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SIMULATION OF GLUCOSE AND INSULIN KINETICS MODEL USING THE GLYCEMIC LOAD OF MIXED MEALS

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Summary

This study aimed to assess how the glycemic load in various mixed meals affects glucose and insulin levels using a mathematical model of glucose and insulin dynamics. Three distinct dietary menus were formulated (high-carbohydrate, diabetic, and low-carbohydrate) each with calculated glycemic loads. The model was then simulated using the WR Mathematica 10.0 software using the data form developed menus. Findings revealed that meals with a high glycemic load significantly influenced blood glucose and insulin levels. Additionally, a negative correlation was observed between carbohydrate proportions and protein (r = -0.9500) as well as fat (r = -0.9855) proportions in the meals. The glycemic load of a single meal can serve as an initial value for simulating the glucose-insulin metabolism model, enabling a personalized approach to meal development through the application of the primary nutrient metabolism model.

Keywords: mathematical model of glucose and insulin kinetics, glycemic load, glucose concentration, model simulation

Introduction

In the human body, the blood glucose concentration depends primarily depends on the diet. Carbohydrates are the exclusive class of macronutrients that undergo direct conversion into glucose within the body, and their catabolism is initiated prior to that of other macronutrient groups (Chandel, 2021). The digestibility of the carbohydrates themselves depends on their structure; therefore, indigestible carbohydrates such as cellulose reach the colon intact and serve as a food source for beneficial bacteria (Kiely and Hickey, 2022). Moreover, indigestible carbohydrates, known as dietary fibers, exert a comprehensive influence on the digestive tract by slowing the absorption of nutrients, reducing serum cholesterol levels, and enhancing feelings of satiety. This, in turn, may lead to decreased caloric intake in subsequent meals, which has been demonstrated to confer protective benefits against diseases associated with obesity (Dayib et al., 2020). Carbohydrate metabolism provides the cell with constant and necessary energy supply. Blood glucose levels are tightly regulated (3.89-4.44 mmol/L during fasting and 7.78-8.89 mmol/L postprandially) by the hormone insulin. Any disruption in insulin synthesis or its interaction with cellular receptors impairs the homeostasis of glucose concentration in both the bloodstream and cells (Dimitriadis et al., 2021). This leads to an increased concentration of glucose in the blood, which can consequently cause numerous health problems such as insulin resistance, cardiovascular diseases, diabetes and similar (Roden and Shulman, 2019).

People suffering from diabetes need to monitor the amount of carbohydrates consumed daily daily in order to mainatin maintain normal blood glucose concentration to prevent further complications of this disease. The American Diabetes Association (ADA) emphasizes the significance of medical nutritional therapy in both the prevention of diabetes and the management of the disease, highlighting its role in mitigating the risk of associated complications (ADA, 2024). For this reason, in 1950, in cooperation with the American Dietetic Association, they developed a system of foods that is divided into six groups according to caloric and nutritional value: bread and substitutes, fruits, vegetables, meat and substitutes, milk and substitutes and fats and substitutes. Foods from these groups is divided into units that have the same energy value, but different mass and quantity (e.g. if the meal contains one unit of bread or substitute, this means 25 g of white bread or 60 g of cooked pasta). One unit from the group of bread and fruit contains 15 g of carbohydrates, from the group of milk 12 g of carbohydrates, and from the group of vegetables 5 g of carbohydrates (Prašek and Jakir, 2009). To facilitate the analysis of the influence of macronutrients on blood glucose concentration, numerous mathematical models have been developed. Mathematical models of metabolism typically offer a simplified representation of the intricate biochemical processes occurring at the cellular level, within specific organs, or throughout the entire organism (Mc Auley, 2020). Despite being founded on specific assumptions, existing mathematical models of metabolism substantially enhance and streamline the analysis of cellular processes and the impact of environmental factors on macronutrient metabolism. These models aim to personalize nutrition based on individual needs,

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*Corresponding author: ana.tusek.jurinjak@pbf.unizg.hr utilizing molecular markers derived from food and disease prevention (Mitchelson et al., 2023; Vyas, 2023). Based on the aforementioned, the aim of this work was to analyse the influence of the proportion of carbohydrates expressed as glycemic load in individual meals on the concentration of glucose and insulin in the blood, using a mathematical model of glucose and insulin kinetics.

