvement in whole-body glucose disposal and insulin sensitivity after fibre

consumption. Yet another study investigated the benefits of increased resistant starch intake on insulin sensitivity, plasma glucose, postprandial metabolites and body fat in type 2 diabetic patients [21]. The results showed significantly lower postprandial glucose concentrations and fasting esterified fatty acids but no effect on hepatic or peripheral insulin sensitivity or on HbA1c. However, one long-term intervention study reported modest beneficial effects of insoluble cereal fibre on glycaemic metabolism [22].

The presence of fats and proteins in mixed meals with carbohydrates has also been shown to have an impact on glycaemic response [23, 24]. One study demonstrated that consumption of a mixed meal containing carbohydrate, fat and protein resulted in greater decrease in postprandial glucose response compared to consumption of a meal containing carbohydrate with fat or protein alone [23]. Another study found that consumption of whey protein before a carbohydrate meal resulted in slow gastric emptying and increase in plasma GIP [24]. Additionally, insulin and cholecystokinin concentrations were high when whey protein was consumed before the carbohydrate meal while GLP-1 was greatest after whey protein consumption [24].

Fatty acids are carboxylic acids that are categorized into three groups: short-chain fatty acids (SCFAs), medium-chain fatty acids (MCFAs), and long-chain fatty acids (LCFAs) [25]. The effect of free fatty acids on plasma glucose and insulin concentration is believed to be as a result of their stimulation of GLP-1 [26]. This hormone decreases plasma glucose concentrations by stimulating insulin production and reducing glucagon secretion [27]. It also delays gastric emptying [27]. Short-chain fatty acids (SCFA) encourage secretion of GLP-1 from L-cells by interacting with free fatty acid receptors two and three (FFAR2 and FFAR3) [26].They are obtained as end products of fermentation of dietary fibre by gut microbes and in fermented foods [26] . This group of fatty acids includes: acetate, propionate and butyrate. Studies indicate that propionate has great affinity for FFAR2 and FFAR3, acetate is more active and selective towards FFAR2, and butyrate is more active towards FFAR3 [26]. A study demonstrated that ingestion of 200mmol/L of inulin-propionate ester raised GLP-1 concentrations 1.6-fold [28]. Free Fatty Acid Receptor 2 is involved in regulation of appetite and insulin signalling while FFAR3 heightens insulin sensitivity via the gut-brain neural circuit by activating the peripheral nerve FFAR3 through SCFAs [25]. Free Fatty Acid Receptor 3 is also found in human pancreatic β-cells and β-cell line EndoC-βH1, which implies its involvement in insulin secretion [25].

Similarly, unsaturated LCFAs derived from dietary triacylglycerol have been reported to stimulate GLP-1 and GIP secretion through their interaction with free fatty acid receptors one and four (FFRA1 and FFAR4) [25, 28]. Free Fatty Acid Receptor 1 signals glucose-stimulated insulin secretion [25]. This has been demonstrated in studies where LCFAs such as linoleic acid and DHA stimulated insulin secretion in mice insulinoma cells [25]. This is supported by another study in which acute treatment with palmitate raised glucose-stimulated insulin secretion in human islets [25]. In the same way, FFAR4 has been shown to promote GLP-1 secretion and increase insulin levels. Oral treatment of mice with α-linoleic acid in a study resulted in higher levels of GLP-1 and plasma insulin [25]. In addition, studies have shown that FFAR4 are highly expressed in enteroendocrine K cells. These cells are found abundant in the upper small intestine and are known to secrete GIP [25]. The relationship between GIP secretion and FFAR4 has been demonstrated in a study in which mice fed with lard oil resulted in GIP secretion and decreased plasma glucose levels [25]. This was not observed in FFAR4-deficient mice in the same study.

