FULL COMMUNICATION

The Effects of Different High-Protein Low-Carbohydrates Proprietary Foods on Blood Sugar in Healthy Subjects

Alessandra Lodi,[1] Bettina Karsten,[2] Gerardo Bosco,[1] Manuel Gómez-López,[3]
Paula Paraguassú Brandão,[4] Antonino Bianco,[5] and Antonio Paoli[1]

[1]*Department of Biomedical Sciences, University of Padova, Padova, Italy.*
[2]*Department of Life and Sports Sciences, University of Greenwich, Medway, United Kingdom.*
[3]*Department of Physical Activity and Sport, University of Murcia, Murcia, Spain.*
[4]*Human Kinetics Laboratory of the Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil.*
[5]*Sport and Exercise Sciences Research Unit, University of Palermo, Palermo, Italy.*

ABSTRACT   The aim of this study was to analyze the effects on blood sugar concentrations through the calculation of the glycemic score (GS) of 10 different high-protein low-carbohydrates (CHOs) proprietary foods that are commonly used as meals during very low-CHO ketogenic diets or during low-CHO diets. Fourteen healthy females were tested for their glycemic response curve elicited by 1000 kJ of glucose three times within a 3-week period (one test each week) compared with one of 10 test foods once on separate days twice a week. After determining the GS of each food in each individual, the mean GS of each test food was calculated. All test foods, compared with glucose, produced a significantly lower glycemic response. The GS of all test food resulted in being lower than 25 and the difference between the mean glycemia after the intake of glucose (mean 122 ± 15 mg/dL) and after the intake of the sweet test foods (mean 89 ± 7 mg/dL) was 33 mg/dL ($P < .001$), whereas the difference between the mean glycemia after the intake of glucose and after the intake of savory test foods (mean 91 ± 8 mg/dL) was of 31 mg/dL ($P < .001$). Conclusions: The reformulation of ultraprocessed ready-to-consume foods in a low-CHO, high-protein version can produce a significantly lower glycemic response whilst maintaining the valued ready-to-use format and high palatability demanded by consumers. The low impact on postprandial glycemia and the nutritional characteristics of these proprietary foods makes them useful in both weight control management strategies and in the care management of diabetes.

KEYWORDS: • *diabetes* • *diets* • *glycemic index*

INTRODUCTION

DESPITE BEING CONSIDERED a "preventable disease" by the World Health Organization, obesity is rising in both high-income and low-income countries.[1] Moreover, overweightness and obesity are one of the major causes of the worldwide burden of the four main noncommunicable diseases: cardiovascular (CV) diseases, chronic respiratory diseases, cancers, and diabetes mellitus (DM).[2]

Among multiple reasons involved in the onset of overweight and obesity, nutrition appears to be the most important one.[3] However, research has yet to produce a generally accepted nutritional approach.[4] Populations experiencing an increase in obesity and CV diseases show common eating and drinking habits, notably a general decrease in intake of minimally processed foods and in an increase in the consumption of ultraprocessed ready-to-consume products.

These foods, based on the accepted definition acknowledged by the Pan American Health Organization,[5] are "industrial formulations manufactured from substances derived from foods or synthesized from other organic sources. (…) Most of these products contain little or no whole food. They are ready-to-consume or ready-to heat, and thus require little or no culinary preparation." Examples of ultraprocessed foods are savory and sweet snacks, ice cream, frozen and chilled ready meals, and soft drinks,[5] and they seem to be the cause of the extra daily diet calorie intake of both the young and the older populations.[6] Ultraprocessed ready-to-consume products present particular characteristics, which make them extremely profitable for producers and retailers and highly attractive for consumers. For example, consumers purchase them because they commonly require a minimal culinary action, they are flavorsome, and are relatively inexpensive. However, when analyzing ultraprocessed products, less protein, potassium, and dietary fiber and more free sugar, total saturated and transunsaturated fats, and sodium are generally evident when compared with traditional foods.[7,8]

All these characteristics appear to be linked to the burden of obesity and metabolic syndrome (MetS).[6] A potential

solution to this scenario could be to review ultraprocessed, ready-to-consume products by reduction of their sugar and fat contents. A particular kind of these new ultraprocessed ready-to-consume products are proprietary foods that are high in proteins and fibers and low in sugar and saturated fats. These are specifically designed for particular diets such as the ketogenic regimen, but are also successfully used in more easy low-carbohydrate (CHO) diets as snacks or meal replacements.[9] During ketosis, CHO intake must be under 30 g/day,[10,11] and in previous studies,[4,9] we demonstrated that these special foods, which mimic the taste and aspect of high-content CHO foods but are low in sugar and high in protein content, were able to increase the compliance of subjects to the ketogenic diet. Moreover, after the termination of a very low-CHO ketogenic diet (VLCKD) intervention, patients tended to maintain the consumption of those proprietary foods during the day (usually at breakfast or during breaks). This can be considered a positive change of behavior, because it is known that meal replacement during the maintenance phase is useful to prevent weight gain.[12] During consumption of a VLCKD, it is mandatory to maintain a low level of glycemia (about 80–90 mg/dL) to avoid insulin spikes.[13] This condition allows subjects to improve their fat oxidation as demonstrated by Paoli *et al.*[14] and by Tagliabue *et al.*[15]

Another important aspect of a VLCKD is the influence of such dietary regimen on the perception of hunger.[16] It has been suggested that ketone bodies reduce hunger through different and complex mechanisms[17]; in contrast it is known that postprandial glucose and insulin spikes, typically produced after the intake of traditional ultraprocessed products that usually show a high glycemic index (GI),[5] elicit food craving and overeating, with a preference for high-GI CHOs,[18] a phenomenon defined as the CHO-craving effect.[19] Conversely, the consumption of nonprocessed foods low in simple sugars may ameliorate overeating and facilitate the maintenance of a healthy weight.[18]

The mentioned positive changes necessitate the need to analyze the effect of different high-protein low-CHO proprietary foods that are commonly used in diets, i.e. during VLCKD and low-CHO diets (LCD), on glycemia compared with glucose.

MATERIALS AND METHODS

Subjects were recruited through advertisement placed in two pharmacies located in the province of Vicenza (Veneto,

72 ± 21 kg, mean BMI: 26 ± 7). Participants were required to report any change of daily habits, such as engaging in a new exercise program, new pharmaceutical interventions, or engaging in other than the present diets during the experimental phase, which would have resulted in the exclusion from the study. The study was approved by the Ethical Board of the University of Padova, Department of Biomedical Sciences, and conformed to standards for the use of human subjects in research as outlined in the Declaration of Helsinki. Investigators explained the purpose of the study, the protocol to be followed, and the experimental procedures to be used before the start of the study. Subjects were required to sign a participation consent form and they did not receive any monetary compensation.