Materials and methods

Menus planning

To achieve the goal of the study, which focuses on the glycemic load of the meal, three menus with different glycemic loads were created: (i) high-carbohydrate (high GL), (ii) diabetic and (iii) low-carbohydrate (low GL) menus. The diabetic menu was designed according to the ADA system of foods and substitutes, establishing a daily energy intake of 1900 kcal. This menu, which includes three main meals and an additional night-time meal before bedtime, follows a meal schedule proven optimal for individuals with type 1 diabetes. They must receive insulin doses at precise times, facilitating glycemic control, making it a common recommendation among experts (Pavić et al., 2023). To ensure better data comparison, the other menus were aligned with this same meal schedule. The energy distribution in each meal adheres to the guidelines, allocating 20-25% of daily energy intake for breakfast, 30-35% for lunch, 25-30% for dinner and 10-15% for snack (night-time meal), with minor deviations. All menus followed different recommendations regarding the proportion of carbohydrates: 45-65% (high-carbohydrate menu), 40-55% (diabetic menu), and 60 to 130 g/day (low-carbohydrate menu). Included are also the daily recommended fiber intake of 25-38 g/day (Pavić et al., 2023; USDA, 2020). The menus were developed using the USDA food composition database (FCDB) allowing calculation of energy and nutrients of daily offers. Glycemic index (GI) values were sourced from Foster-Powell et al. (2002). For each meal, the glycemic load (GL) was calculated (Eq. 1):

$$GL = \frac{amount\ of\ carbohydrates\ (g) - amount\ of\ fiber\ (g)}{100} \cdot GI \tag{1}$$

Simulation of the mathematical model of glucose and insulin metabolism

This work is based on the mathematical model of glucose and insulin metabolism in people with type 1 diabetes, created by Noguchi et al. (2014). The model is divided into three main subsystems shown in Figure 1. The first subsystem (carbohydrate metabolism) describes the influence of carbohydrates on blood glucose concentration, considering not only the amount of carbohydrates but also absorption parameters. The next subsystem (subcutaneous insulin) describes the kinetics of insulin from subcutaneous administration, denoted as $u_s(t)$ (in units of insulin per minute) to plasma insulin concentration, denoted as $I(t)$ (in micro-units per milliliter). Here, $u_s(t)$ represents the rate at which insulin is administered subcutaneously over time, while $I(t)$ indicates the concentration of insulin in the plasma at any given time. Furthermore, these two subsystems serve as inputs to the glucose and insulin metabolism subsystem, which is based on Bergman's minimal model (Bergman et al., 1979); however, Noguchi et al. (2014) adjusted certain parameters to apply their model to individuals with type 1 diabetes, with blood glucose concentration as an output variable. The model includes 10 differential equations and 20 kinetic parameters.

Simulations of the model were performed using the software WR Mathematica 10.0 (Wolfram Research, Inc., Champaign, IL, USA) based on the different glycemic load of each meal of the developed menus. The influence of GL on blood glucose concentration and the concentration of subcutaneous insulin was monitored over 300 minutes, a period chosen to capture the complete physiological response and insulin activity cycle.

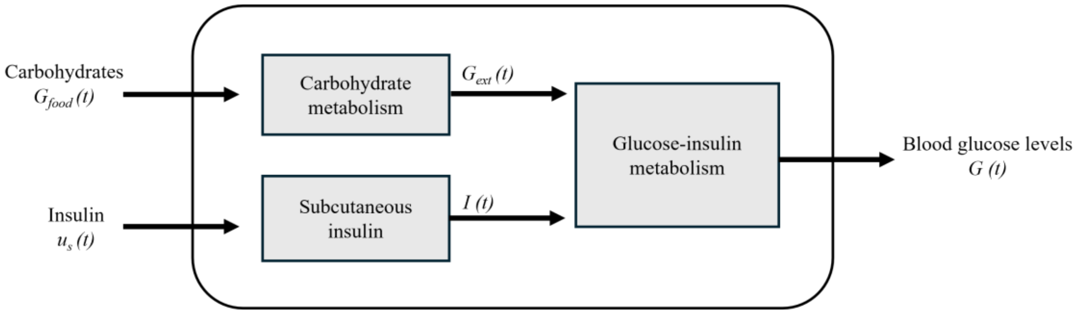

Figure 1. Diagram of proposed mathematical model (adapted from Noguchi et al., 2014)