Proteins are made up of amino acids. Amino acids play many roles in glucose metabolism. Several studies have demonstrated amino acids' ability to modulate pancreatic β-cell insulin secretion thus promoting blood glucose uptake and utilization of tissues [29]. Depending on the type of amino acid, concentration, and duration of exposure, they can either elicit a positive or negative effect on insulin secretion [29]. The dietary amino acids that have been reported to influence plasma glucose and insulin dynamics are the branched-chain amino acids. Branched-chain amino acids, composed of leucine, isoleucine and valine have been reported to play a role in mediating insulin exocytosis [30]. Studies have demonstrated that consumption of dairy products such as whey protein and casein, which are rich sources of branched-chain amino acids, has beneficial effects on glucose-insulin dynamics. Milk-derived whey and casein proteins have been demonstrated to have a stimulating effect on insulin secretion in healthy, obese, pre-diabetic and type 2 diabetic individuals [30]. A research study reported that whey protein affected glycaemia, insulinaemia and plasma amino acids to a glucose load in a dose-dependent manner in twelve healthy individuals [31]. While caseins have not received much attention, a study demonstrated that both 50 g sodium caseinate and 50 g whey protein isolate administered with maltodextrin equivalently increased insulin secretion by 96 % compared with maltodextrin alone in pre-diabetic adults [32]. The enhanced insulin secretion was accompanied by a 21 % decrease in postprandial plasma glucose following both protein meals. Bioactive peptides may also act to regulate glucose uptake in skeletal muscle. Another study found several dipeptides identified in whey protein hydrolysates,

including Ile-Val, Leu-Val, Val-Leu, Ile-Ile, Leu-Ile, Ile-Leu and Leu-Leu, to stimulate glucose uptake in isolated skeletal muscle *in-vitro* [33]. However, high plasma concentrations of branched-chain amino acids have also been reported to increase insulin resistance in the presence of lipids [29].

Relationship between bioavailability of macronutrients and plasma glucose control

Carbohydrates, fats and proteins influence plasma glucose concentrations through different mechanisms. Carbohydrates are broken down directly into glucose and absorbed into the circulation system while the presence of fats and proteins-and to a smaller extent carbohydrates- in the gut stimulate production of incretin hormones which increase insulin secretion. The overall effect that carbohydrates have on plasma glucose concentrations is largely determined by its bioavailability but other factors such as rate of gastric emptying and absorption rate also play a role. The physiological relationship between bioavailability and plasma glucose concentration and the effect of incretin hormones has been aptly described by various authors.

The Hovorka model uses a two-compartment model with identical fractional transfer rates to describe the breakdown and absorption of carbohydrates [34]. The rate of appearance of glucose is assumed be a saturable process as is described by Hovorka *et al.* [34] as:

$$Ra(t) = \frac{Dfte^{-t/t_{max,G}}}{t_{max,G}^2} \tag{1}$$

where $t_{max,G}$ is the time-of-maximum appearance rate of glucose in the accessible glucose compartment, D is the amount of carbohydrates digested, and f is carbohydrate bioavailability.

Another model describes the process of absorption of carbohydrates using a partial differential equation, where glucose is progressively absorbed while passing through the intestine, and gastric emptying is assumed to be exponential [35]. The uptake of glucose from the gut lumen into plasma is described as [35]:

$$R_a(t)$$

$$= \begin{cases} fD\dfrac{k\gamma}{k-\gamma}[\exp(-\gamma t) - \exp(-kt)], & 0 \le t \le \dfrac{L}{u} \le \quad (2a) \\[3mm] fD\dfrac{k\gamma}{k-\gamma}[\exp[-k(t-L/u) - \gamma L/u] - \exp(-kt)], & t > L/u \quad (2b) \end{cases}$$

Equation 2(a) and 2(b), give the rate of appearance Ra(t) that would be provided by a two-compartment system, where the first compartment (stomach) delivers a bolus of glucose, D, with a rate constant, k, to a second compartment (gut) that delivers its contents to plasma with a rate constant, γ, and a loss factor, *f* [35]. f is the bioavailability of the glucose. In equation 2(b), the same rate of appearance of glucose time course is obtained by interchanging the values of k and γ which results in Ra values smaller than those obtained by equation 2(a) which translates in reduction of amount of glucose entering plasma [35]. In most literature, the area under the curve of Ra from 0 to ∞ of the two-compartment model is constrained to the fraction of glucose that is absorbed fD. However, in this description, the area under the curve of Ra from 0 to ∞ is described as, $fD[1 - \exp(-\gamma L/u)]$, which is smaller than the maximal value fD because a fraction of glucose (that may actually be very small) traverses the whole gut length L escaping absorption [35].