Subjects were tested for individual glycemic response curves elicited by the ingestion of 1000 kJ of glucose three times within a 3-week period (one test per week) and that of each of 10 high-protein low-CHO proprietary test foods once on separate days twice a week (Fig. 1). Tests were performed in the morning after 10–12 h overnight fast. Subjects were asked to have a regular meal, not to consume any alcohol, and to avoid any unaccustomed exercise the night before tests. During the study period, participants maintained a constant foods supply, without changing their usual eating habits.

Fingertip capillary blood samples were collected in the fasted state and after 15, 30, 45, 60, 90, and 120 min after starting to eat, changing the finger each time to avoid traumatization of the skin. The puncture was performed with the lancet Accu-Check Safe-T-Pro Plus (Roche Diagnostics, Basel, Switzerland) and blood was collected directly and immediately analyzed using test strip *Reflotron® Glucose.*[20–22] Postprandial effect of sugar content on glycemia is commonly defined through three methods: the GI, the glycemic load (GL), and the glycemic score (GS).

The GI method was developed to rank foods according to the extent to which they increase blood sugar concentrations[23] and it is a number that ranges from 0 to 100, where 100 represents the GI of the reference food glucose. To calculate the GI of a particular food, the area under the curve (AUC) of the rise in blood sugar for a 2 h postprandial period is calculated. This value is consequently expressed as a percentage of the incremental AUC after the consumption of a reference food (commonly white bread or glucose) consumed by the same person on a different day.[24]

The test food and the reference food must contain the same amount of available CHO (25 or 50 g) and the individual has to perform the test under standardized conditions.

$$GI = \frac{120\,\text{min iAUC(blood sugar) for portion size of test foods containing 50g (or 25g) of available carbohydrate}}{120\,\text{min iAUC (blood sugar) for portion size of reference food containing 50g (or 25g) of available carbohydrate}} \times 100$$

Italy). Exclusion criteria for this study were the presence of diabetes or prediabetes, being on a food diet, and females who were either pregnant or breast feeding. After a preselection process of 32 participants, 14 females were eligible to participate in this study (mean age: 42 ± 13, mean weight:

The GL method takes into account not only the magnitude of the glucose blood spike but also the content (grams) of CHO in the portion of food consumed, and it is calculated as the mathematical product of the GI for the available CHO content of the food.[25]

$$GL = \frac{\text{GI (test food) X available grams of CHO in the quantity of test food consumed}}{100}$$

The GS method tests the glycemic response after the ingestion of low-CHO foods and differs from the GI as it does not compare a standard amount of available CHO.

However, it compares the effect on glycemia of a 1000 kJ portion of both test food and reference food.[25]

$$GS = \frac{120 \min \text{iAUC(blood sugar) for 1000 kJ test food}}{120 \min \text{iAUC(blood sugar)for 1000 kJ reference glucose}} \times 100$$

Due to the very low-CHO content of the tested foods and because of the quantity of food required to reach the 25 g of available CHO for the calculation of GI being too large, this study utilized the GS method.[25]

Each tested food was served as a 1000 kJ portion with 220 mL warm (no sugar) tea for a better compliance of subjects in cold winter mornings after an overnight fast (tea does not alter the incremental area under the glycemic response curve[26]) and consumed within a period of 10 min. This study tested 10 proprietary foods selected from the product range of Tisanoreica® snacks and meals (Gianluca Mech S.p.A., Asigliano Veneto, Vicenza, Italy). These are ready-to-consume foods high in protein and fiber content and low in CHO content designed to be consumed during a VLCKD or an LCD regimen.[4,9,27]

Among the products selected, six of them were sweet (chocolate biscuits [CB; Cioco-Mech], chocolate and hazelnut balls [CHB; Bon Mech], apple–cinnamon biscuits [ACB; T-Biscuit], chocolate–almonds–pistachio bar [CAPB; T-Smart], nuts and chocolate muffin [NCM; T-Muffin], and chocolate drink [CD; Cocoa Drink]). The other four products tested were savory (two different types of pasta P1 [Original Tisanopast] and P2 [Tisanopast Style], the rosemary breadsticks [RB; T-Smech], and the pizza dough [PD; Pizza Dough]) (Table 1). Glucose was used as reference food. This

was dissolved in 220 mL of water and served as 1000 kJ portions (15.68 kJ/g)[28] and had to be consumed within a 10 min period.

All statistical analyses were performed using package GraphPad Prism version 6.00 for Mac, GraphPad Software (San Diego, CA, USA). The AUC values above the fasting

glucose concentration for each test food and for the reference food were used to calculate the GS of each test food and assessed using an XY data table by selecting the AUC analysis. The effect of each test food on glycemia compared with that of the reference food over time was assessed using a mixed model ANOVA (time × treatment). A *post hoc* Sidak's multiple comparison test was performed.

To select those test foods with a significant difference of blood sugar values compared with the other test foods, a two-way repeated measure ANOVA (time vs. nominal variables test foods vs. measures) was performed. Each row represented a different time point, so matched values were stocked into a subcolumn. Tukey's multiple comparison test was chosen to compare columns within each row.

A bivariate analysis was used to test, through a linear regression analysis, the significance of the associations between GS and sugars, and protein and fiber in the 10 foods tested. An alpha level of $P < .05$ was used to denote a significant effect.

RESULTS

Mean GS, mean glycemia, and mean glycemia in the different time points of the 10 test foods and the reference food among the subjects tested are listed in Table 2.

TABLE 1. TEST FOODS CHARACTERISTICS

Test food name	kJ/100 g	Protein/100 g, g	CHO/100 g (of which sugars/ of which polyalcohols), g	Fat/100 g (of which saturated), g	Fiber/100 g, g	Salt/100 g
CB	1666.35 kJ/100 g	23.5	18 (0.1/14.5)	25.3 (11.2)	37.1	—
PD	1356 kJ/100 g	53.2	14.2 (1.6)	2.4 (0.9)	16.4	887 mg
CAPB	1498.87 kJ/100 g	34	10.9 (4/4.3)	14.4 (7.5)	28	1.13 g
NCM	1570 kJ/100 g	15.5	35.3 (0.1/30.1)	22.6 (5.5)	7.4	1.3 g
CD	1515.62 kJ/100 g	62.2	18.2 (0.4)	3.4	9.8	—
CHB	1775.2 kJ/100 g	6.1	51.6 (30.1/18.9)	28.2 (12)	7.6	0.02 g
RB	1900 kJ/100 g	49.10	8.96 (0.06)	21.06 (6.07)	16.12	0.80 g
ACB	1678 kJ/100 g	31.36	5.88 (0.06)	21.32 (12.42)	30.13	0.55 g
P1	962 kJ/100 g	44	5.9 (0.03)	3.3	34	720 mg
P2	1389 kJ/100 g	50	22.5 (0.7)	2.1 (1.6)	12.9	0.05 g

ACB, apple and cinnamon biscuits; CAPB, chocolate–almonds–pistachio bar; CB, chocolate biscuits; CD, chocolate drink; CHB, chocolate and hazelnut balls; CHO, carbohydrate; NCM, nuts and chocolate muffin; P1, pasta type 1; P2, pasta type 2; PD, pizza dough; RB, rosemary breadsticks.