Results and discussion

Menu analysis

The high-carbohydrate menu exhibits the highest carbohydrate content - 294.5 g (61.8%) and predominantly comprises simple carbohydrates, contributing to a high glycemic index. This menu archetype mirrors contemporary dietary trends characterized by widespread consumption of convenience foods, often deep-fried, necessitating minimal preparation. Concurrently, there is a surge in processed food consumption laden with high levels of fats and sugars, culminating in adverse health effects and heightened susceptibility to chronic non-communicable ailments such as insulin resistance, cardiovascular diseases and diabetes (Christ et al., 2019). The diabetic menu adheres to dietary guidelines tailored for individuals with diabetes, emphasizing meal planning based on the carbohydrate counting principle. This dietary approach prescribes a carbohydrate unit equivalent to 15 g, facilitating the dispersion of carbohydrate intake throughout the day (60 to 75 g per meal). This facilitates insulin therapy application and blood glucose regulation efficacy (Pavić et al., 2023; Franz 2016). Notably, the menu registers a total carbohydrate content of 202.3 g (42.6%), incorporating whole grains and fiber-rich foods like fruits, vegetables and seeds. Despite their limited nutritional value, these constituents contribute to gradual glucose release in the intestines, mitigating abrupt spikes in blood glucose levels. Widely recommended for diabetics, the traditional Mediterranean diet stands out for its holistic health benefits in managing obesity, cardiovascular diseases and diabetes, attributed to its inclusion of fruits, vegetables, whole grains, seeds, nuts, fish and olive oil (Dominguez et al., 2023; Martín-Peláez et al., 2022). However, recent American Diabetes Association guidelines advocate for a personalized dietary approach, promoting reduced overall carbohydrate intake to mitigate blood glucose elevation (Evert et al., 2019).

Table 1 depicts the menu embodying a low-carbohydrate dietary regimen, aiming for an intake between 60 to 130 g, alongside increased protein and fat consumption. With a carbohydrate content of 114 g (24%), this plan boasts the lowest glycemic load. Conceived for experimental purposes, this menu facilitates comparative analysis of varying carbohydrate and blood glucose levels, delineating disparities between high and low glycemic loads. Furthermore, several studies affirm the efficacy of low-carbohydrate and ketogenic diets (carbohydrate intake up to 50 g/day) in reducing glycated hemoglobin and maintaining glycemic levels in diabetic individuals, while elevated protein and fat proportions enhance satiety, potentially aiding weight loss in obese individuals (Turton et al., 2023; Hancock et al., 2023). Despite the favourable outcomes of such dietary interventions on blood glucose variability, long-term benefits remain unverified, accompanied by inherent apprehensions. Clerc (2023) underscores that meals rich in fat (>40 g) and/or protein (>40-75 g) lack balance and are therefore unsuitable for inclusion in the daily diet of type 1 diabetes patients. For instance, Leow et al (2018) study unveiled the ketogenic diet's efficacy in regulating blood glucose levels among type 1 diabetes patients, although with potential complications like dyslipidemia and increased hypoglycemic episodes.

Menu compositions were formulated based on an energy intake target of 1900 kcal, with energy allocation distributed across meals as detailed in Table 2. Most meals met the recommended energy distribution guidelines with exceptions such as the breakfast of the high glycemic (29%) and diabetic menu (32%).

Table 1. Proposed menus

	Meal	Energy (kcal)	CHO (g)	Fibres (g)	GL
High GL menu	**Breakfast:** fruit and hazelnuts muesli (90 g), milk (1.9% m.f., 220 g), black coffee (100 g), brown sugar (5 g), medium banana (130 g)	551.7	115.2	10	65
	Lunch: baked chicken (150 g), French fries (150 g), tomato (100 g), fresh cucumber (90 g), apple juice (200 g)	695.3	72.6	6.6	38
	Dinner: Hazelnut spread (45 g), white bread (90 g)	486.5	72.5	6.2	37
	Night meal: fruit yogurt (180 g)	171.0	34.2	0	11
Diabetic menu	**Breakfast:** Low-fat yogurt (240 g), raspberries (100 g), flax seeds (5 g), boiled eggs (100 g), rye bread (70 g), butter (5 g)	611.4	67.1	13.0	19
	Lunch: chicken soup (250 g), stewed dark chicken meat (90 g), cooked brown rice (150 g), broccoli (100 g), olive oil (15 g), green salad (100 g), vinegar (5 g), plums (100 g)	661.7	64.7	8.7	20
	Dinner: drained canned sardines (60 g), cooked quinoa (100 g), cooked green beans (100 g), salad iceberg (100 g), olive oil (5 g), cashew nuts (15 g), pear (140 g), vinegar (5 g)	507.4	59.0	13.0	17
	Night meal: low fat milk (240 g)	120.0	11.5	0	4

Table 1. Continued...