Yet another study proposes a 6-compartment model to describe the process of carbohydrate metabolism [36]. In their model, glucose absorption is traced from the stomach, jejunum, and ileum. Of interest to this review is the description of plasma glucose concentration and the effect of incretin hormones on insulin dynamics which are described as follows [36]:

$$\begin{cases} \dfrac{dG}{dt} = -k_{xg}G - k_{xgi}IG + G_{PROD} + f\left[\dfrac{k_{gj}J + k_{gl}L}{V \times BW}\right] & G(0) = G_b \quad (3a) \\[4mm] \dfrac{dI}{dt} = -k_{xi}I + k_{ig}^{max}\dfrac{\widetilde{G}^\gamma}{G^{*\gamma} + \widetilde{G}^\gamma} & I(0) = I_b \quad (3b) \end{cases}$$

The first equation, 3(a), depicts glucose dynamics. The first term in the equation describes glucose elimination rate and the second term glucose tissue uptake due to insulin. The parameter k_{xgi} depicts insulin-dependent glucose elimination rate [36]. The term G_{PROD} represents hepatic glucose production which is dependent on circulating plasma glucose. The last term represents glucose rate of appearance as a result of ingested carbohydrate D, which goes through the jejunum, J, and is absorbed from the ileum, L. Since not all of the ingested glucose amount is effectively absorbed, this term is multiplied by a fraction of absorption f,

which represents the bioavailability. Equation (3b) describes the incretin effect as a nonlinear function determined by the amount of glucose in the gastrointestinal tract [36]. While this description considers the effect of bioavailability on plasma glucose concentration, it does not take into consideration the incretin effect that could be due to mixed meals. It only considers the effect as elicited by carbohydrates.

Another model describes the dynamics of carbohydrate absorption in the gut [37]. The model consists of two stomach compartments and one intestinal-tract compartment. The model is described mathematically as follows [37]:

$$
\begin{cases}
Q_{sto}(t) = Q_{sto1}(t) + Q_{sto2}(t) & Q_{sto}(0) = 0 & (4a) \\
\dot{Q}_{sto1}(t) = -k_{gri} \cdot Q_{sto1}(t) + D \cdot \delta(t) & Q_{sto1}(0) = 0 & (4b) \\
\dot{Q}_{sto2}(t) = -k_{empt}(Q_{sto}) \cdot Q_{sto2}(t) + k_{gri} \cdot Q_{sto1}(t) & Q_{sto2}(0) = 0 & (4c) \\
\dot{Q}_{gut} = -k_{abs} \cdot Q_{gut}(t) + k_{empt}(Q_{sto}) \cdot Q_{sto2}(t) & Q_{gut}(0) = 0 & (4d) \\
Ra(t) = \dfrac{f \cdot k_{abs} \cdot Q_{gut}(t)}{BW} & Ra(0) = 0 & (4e)
\end{cases}
$$

where, equation 4(a) represents glucose mass in the stomach which consists of a liquid, Q_{sto2}, and a solid, Q_{sto1}, phase [37]. Glucose mass in solid phase, Q_{sto1}, is determined by the amount of glucose ingested, rate of grinding and responsivity of α-cells to rate of change in glucose, δ [37]. Glucose mass in the liquid phase is determined by the rate of gastric emptying k_{empt} and rate of grinding k_{gri}. Glucose mass in the gut, Q_{gut} is affected by the rate of absorption of glucose and rate of gastric emptying [37]. Ultimately, the rate of appearance of glucose, $Ra(t)$, in the systemic circulation is determined by the bioavailability of the amount of glucose in the gut, rate of absorption and the body weight of a subject.

Models that explicitly describe the incretin effect of macronutrients and plasma glucose concentrations are captured in the table 1.