TABLE 2. MEAN GS, MEAN GLYCEMIA AND MEAN GLYCEMIA IN THE DIFFERENT TIME POINTS OF THE 10 TEST FOODS AND OF THE REFERENCE FOOD GLUCOSE

Food tested	0	15	30	45	60	90	120	Mean glycemia (mg/dL)	Mean GS
Glucose	86±6	135±12	148±20	141±24	130±20	118±14	98±12	122±15	100
CB	85±7	90±6	89±6	92±8	90±7	88±6	88±7	89±7	14±9
CHB	86±7	100±10	102±9	94±8	90±8	84±11	83±8	91±9	23±15
CD	85±7	99±9	94±11	86±6	86±7	88±5	88±6	89±7	18±10
ACB	85±8	92±10	92±6	90±7	88±6	85±5	86±5	88±7	19±7
NCM	87±9	96±10	93±9	89±7	88±5	88±5	86±6	89±7	17±8
CAPB	84±7	91±9	88±8	85±7	85±6	86±6	85±5	86±7	14±7
PD	86±6	98±12	89±6	88±5	86±7	85±4	84±6	88±6	15±7
RB	82±7	90±7	91±8	90±7	89±8	88±6	88±6	88±7	18±8
P2	88±8	106±13	100±13	89±10	85±7	87±4	88±6	92±9	19±7
P1	87±8	101±10	99±10	94±5	94±8	93±9	90±6	94±8	21±11

Time is given in minutes. Mean glycemia (mg/dL) is reported at the different time points.
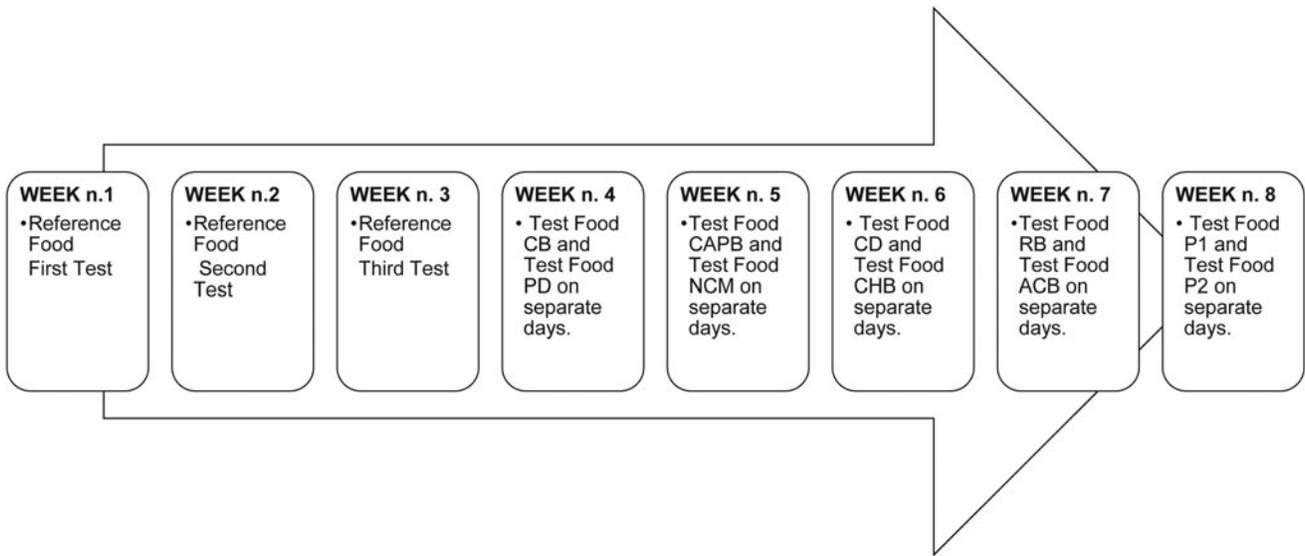
GS, glycemic score.

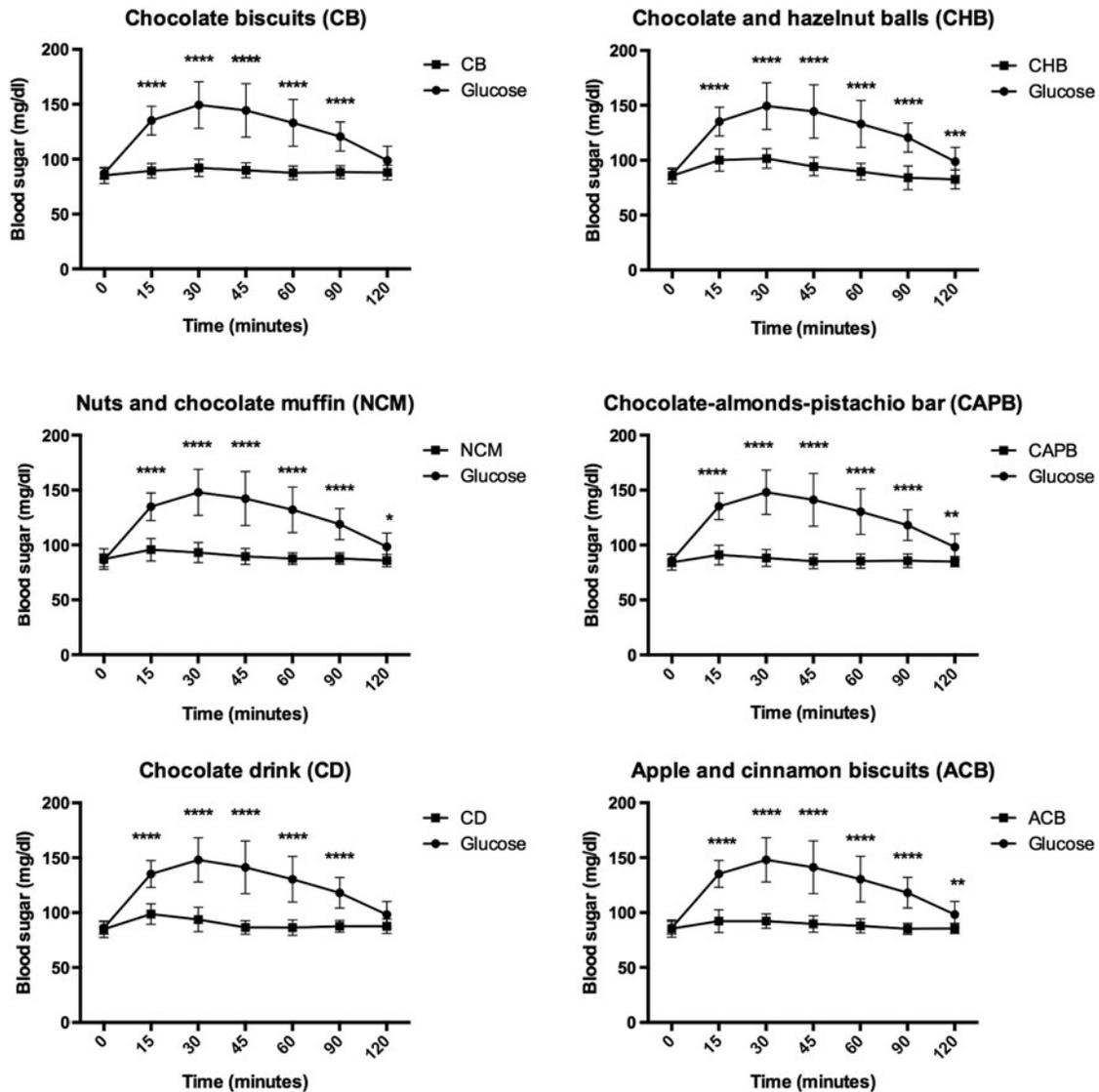**FIG. 1.** Experimental design.