Low GL menu	**Breakfast:** olive oil (5 g), iceberg salad (100 g), scrambled eggs (120 g), hard goat cheese (25 g), cooked turkey ham (30 g), orange (160 g)	476.8	24.7	5	6
	Lunch: cooked salmon (160 g), cooked whole grain macaroni (100 g), olive oil (15 g), feta cheese (25 g), tomato (100 g)	611	31.4	4	11
	Dinner: roasted turkey (170 g), white sauce (100 g), mushrooms (100 g), onions (50 g), rye bread (35 g)	574.3	36	5.3	6
	Night meal: cashew nuts (15 g), low-fat yogurt (240 g)	237.3	21.8	0.5	7

CHO - carbohydrates; GL - Glycemic load**;** m.f. - milk fat

Table 2. Energy allocation per meal according to guidelines

Meals	High GL menu (%)	Diabetic menu (%)	Low GL menu (%)	Guidelines (%)
breakfast	29	32	25	20-25
lunch	37	35	32	30-35
dinner	26	27	30	25-30
night meal	9	6	12	10-15

Furthermore, the proportions of macronutrients in each menu were analysed (Figure 2). In the high glycemic load menu (High GL), macronutrient proportions adhered to general population dietary guidelines, with carbohydrate intake comprising 62% (recommended range: 45-65%), protein at 19% (recommended range: 10-35%) and fat at 23% (recommended < 35%). Conversely, the diabetic menu exhibited a slight excess of fat intake beyond recommendations, possibly influenced by database food choices. The low glycemic load menu (Low GL) displayed elevated proportions of fats (44%) and proteins (32%), with carbohydrates making up only 24%, yet remaining within the confines of a low-carbohydrate dietary regimen characterized by a daily carbohydrate intake of 60-130 g.

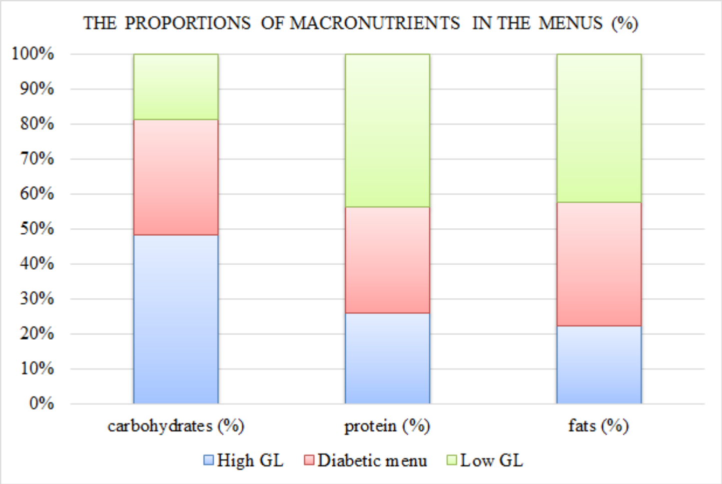

Figure 2. The proportions of macronutrients in the menus

The diabetic menu registered the highest fiber content (34.7 g), meeting or exceeding daily recommended intake levels (25-38 g/day), attributable to the inclusion of various fibrous fruits, vegetables, whole grains, and seeds. Despite comprising grains and carbohydrates, the high glycemic load menu contained 22.8 g of fiber, approaching recommended levels, reflecting the substantial quantity of these fibrous foods within the menu. Conversely, the low glycemic load menu, characterized by elevated protein and fat proportions but devoid of fiber (14.8 g), demonstrated diminished overall fiber intake.

Macronutrient distribution in the menus

Figure 3A illustrates substantial variability in carbohydrate quantities, particularly noticeable during breakfast, across the various menus. Carbohydrate quantities are relatively uniform across other meals. Meals characterized by high glycemic load exhibit the greatest carbohydrate variability, a pattern mirrored in protein and fat distributions across menus. Notably, meals with elevated carbohydrate content coincide with diminished protein and fat quantities, exemplified by the evening meal. Conversely, the diabetic menu displays consistent macronutrient distribution without notable daily fluctuations. In the context of low glycemic load menus, higher protein content inversely correlates with lower fat content and vice versa, while carbohydrate quantities remain relatively uniform.