CONCLUSION, AND RECOMMENDATIONS FOR DEVELOPMENT

This review set out to investigate the relationship between bioavailability of macronutrients and plasma glucose control in type 2 diabetic patients. It has shown that carbohydrates impact plasma glucose concentration directly by increasing glucose concentrations in the circulatory system. Physiological models have demonstrated that the effect of carbohydrates on plasma glucose concentration is determined by bioavailability, rate of absorption and rate of gastric

emptying. Proteins and lipids have been shown to affect the glucose-insulin regulatory system through their ability to stimulate release of incretin hormones which regulate insulin secretion. However, physiological models describing the mechanism by which proteins and lipids affect the glucose-insulin regulatory system have not demonstrated a correlation between the bioavailability of dietary proteins and lipids and their stimulatory effect on incretin hormones. Therefore, more research is warranted in this area. This review recommends that physiological models describing the relationship between macronutrients and plasma glucose control should be used to ascertain the exact quantities of macronutrients a type 2 diabetic patient should consume in order to regulate plasma glucose levels. These models should take into consideration the various factors that affect the bioavailability of macronutrients such as chemical structure, food processing, and food matrix. Most physiological models place the bioavailability of macronutrients at 90%, but considering the various factors that affect bioavailability, the value may vary. Therefore, when recommending foods to a type 2 diabetic patient, the impact of these factors on bioavailability should be considered so that the diet recommended is effective in controlling plasma glucose concentrations. The quality of macronutrients should also be considered when selecting foods, as some types of foods such as dietary fibres and whey proteins, have been shown to be more potent on their effect on the glucose-insulin regulatory system. These types of foods should be explored for management of plasma glucose concentration in type 2 diabetic patients.

ACKNOWLEDGEMENTS

Table 1: Models describing effect of proteins and lipids on glucose-insulin regulatory system

Model	Model description
Salvucci *et al.* [38]	Model describes amino acid and glucose stimulation of insulin secretion. It focuses on the role played by one type of amino acid, L-alanine, and the effect of D-glucose-stimulated insulin secretion. The relationship between L-alanine and D-glucose with insulin secretion is described using two models: a model of the metabolic pathway leading to ATP production, and electrical activity of ATP concentration-driven channels that leads to Ca^{2+} influx resulting in insulin granule exocytosis. The model only focuses on the effect of amino acids on incretin hormones but not fats and carbohydrates.
Salinari *et al.* [39]	Model describes insulin secretion as a function of plasma glucose and non-esterified fatty acids. They base this on experimental results that show that fatty acids support insulin secretion. However, the bioavailability of the lipids is not taken into consideration.
Dalla Man *et al.* [40]	The study presents a model that quantifies the effect of GLP-1 on insulin secretion in response to a mixed meal challenge. They base their model on the oral C-peptide minimal model and assume that over basal insulin secretion depends linearly on GLP-1 concentration. Although useful in its description, it does not include the effect of GIP on insulin secretion and neither does it consider the effect of bioavailability of macronutrients on their ability to stimulate incretin hormones.

REFERENCES

1. **Ajmera I, Swat M, Laibe C, Le Novere N and V Chelliah** The impact of mathematical modelling on the understanding of diabetes and related complications. *CPT Pharmacometrics Syst Pharmacol*. 2013; **2:** 1-14.

2. **Mari A, Tura A, Grespan E and R Bizzotto** Mathematical modelling for the physiological and clinical investigation of glucose homeostasis and diabetes. *Front Physiol*. 2020; 11.

3. **Diabetes UK.** Evidence based nutrition guidelines for the prevention and management of diabetes. 2018; 1-114.

4. **Snorgaard O, Poulsen G, Anderson H and A Astrup** Systemic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. *BJM Open Diabetes Res Care*. 2017; **5:** 1-10.

5. **Wen-Ting Z, Yu L, Ying Z, Yun Z and Z Ting-Ting** High protein diet is of benefit for patients with type 2 diabetes: an updated meta-analysis. *Medicine*. 2018; **97(46):** pe13149.

6. **Englyst K and H Englyst** Carbohydrate bioavailability. *Br J Nutr.* 2005; **94:**1-11.

7. **Miao M and B Hamaker** Food matrix effects for modulating starch bioavailability. *Annu Rev Food SciTechnol.* 2021; **12:** 169-191.

8. **Livesey G, Wilkinson J, Roe M, Faulks R, Clark S, Brown J, Kennedy H and M Elia** Influence of the physical form of barley grain on the digestion of its starch in the human small intestine and implications for health. *Am J Clin Nutr.* 1995; **61(1):** 75-81.