FIG. 2. Comparison of mean blood sugar concentrations between glucose and sweet test foods (*$P < .05$; **$P < .01$; ***$P < .001$; ****$P < .0001$). Foods were tested among 14 healthy subjects. All tested foods and the reference food glucose were served as a 1000 kJ portion and consumed within 10 min.

FIG. 3. Comparison of blood sugar concentrations between glucose and savory test foods (*$P < .05$; **$P < .01$; ****$P < .0001$). Foods were tested among 14 healthy subjects. All tested foods and the reference food glucose were served as a 1000 kJ portion and consumed within 10 min.
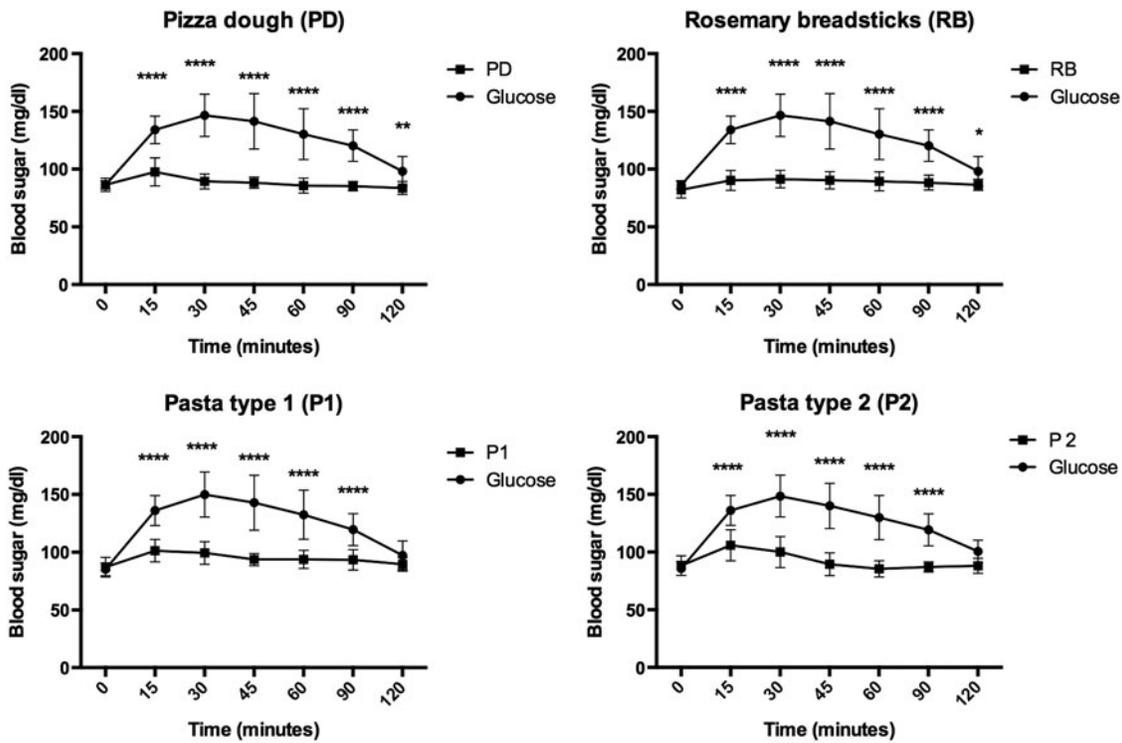
Mean glycemia after taking the reference food glucose resulted in 122 ± 15 mg/dL, that after taking the sweet test foods was 89 ± 7 mg/dL, and that after ingestion of the savory test foods was 91 ± 8 mg/dL.

Figure 2 shows the comparison of mean blood sugar concentrations at the different time points between glucose and sweet test foods, whereas Figure 3 shows that between glucose and savory test foods. After the ingestion of all sweet and savory test foods, the blood sugar showed always a significantly lower trend compared with that after the intake of the reference food glucose after 15, 30, 45, 60, and 90 min, although several test foods (CHB, CAPB, NCM, ACB, PD, and RB) were able to maintain this significance even after 120 min.

Figure 4 shows the comparison of blood sugar concentrations between sweet test foods and savory test foods. Comparison of mean blood sugar concentrations at the seven different time points highlighted a significant higher increase of glycemia, particularly 15 and 30 min after taking the CHB and the two kinds of pasta P1 and P2 compared with the other test foods (Fig. 4).

In particular, the mean glycemia increased significantly 15 and 30 min after the intake of CHB compared with the mean glycemia after the ingestion of the CB, the CAPB, the RB, and the PD (Fig. 5).

After the intake of P2, the mean glycemia increased significantly after 15 and 30 min. compared with the sweet test foods CB, CAPB, and NCM and with the savory test foods PD and SB (Fig. 6).

After the intake of P1, the mean glycemia increased significantly after 15 and 30 min. compared with the sweet test foods CB and CAPB and with the savory test foods PD and RB (Fig. 7).