These macronutrient distributions, particularly evident in menus with high glycemic load, significantly influence blood glucose variability, as corroborated by Dimova et al. (2023). Their investigation assessed the relationship between glycemic variability and dietary patterns among individuals with normal and impaired glucose tolerance. Findings revealed heightened glucose variability parameters among those with impaired glucose tolerance, exacerbated by increased consumption of refined grain carbohydrates. Conversely, augmented consumption of whole grains was associated with improved glycemic parameters. Furthermore, a combination of protein intake with whole grains mitigated glucose variability. Graphical representation (Figure 3) underscores the marked disparity between protein intake and carbohydrate quantity, particularly noticeable in menus featuring high glycemic load, barring lunch. Notably, protein intake in high glycemic load menu remains substantially lower compared to carbohydrate intake, a contrast observed across other meal menus as well. The diabetic menu, characterized by consistent distribution of carbohydrates primarily from whole grains and high protein content, lends credence to the findings mentioned above (Dimova et al., 2023).

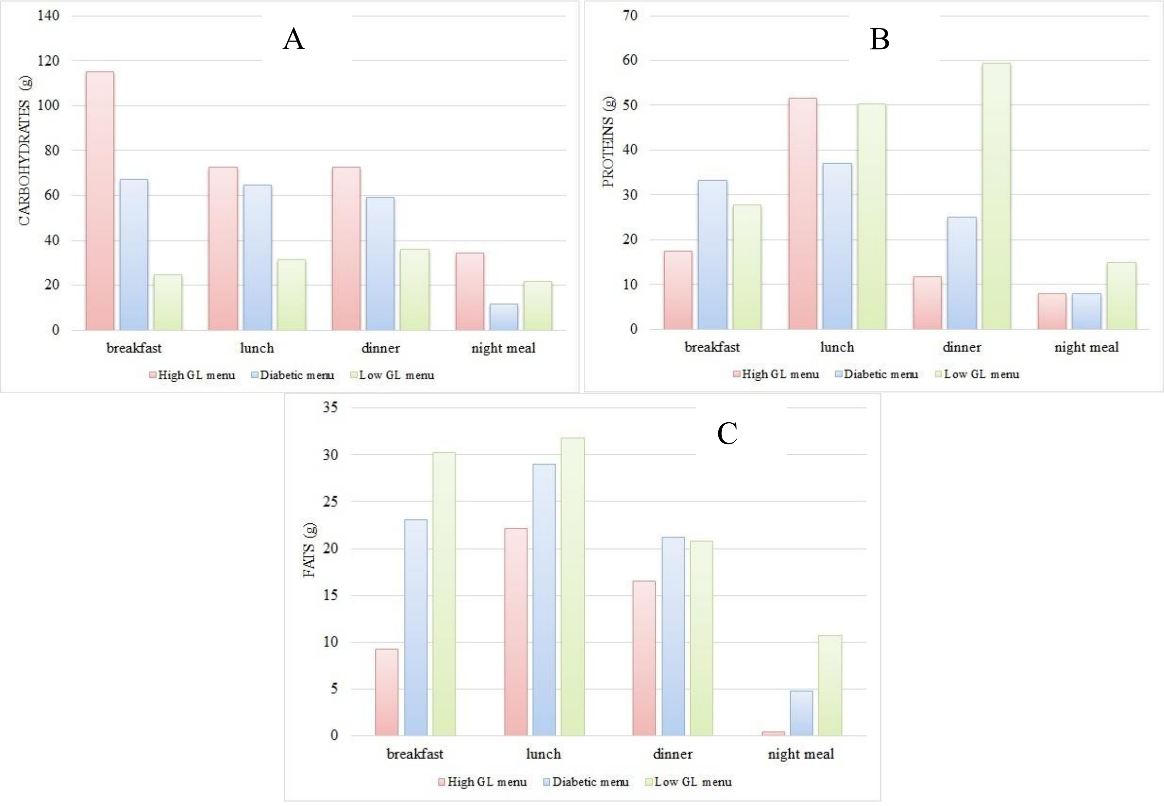

Figure 3. Macronutrient distribution in the menus

The correlation matrix

To gain insight into the interrelationships among macronutrient quantities (carbohydrates, proteins, fats and fibers) within the developed menus, Spearman correlation analysis was conducted. The results presented in Table 3 reveal significant negative correlations between carbohydrate proportions and both protein (r = -0.9500) and fat proportions (r = -0.9855), indicating an inverse relationship. Consequently, as the proportion of carbohydrates increases, the proportions of proteins and fats decrease within the menus. Additionally, a positive correlation was observed between protein and fat proportions (r = 0.8834), while negative correlations were found between protein proportions and fiber (r = -0.6564), as well as between fat proportions and fiber (r = -0.2262). Notably, Amankwaah et al. (2017) demonstrated in their study that proteins and fibers independently influence glucose metabolism regulation, a finding consistent with the correlation analysis results of the menus in this study. Their randomized controlled crossover trial investigated the independent and combined effects of normal versus higher protein and fiber intake, focusing on breakfast due to typically lower protein and fiber consumption during this meal compared to lunch and dinner. Results indicated that a breakfast with elevated protein and fiber content did not significantly alter postprandial glucose response, or 24-hour glucose patterns compared to control breakfasts. However, increased fiber intake mitigated postprandial insulin response. Thus, while doubling protein and quadrupling fiber intake for breakfast may not notably enhance insulin and glucose responses, higher fiber intake could effectively reduce postprandial insulin response in healthy overweight young adults.