9. **Svihus B, Uhlen A and O Harstad** Effect of starch granule structure, associated components and processing on nutritive value of cereal starch: a review. *Anim Feed Sci Technol.* 2005; **122:** 303-320.

10. **Russell W, Baka A, Bjorck I, Delzenne N, Gao D, Griffiths H, Hadjilucas E, Juvonen K, Lahtinen S, Lansink M, Loon V, Mykkanen H, Ostman E, Riccardi G, Vinoy S and M Weeikert** Impact of Diet Composition on Blood Glucose Regulation. *Crit Rev Food Sci Nutr.* 2016; **56(4):** 541–590.

11. **Cesbron-Lavau G, Goux A, Atkinson F, Meynier A and S Vinoy** Deep dive into the effects of food processing on limiting starch digestibility and lowering the glycaemic response. *Nutrients*. 2021; **13(2):** 381.

12. **Aberg S, Mann J, Neumann S, Ross A and A Reynolds** Whole-grain processing and glycaemic control in type 2 diabetes: a randomized crossover trial. *Diabetes Care*. 2020; **43(8):** 1717-1723.

13. **Gilani G, Xiao C and K Cockell** Impact of antinutritional factors in food proteins on the digestibility of protein and the bioavailability of amino acids and on protein quality. *Br J Nutr.* 2012; **108:** S315-S332.

14. **Gu J, Bk A, Wu H, Lu P, Nawaz A, Barrow C, Dunshea F and H Suleria** Impact of processing and storage on protein digestibility and bioavailability of legumes. *Food Reviews International.* 2022; 1-29.

15. **Seiquer I, Diaz-Alguacil J, Delgado-Andrade C, Lopez-Frias M, Hoyos A, Galdo G and M Navarro** Diets rich in maillard reaction products affect protein digestibility in adolescent males aged 11-14y. *Am J Clin Nutr.* 2006; **83(5):** 1082-1088.

16. **Michalski M, Genot C, Gayet C, Lopez C, Fine F, Joffre F, Vendeuvre J, Bouvier J, Chardigny J and K Raynal-Ljutovac** Multiscale structures of lipids in foods as parameters affecting fatty acid bioavailability and lipid metabolism. *Prog Lipid Res.* 2013; **52:** 354-373.

17. **Hils M, Wolbing F, Hilger C, Fischer J, Hoffard N and T Biedermann** The history of carbohydrates in type 1 allergy. *Front Immunol.* 2020; **11:** 586924.

18. **Beech D, Beech J, Gould J and S Hill** Effect of amylose/amylopectin ratio and extent of processing on the physical properties of explained maize starches. *Int J Food Sci Technol.* 2022; **57(4):** 2298-2309.

19. **Weickert M, Mohlig M, Koebnick C, Holst J, Namsolleck P, Ristow M, Osterhoff M, Rochlitz H, Rudovich N, Spranger J and A Pfeiffer** Impact of cereal fibre on glucose-regulating factors. *Diabetologia*. 2005; **48(11):** 2343–2353.

20. **Weickert M, Mohlig M, Schofl C, Arafat A, Otto B, Viehoff H, Koebnick C, Kohl A, Spranger J and A Pfeiffer** Cereal fibre improves whole-body insulin sensitivity in overweight and obese women. *Diabetes Care*. 2006; **29(1):** 775–780.

21. **Bodinham C, Smith L, Thomas E, Bell J, Swann J, Costabile A, Russell-Jones D, Umpleby A and M Robertson** Efficacy of increased resistant starch consumption in human type 2 diabetes. *Endocrine Connections*. 2014; **3(2):** 75-84.

22. **Honsek C, Kabisch S, Kemper M, Gerbracht C, Arafat M, Birkenfeld L, Dambeck U, Osterhoff M, Weickert M and A Pfeiffer** Fibre supplementation for the prevention of type 2 diabetes and improvement of glucose metabolism: The randomised controlled Optimal Fibre Trial (OptiFiT). *Diabetologia.* 2018; **61:** 1295–1305.

23. **Kim J, Nam K and S Chung** Effect of nutrient composition in a mixed meal on the postprandial glycaemic response in healthy people: a preliminary study. *Nutr Res Pract.* 2019; **13(2):** 126-133.