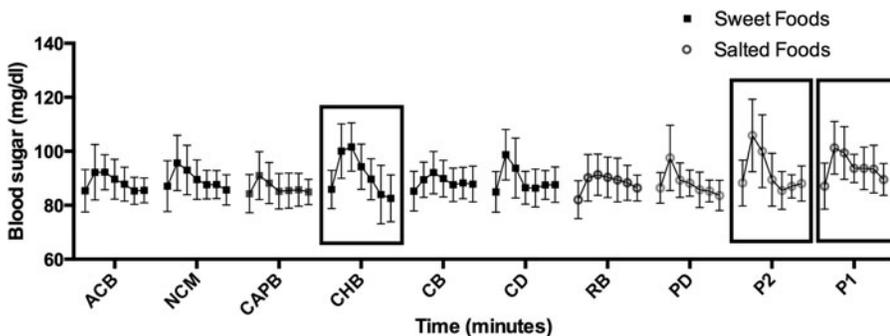**FIG. 4.** Comparison of blood sugar concentrations between sweet test foods and savory test foods. Among sweet test foods, the CHB show a higher increase in blood sugar than other test foods (significant differences are shown in Fig. 5). Among savory test foods, both pasta type 2 (P2) and pasta type 1 (P1) show a higher blood sugar trend (significant differences are shown in Figs. 6 and 7). CHB, chocolate and hazelnut balls.
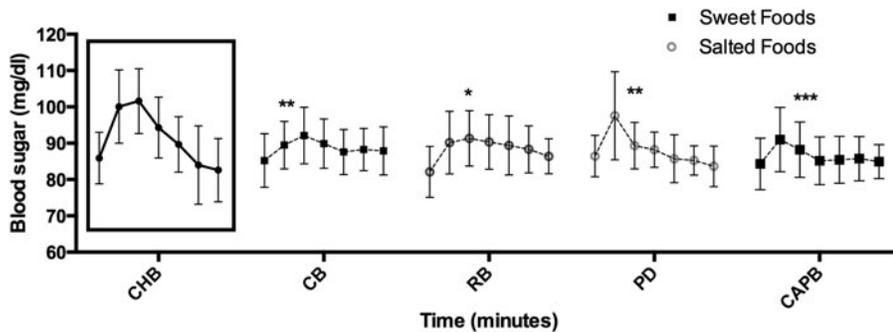
FIG. 5. Comparison of mean blood sugar concentrations between the CHB and the other test foods. Results show significant differences after 15 or 30 min between CHB and CB, RB, PD, and CAPB. $*P < .05$; $**P < .01$; $***P < .001$. CAPB, chocolate–almonds–pistachio bar; CB, chocolate biscuits; PD, pizza dough; RB, rosemary breadsticks.

The statistical two-way ANOVA of the trend of blood sugar from before starting to eat up to 2 h after the intake of the reference food or of the test foods shows that, on average, the 40% of the total variation observed is because of the difference between the foods eaten (glucose or test foods). This result shows that, among all the ''Sources of Variation'' analyzed (time, food, and subjects), the variable ''food'' appears to be the one that explains most of the variation observed between the blood sugar trends after the intake of test foods and the blood sugar trend after the intake of the reference food.

The results did not show any correlation between GS and fiber content ($r = -0.08$; $P = .37$), neither between GS and sugar content ($r = 0.17$; $P = .09$), nor between GS and protein content (Fig. 8).

The average GS of each test food, calculated as the mean of GS values of each test food resulted from every subject, was always less than 25 compared with the GS reference value of glucose, which is 100 (Table 2). The test food with the highest GS is the sweet test food Bon Mech with a GS of 23. The test food with the lowest GS is the sweet test food Cioco Mech and T-Smart, with a GS of 14.

DISCUSSION

In this study, the GS of 10 proprietary foods high in proteins and fibers and low in sugars and saturated fats was tested. These proprietary foods claim to replicate the taste and aspect of high-CHO foods and are commonly used as meals during VLCKD regimens. In our study, the products tested showed a significant lower blood sugar response and lower GS than an isoenergetic amount of glucose. Among the six sweet and four savory test foods, the CHB showed the highest GS (GS = 23). This result is consistent with the higher quantity of available sugars of CHB compared with the other test foods. The CB and the CAPB had the lowest GS of 14. This GS value is, according to the data available,[25] similar to the GS value of a low-fat processed cheese.

The macronutrient composition is important for glucose response, with CHO as the food component that acts directly on glycemia, rising it and stimulating insulin secretion. However, even if CHO counting is still the basis for insulin dose adjustment in diabetes care management,[29] data show[25] that sugar content could be a stronger predictor of the observed glucose response than CHO. Other studies show that the structure of CHOs should also be kept under consideration: a disrupted structure, typical of processed whole grains, has a different effect on glycemia compared with intact grains.[30]

Even if there is a strong evidence supporting fibers' beneficial effect in reducing disease risk,[25] only soluble fibers with gel-forming properties show a distinguishable effect for glycemic control.[31,32]

This study does not show any significant relationship between GS and fiber content, but, differently from them, it does not show any correlations between GS and sugar content (Fig. 8). This conflicting result might be because of the very low quantity of available sugars in the test foods. Finally, protein content, despite being considered predictive for the GS,[25] did not show such correlation in this study.

The low postprandial glycemia produced by the proprietary foods tested is an important factor, because ultra-processed ready-to-consume products are commonly high in

FIG. 6. Comparison of mean blood sugar concentrations between pasta type 2 (P2) and the other test foods. Results show significant differences after 15 or 30 min between P2 and CB, CAPB, PD, NCM, and RB. $*P < .05$; $**P < .01$; $****P < .0001$. NCM, nuts and chocolate muffin.
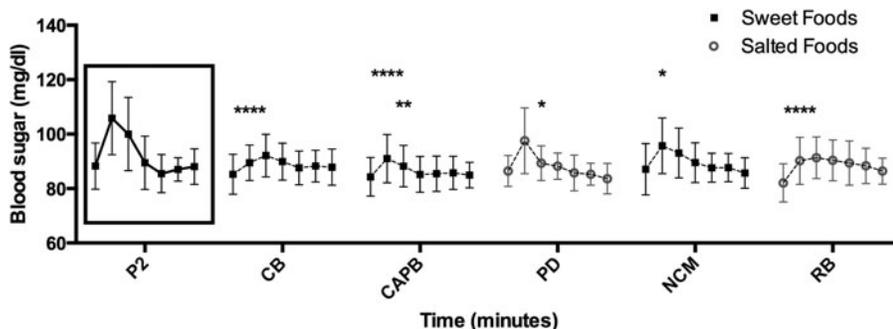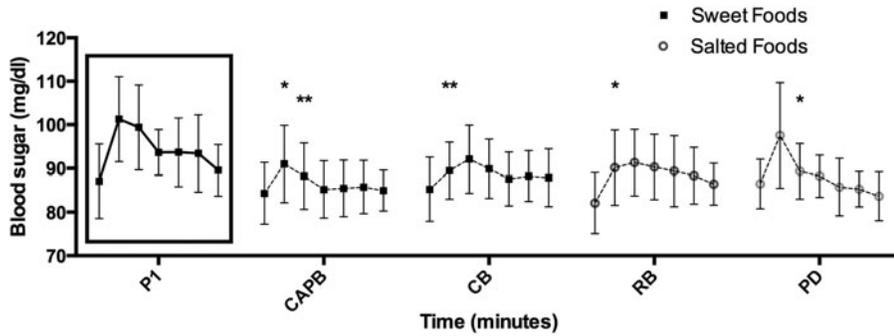
FIG. 7. Comparison of mean blood sugar concentrations between the pasta type 1 (P1) and the other test foods. Results show significant differences after 15 or 30 min between P1 and CB, CAPB, PD, and RB. *$P < .05$; **$P < .01$; ***$P < .001$; ****$P < .0001$.