Table 3. Correlation matrix among macronutrient quantities (carbohydrates, proteins, fats and fibers) within the developed menus. Significant correlations (p<0.05) are highlighted in bold (negative correlations – shades of red, positive correlations – shades of green).

	carbohydrates	protein	fats	dietary fiber
carbohydrates	1.0000			
protein	**-0.9500**	1.0000		
fats	**-0.9855**	**0.8834**	1.0000	
dietary fiber	**0.3880**	**-0.6564**	**-0.2262**	1.0000

Glycemic load

Figure 4 illustrates the spectrum of glycemic loads across meals. In menus characterized by high glycemic loads, breakfast emerges with the highest load, gradually declining towards later meals, while still exceeding counterparts in other menus by roughly double. This disparity is attributable to elevated carbohydrate quantities in the meals, compounded by their composition, primarily comprising foods rich in simple carbohydrates with a high glycemic index. Conversely, the diabetic menu exhibits uniform glycemic loads across main meals, facilitated by evenly distributed carbohydrate quantities tailored to insulin doses, ensuring consistent glucose release into the bloodstream throughout the day. Furthermore, the carbohydrate quality is enhanced, featuring whole grains and increased dietary fiber content. A similar trend is observable in the low glycemic load menu, with lunch registering the highest value, while remaining meal values are relatively uniform.

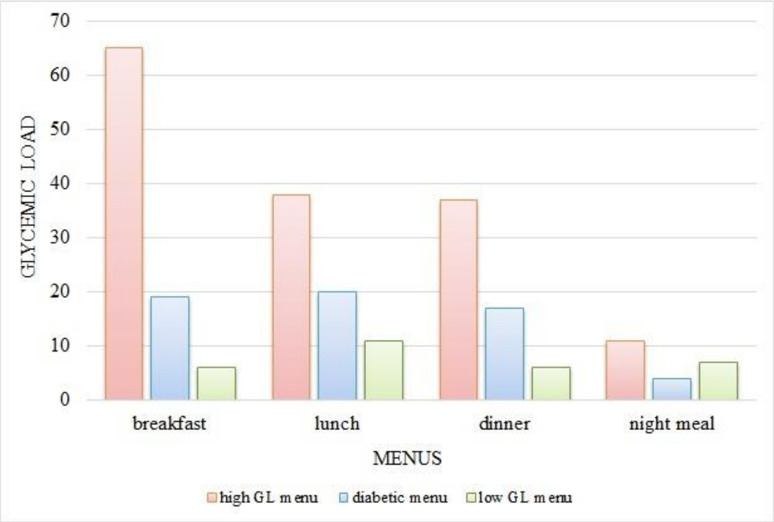

Figure 4. Glycemic load across meals

Simulation of glucose and insulin kinetics model

Initial simulation conditions were set to represent fasting conditions without insulin therapy to assess the influence of meal carbohydrate content on blood insulin concentration profiles across various meals. As depicted in Figure 5, changes in blood glucose concentration exhibit a consistent pattern across all daily meals. Following meal consumption, blood glucose concentration rises, peaking at approximately 80 minutes before gradually declining to around 5 mmol/L. Meals with high glycemic load notably yield the highest blood glucose values, particularly breakfast and lunch, elevating blood glucose concentration to approximately 13 mmol/L. Moreover, lunch with a high glycemic load demonstrates a sinusoidal glucose concentration profile with damping, attributed to the meal's high carbohydrate content. Notably, simulation results for diabetic meals indicate blood glucose concentration stabilizes after approximately 240 minutes, underscoring the multifactorial influence on blood glucose levels, including pre-meal glucose levels, insulin therapy timing and administration method, insulin sensitivity, exercise, stress, other medications and illnesses (Bevier et al., 2007).