24. **Ma J, Stevens J, Cukier K, Maddox A, Wishart J, Jones K, Clifton P, Horowitz M and C Rayner** Effects of a protein preload on gastric emptying, glycemia, and gut hormones after a carbohydrate meal in diet-controlled type 2 diabetes. *Diabetes Care*. 2009; **32:** 1600–1602.

25. **Kumura I, Ichimura A, Ohue-Kitano R and M Igarashi** Free fatty acid receptors in health and disease. *Physiol Rev*. 2019; **100(1):** 171-210.

26. **Zhang J, Sun Y, Zhao L, Chen T, Fan M, Jiao H, Zhao J, Wang X, Li F, Li H and H Lin** SCFAs-induced GLP-1 secretion links the regulation of gut microbiome on hepatic lipogenesis in chickens. *Front Microbiol.* 2019; **10.**

27. **Holst J** The incretin system in healthy humans: the role of GIP and GLP-1. *Metabolism*. 2019; **96:** 46-55.

28. **Thombare K, Mtika S, Wang X and C Krizhanovskii** Long chain saturated and unsaturated fatty acids exert opposing effects on viability and function of GLP-1-producing cells: mechanisms of lipotoxicity. *PloS One*. 2017; **12(5):** e0177605.

29. **Newsholme P, Cruzat V, Arfuso F and K Keane** Nutrient regulation of insulin secretion and action. *J Endocrinol.* 2014; **221:** R105-R120.

30. **Horner K, Drummond E and L Brennan** Bioavailability of milk protein-derived bioactive peptides: a glycaemic management perspective. *Nutr Res Rev.* 2016; **29(1):** 91-101.

31. **Gunnerud U, Ostman E and I Bjorck** Effects of whey proteins on glycaemia and insulinaemia to an oral glucose load in healthy adults: a dose–response study. *Eur J Clin Nutr.* 2013; **67:** 749–753.

32. **Hoefle A, Bangert A, Stamfort A, Gedrich K, Rist M, Lee Y, Skurk T and H Daniel** Metabolic responses of healthy or prediabetic adults to bovine whey protein and sodium caseinate do not differ. *J Nutr.* 2015; *145(3):* 467-475.

33. **Morifuji M, Koga J, Kawanaka K and M Higuchi** Branched-chain amino acid containing dipeptides identified from whey protein hydrolysates stimulate glucose uptake rate in l6 myotubes and isolated skeletal muscles. *J Nutr Sci Vitaminol.* 2009; **55(1):** 81-86.

34. **Hovorka R, Canonico V, Chassin L, Haueter U, Massi-Benedetti M, Federici M, Pieber T, Schaller H, Schaupp L, Vering T and M Wilinska** Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiol Meas.* 2004; 905-920.

35. **Salinari S, Bertuzzi A and G Mingrone** Intestinal transit of a glucose bolus and incretin kinetics: a mathematical model with application to the oral glucose tolerance test. *Am J Physiol endocrinol Metab.* 2011; **300:** E955-E965.

36. **De Gaetano A, Panunzi S, Matone A, Samson A, Vrbikova J, Bendlova B and G Pacini** Routine OGTT: a robust model including incretin effect for precise identification of insulin sensitivity and secretion in a single individual. *PLoS One*. 2013; **8(8):** e70875.

37. **Dalla Man C, Camilleri M and C Cobelli** A system model of oral glucose absorption: validation of gold standard data. *IEEE Trans Biomed Eng*. 2006; **53(12):** 2472-2478.

38. **Salvucci M, Neufeld Z and P Newsholme** Mathematical model of metabolism and electrophysiology of amino acid and glucose stimulated insulin secretion: *in-vitro* validation using a β-cell line. *PLoS One.* 2013; **8(3):** e52611.

39. **Salinari S, Bertuzzi A, Manco M and G Mingrone** NEFA-glucose comodulation model of β-cell insulin secretion in 24-h multiple-meal test. *Am J Physiol Endocrinol Metab.* 2007; **292:** E1890-E1898.

40. **Dalla Man C, Micheletto F, Sathananthan M, Vella A and C Cobelli**
Model-based quantification of glucagon-like peptide-1-induced potentiation
of insulin secretion in response to a mixed meal challenge. *Diabetes Technol
Ther.* 2016; **18(1):** 39-46.