simple sugars that negatively affect a number of health parameters. Postprandial hyperglycemia and compensatory hypoglycemia are factors linked to the development of diabetes and CV diseases.[33] Furthermore, the consumption of high-sugar snacks seems to be the main cause for the increase in intrahepatic triglyceride content.[34] Finally, the usual rapid and high glycemic peak caused by ultraprocessed products, together with their lack in fiber, proteins, and water, triggers an excessive consumption.[19,35]

Sugar is rapidly absorbed and produces a consequent high blood sugar spike that acts centrally, increasing the production and utilization of dopamine, which imitates the typical neuromodulation of addictive substances.[36]

The abuse of high sugary ultraprocessed foods leads to the synthesis and the accumulation of fat and results in weight gain,[8] which increases the risk of obesity and MetS. According to the definition by the World Health Organization, MetS is the simultaneous presence of insulin resistance along with two other risk factors from high blood pressure, raised triglycerides, low HDL, and increased BMI (or increased waist:hip ratio) and microalbuminuria.[37] The prevalence of this disease, once suggested to be exclusive of adulthood, is becoming a major worldwide concern among both children and adolescents,[38,39] and the consumption of ultraprocessed foods is considered an important risk factor for its development.[40] Bielemann *et al.*[41] recently demonstrated that ultraprocessed foods were responsible for 50%

of the daily caloric intake among a cohort of 23-year-old participants in Brazil. Interestingly, the household availability of ultraprocessed ready-to-eat foods was associated with a low percentage of proteins and fibers intake.

Appetite control is related not only to glucose content and postprandial glycemia but also to other factors[42] among which the reward system in the brain, aside from the homeostatic control by the hypothalamus, has been the focus of recent interest, since food reward is a goal that drives both appetite and eating.[43,44]

The larger the portion size, the more food is eaten,[44] but eating is only indirectly related to energy balancing because it seems that we eat essentially for pleasure.[44] These new low-calorie proprietary foods could help to reduce energy intake, useful for a better weight maintenance or a more successful weight loss. Moreover, since high-energy-dense foods have the lowest satiating capacity even if they usually have a high palatability,[44] the high level of proteins and fibers and the high palatability, despite the low sugar content, of these new ultraprocessed foods, are important features that contribute to both food reward and satiety.[45]

The tendency to prefer sugary fatty foods over savory foods is considered innate and universal and finds its roots in very important adaptive processes: a bitter taste is considered predictive of toxicity and then avoided (alkaloids, glycosides, and other toxins have a bitter taste), whereas sweet taste is associated with energy and nourishment.[46]
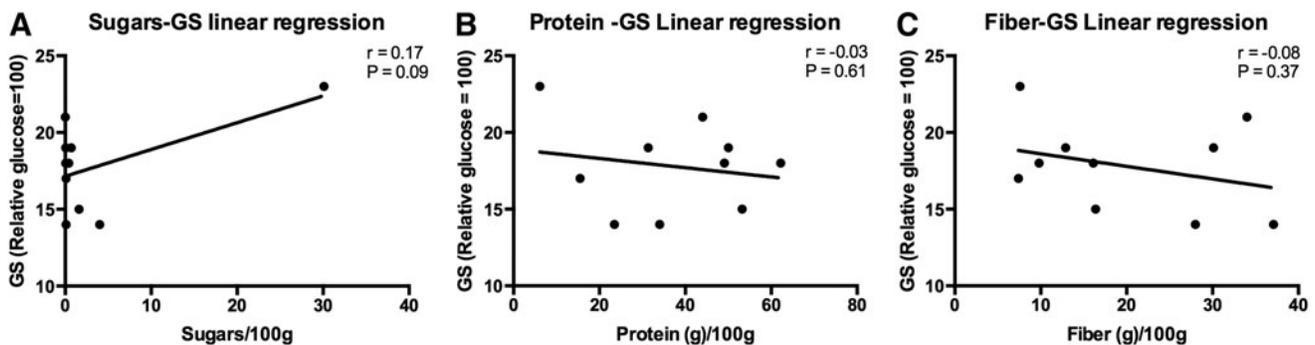
FIG. 8. Bivariate correlations between observed glucose responses (GS) (relative to 1000 kJ glucose = 100), the available sugars, protein, and fiber contents of the 10 single test foods. Linear regression analysis was used to test the significance of the associations. Each point on the graph represents the mean result for each test meal (14 subjects). **(A)** Sugars—GS linear regression; **(B)** protein—GS linear regression; **(C)** fiber—GS linear regression. GS, glycemic score.
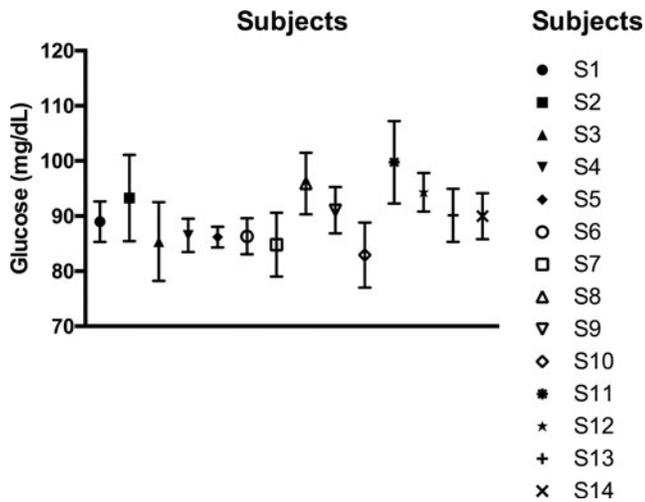
FIG. 9. Subjects' glycemic variability in response to the tested proprietary foods (mean of all foods and SD are reported in the figure).