Simulation outcomes reveal that meals with low glycemic load consistently yield the lowest blood glucose values. Papakonstantinou et al. (2019) highlighted in their study that the addition of a small amount of fat affected glucose response primarily following the consumption of high-energy foods, suggesting a potential energy threshold beyond which fat exerts a heightened impact on glucose response, potentially inducing persistent or delayed hyperglycemia.

Simulation results from the insulin model mirror glucose concentration trends across all meals (Figure 6). Meals eliciting the highest blood glucose values correspondingly produce the highest insulin concentration values, although with varying timeframes to reach peak concentrations. While glucose peaks around 80 minutes post-meal, insulin peaks around 200 minutes post-meal.

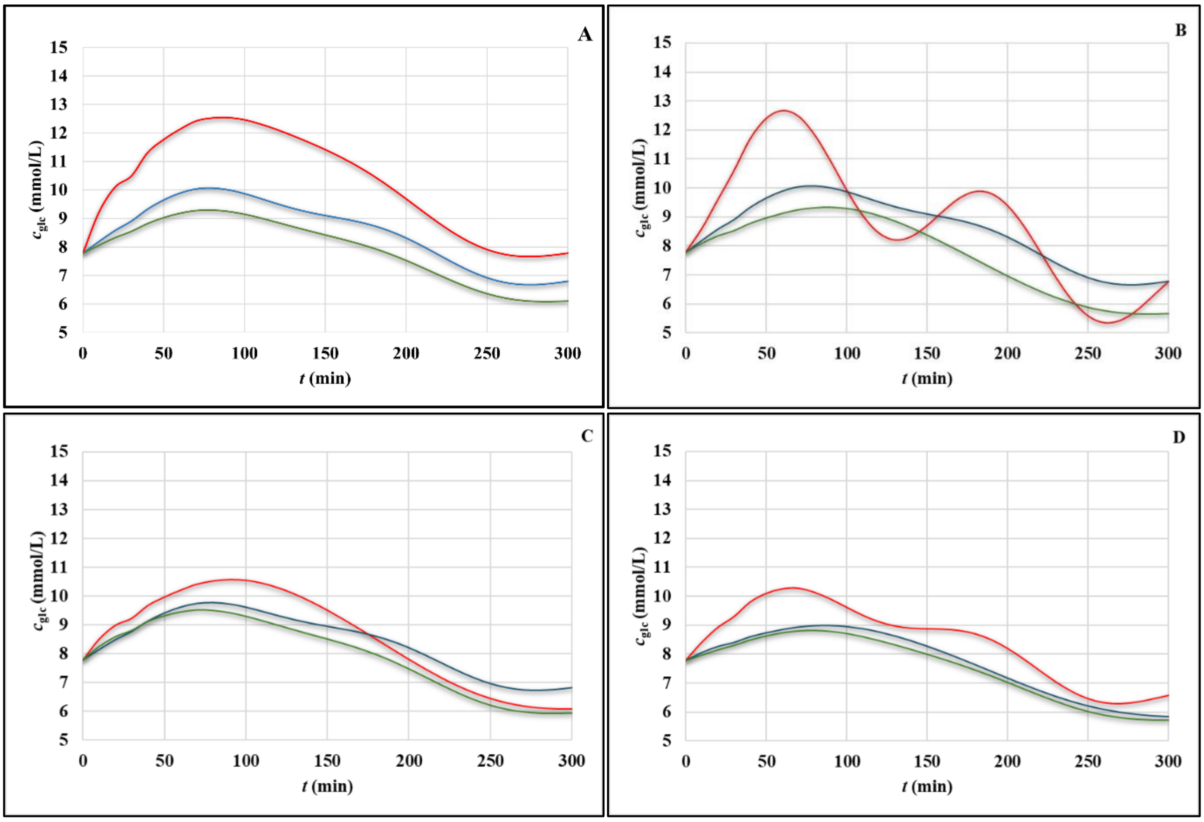

Figure 5. Graphical representation of the change in concentration of glucose (c_{Glc}) over a period of 300 minutes after (A) breakfast, (B) lunch, (C) dinner, (D) night meal consumption (red - high glycemic load menu, blue - diabetic menu, green - low glycemic load menu)