Although it is recognized that the VLCKDs lead to greater weight losses than a low-calorie balanced diet at least in the short term,[47] subjects with a sweet food preference may not adhere to this diet because of the lack of their preferred taste.[48,49] A VLCKD that includes these proprietary foods that imitate taste and aspects of high-CHO food but have a low glucose content can consequently produce a higher level of adherence and a reduced drop-out rate.[4,50]

Sweet foods are usually rich in refined CHO, have a high GI, and are related to an increased risk of overweight, obesity,[51] and type 2 diabetes mellitus (T2DM).[52] T2DM is increasing among young people[53] and a dietary management is the most important factor to be considered to prevent the progression of impaired glucose tolerance to clinical DM. A dietary management is also important to minimize the glycemic variability, which is the measure of blood sugar concentration changes over time.[54] An uncontrolled blood sugar concentration is the major risk factor in the development of T2DM complications such as retinopathy, neuropathy, nephropathy, and CV diseases.[55–58] It is important to make healthier nutritional choices to prevent these complications, which are associated with high economic, social, and personal costs. Low-CHO high-protein diets help to normalize glycemic fluctuations in T2DM management.[59] As suggested by the European Association for the Study of Diabetes (EASD), dietary fibers can further positively influence blood sugar variability. The EASD consequently recommends the consumption of high-fiber, low-GI foods as CHO source.[54]

Dietary amino acids contribute to the *de novo* synthesis of glucose through gluconeogenesis and participate in the recycling of glucose carbon through the glucose–alanine cycle.[60] However, dietary proteins have a minimal impact on glycemia and insulin secretion compared with CHOs,[61] and a high-quality protein supplementation has been suggested during weight loss programs to preserve muscle mass, to improve glycemic regulation, and to maintain euglycemia.[62,63] The 10 proprietary foods tested in this study are formulated with whey proteins. These, because of their high content of leucine, which promotes muscle mass synthesis and because of their fast digestion and delivery of amino acids in the circulation, are consequently considered the best type of proteins.[62]

Moreover, whey protein decreases appetite better than other types of proteins[64] and increases satiety through an increase of the release of CCK and GLP-1 and a reduction of ghrelin levels.[65]

The sweet proprietary foods tested in this study also contained low-calorie sweeteners. These are compounds able to stimulate, in the same way as sugar does, the sweet taste receptors.[66]

Unlike sugar, low-calorie sweeteners do not release energy and hence they are used in weight loss programs even though perceived as controversial by the scientific community. This is due to low-calorie sweeteners producing possible adverse metabolic effects, such as increase of appetite, weight gain, and metabolic disorders.[67–69] However, more studies are required to confirm these negative suggestions, since a recent review shows that there is no evidence for a limitation of their use to reduce energy intake.[70] The same author states that our congenitally liking for sweetness implies that the reward value from sugar and low-calorie sweeteners is the same, but low-calorie sweeteners should be preferred, because they avoid the high-calorie intake side effect of sugar.[44] These compounds could be useful in the prevention of overweightness and obesity in populations that are less sensitive to sweetness, predisposing them to consume more sugar to have the same "taste sensation" as people more sensitive to sweetness.[71] Nowadays low-calorie sweeteners are important tools in DM management, in which dietary adherence is among the most difficult cornerstones,[72] especially for children and adolescents with T2DM who suffer from the perceived lack of normality in their diet and consequently desire nonrecommended sweet foods.[73]

Ready-to-consume proprietary foods, high in quality proteins and fibers, could improve both the diet of young people and the diet of T2DM patients. In the former population, this could prevent them from eating high-sugary fatty foods, predisposing them to the development of T2DM, and in the latter to minimize blood sugar variability that often complicates the pathology. The 10 proprietary foods tested showed a significant lower glycemia than the standard food glucose and their GS resulted in always lower than 25. This low glycemic response, together with their valuable ready-to-use format, makes these proprietary foods a valid tool during both weight management and weight loss programs, facilitating the adherence to an LCD of individuals who tend to have a high preference for sweet foods.

ACKNOWLEDGMENT

AUTHORS' CONTRIBUTIONS

design, data collection, data analysis, data interpretation, or writing of the article. All authors contributed to data analysis and interpretation, and writing and/or editing of the article. All authors gave their final approval of the version to be published.

AUTHOR DISCLOSURE STATEMENT

REFERENCES

1. Seidell JC, Halberstadt J: The global burden of obesity and the challenges of prevention. *Ann Nutr Metab* 2015;66(Suppl 2):7–12.

2. Kontis V, Mathers CD, Rehm J, *et al.*: Contribution of six risk factors to achieving the 25×25 non-communicable disease mortality reduction target: A modelling study. *Lancet* 2014;384: 427–437.

3. Mutch DM, Clement K: Unraveling the genetics of human obesity. *PLoS Genet* 2006;2:e188.

4. Paoli A, Bianco A, Grimaldi KA, Lodi A, Bosco G: Long term successful weight loss with a combination biphasic ketogenic mediterranean diet and Mediterranean diet maintenance protocol. *Nutrients* 2013;5:5205–5217.

5. Pan American Health Organization WHO: *Consumption of Ultra-Processed Food and Drink Products in Latin America: Trends, Impact on Obesity, and Policy Implications.* PAHO, Washington, DC, 2014.

6. Monteiro CA, Moubarac JC, Cannon G, Ng SW, Popkin B: Ultra-processed products are becoming dominant in the global food system. *Obes Rev* 2013;14(Suppl 2):21–28.

7. Monteiro CA, Levy RB, Claro RM, de Castro IR, Cannon G: Increasing consumption of ultra-processed foods and likely impact on human health: Evidence from Brazil. *Public Health Nutr* 2011;14:5–13.

8. Moubarac JC, Batal M, Martins AP, *et al.*: Processed and ultra-processed food products: Consumption trends in Canada from 1938 to 2011. *Can J Diet Pract Res* 2014;75:15–21.

9. Paoli A, Cenci L, Grimaldi KA: Effect of ketogenic Mediterranean diet with phytoextracts and low carbohydrates/high-protein meals on weight, cardiovascular risk factors, body composition and diet compliance in Italian council employees. *Nutr J* 2011;10:112.

10. Paoli A: Ketogenic diet for obesity: Friend or foe? *Int J Environ Res Public Health* 2014;11:2092–2107.

11. Paoli A, Rubini A, Volek JS, Grimaldi KA: Beyond weight loss: A review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. *Eur J Clin Nutr* 2013;67:789–796.

12. Vazquez C, Montagna C, Alcaraz F, *et al.*: Meal replacement with a low-calorie diet formula in weight loss maintenance after weight loss induction with diet alone. *Eur J Clin Nutr* 2009;63:1226–1232.