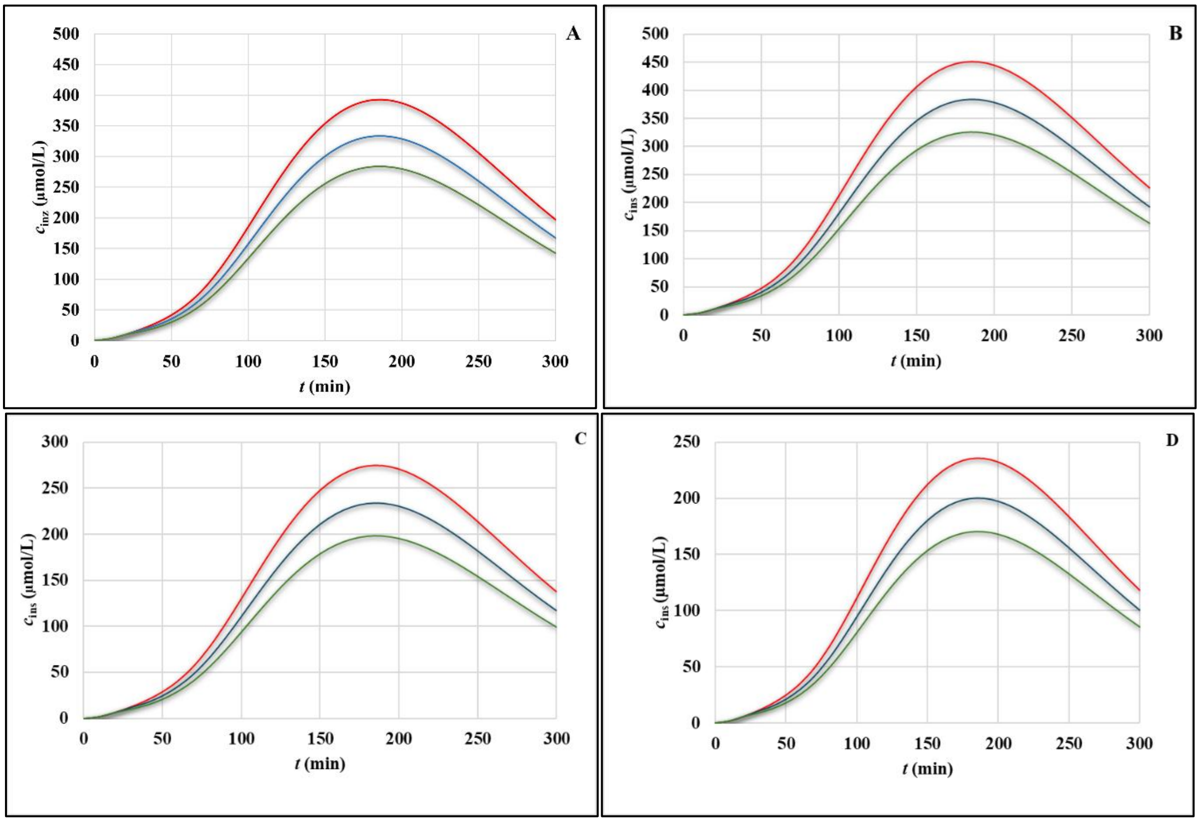

Figure 6. Graphical representation of the change in concentration of insulin (c_{ins}) over a period of 300 minutes after (A) breakfast, (B) lunch, (C) dinner, (D) night meal consumption (red - high glycemic load menu, blue - diabetic menu, green - low glycemic load menu)

Conclusion

The analysis of the menus and the simulation of the glucose-insulin metabolism model lead to several key conclusions. The developed menus show a very strong negative correlation between the proportion of carbohydrates and proteins (r = -0.9500), as well as between the proportions of carbohydrates and fats (r = -0.9855). The glycemic load of a single meal proves useful as an initial parameter for simulating glucose and insulin metabolism models. Furthermore, the glucose and insulin kinetics model simulation accurately describes the blood glucose and insulin concentration profiles, consistent with the available experimental data. Applying the metabolism model of the primary nutrients facilitates a personalized approach to menu development. Additionally, a diet with a low glycemic load demonstrates a reduced response in blood glucose concentration, making it a beneficial choice for individuals with diabetes.

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