13. Paoli A, Canato M, Toniolo L, *et al.*: The ketogenic diet: An underappreciated therapeutic option? *Clin Ter* 2011;162:e145–e153 [in Italian].

14. Paoli A, Grimaldi K, Bianco A, Lodi A, Cenci L, Parmagnani A: Medium term effects of a ketogenic diet and a Mediterranean diet on resting energy expenditure and respiratory ratio. *BMC Proc* 2012;6:P37.

15. Tagliabue A, Bertoli S, Trentani C, Borrelli P, Veggiotti P: Effects of the ketogenic diet on nutritional status, resting energy expenditure, and substrate oxidation in patients with medically refractory epilepsy: A 6-month prospective observational study. *Clin Nutr* 2012;31:246–249.

16. Gibson AA, Seimon RV, Lee CM, *et al.*: Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. *Obes Rev* 2015;16:64–76.

17. Paoli A, Bosco G, Camporesi EM, Mangar D: Ketosis, ketogenic diet and food intake control: A complex relationship. *Front Psychol* 2015;6:27.

18. Lennerz BS, Alsop DC, Holsen LM, *et al.*: Effects of dietary glycemic index on brain regions related to reward and craving in men. *Am J Clin Nutr* 2013;98:641–647.

19. Ventura T, Santander J, Torres R, Contreras AM: Neurobiologic basis of craving for carbohydrates. *Nutrition* 2014;30:252–256.

20. Bijster P: A multi-centre evaluation of the measurement of high density lipoprotein cholesterol by the Reflotron assay. *Eur J Clin Chem Clin Biochem* 1993;31:173–178.

21. Richter V, Rassoul F, Luttge F, Thiery J: Cardiovascular risk factor profile on a population basis: Results from the Lipid Study Leipzig (LSL). *Exp Clin Cardiol* 2007;12:51–53.

22. Warnick GR, Boerma GJ, Assmann G, *et al.*: Multicenter evaluation of Reflotron direct dry-chemistry assay of high-density lipoprotein cholesterol in venous and fingerstick specimens. *Clin Chem* 1993;39:271–277.

23. Holt SH, Miller JC, Petocz P: An insulin index of foods: The insulin demand generated by 1000-kJ portions of common foods. *Am J Clin Nutr* 1997;66:1264–1276.

24. FAO: *Carbohydrates in Human Nutrition: Report of a Joint FAO/WHO Expert Consultation.* FAO, Rome, Italy, 1998.

25. Bao J, Atkinson F, Petocz P, Willett WC, Brand-Miller JC: Prediction of postprandial glycemia and insulinemia in lean, young, healthy adults: Glycemic load compared with carbohydrate content alone. *Am J Clin Nutr* 2011;93:984–996.

26. Brouns F, Bjorck I, Frayn KN, *et al.*: Glycaemic index methodology. *Nutr Res Rev* 2005;18:145–171.

27. Paoli A, Grimaldi K, D'Agostino D, *et al.*: Ketogenic diet does not affect strength performance in elite artistic gymnasts. *J Int Soc Sports Nutr* 2012;9:34.

28. Plowman SA, Smith DL: *Exercise Physiology for Health Fitness and Performance.* Lippincott Williams & Wilkins, Philadelphia, 2013.

29. Campbell MD, Walker M, King D, *et al.*: Carbohydrate counting at meal time followed by a small secondary postprandial bolus injection at 3 hours prevents late hyperglycemia, without hypoglycemia, after a high-carbohydrate, high-fat meal in type 1 diabetes. *Diabetes Care* 2016;39:e141–e142.

30. Foster-Powell K, Holt SH, Brand-Miller JC: International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr* 2002;76:5–56.

31. Venn BJ, Mann JI: Cereal grains, legumes and diabetes. *Eur J Clin Nutr* 2004;58:1443–1461.

32. Gibb RD, McRorie JW Jr., Russell DA, Hasselblad V, D'Alessio DA: Psyllium fiber improves glycemic control proportional to loss of glycemic control: A meta-analysis of data in euglycemic subjects, patients at risk of type 2 diabetes mellitus, and patients being treated for type 2 diabetes mellitus. *Am J Clin Nutr* 2015;102:1604–1614.

33. Zeevi D, Korem T, Zmora N, *et al.*: Personalized nutrition by prediction of glycemic responses. *Cell* 2015;163:1079–1094.

34. Koopman KE, Caan MW, Nederveen AJ, *et al.*: Hypercaloric diets with increased meal frequency, but not meal size, increase

intrahepatic triglycerides: A randomized controlled trial. *Hepatology* 2014;60:545–553.

35. Blum K, Thanos PK, Gold MS: Dopamine and glucose, obesity, and reward deficiency syndrome. *Front Psychol* 2014;5:919.
36. Blum K, Braverman ER, Holder JM, *et al.*: Reward deficiency syndrome: A biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. *J Psychoactive Drugs* 2000;32 Suppl:i–iv, 1–112.
37. Grundy SM, Brewer HB Jr., Cleeman JI, *et al.*: Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Arterioscler Thromb Vasc Biol* 2004;24:e13–e18.
38. Tailor AM, Peeters PH, Norat T, Vineis P, Romaguera D: An update on the prevalence of the metabolic syndrome in children and adolescents. *Int J Pediatr Obes* 2010;5:202–213.
39. Kursawe R, Santoro N: Metabolic syndrome in pediatrics. *Adv Clin Chem* 2014;65:91–142.
40. Tavares LF, Fonseca SC, Garcia Rosa ML, Yokoo EM: Relationship between ultra-processed foods and metabolic syndrome in adolescents from a Brazilian Family Doctor Program. *Public Health Nutr* 2012;15:82–87.
41. Bielemann RM, Motta JV, Minten GC, Horta BL, Gigante DP: Consumption of ultra-processed foods and their impact on the diet of young adults. *Rev Saude Publica* 2015;49:1–10.
42. Farr OM, Li CS, Mantzoros CS: Central nervous system regulation of eating: Insights from human brain imaging. *Metabolism* 2016;65:699–713.
43. Rolls ET: Reward Systems in the Brain and Nutrition. *Annu Rev Nutr* 2016;36:435–470.
44. Rogers PJ, Brunstrom JM: Appetite and energy balancing. *Physiol Behav* 2016;164(Pt B):465–471.
45. Tovar AR, Caamano Mdel C, Garcia-Padilla S, Garcia OP, Duarte MA, Rosado JL: The inclusion of a partial meal replacement with or without inulin to a calorie restricted diet contributes to reach recommended intakes of micronutrients and decrease plasma triglycerides: A randomized clinical trial in obese Mexican women. *Nutr J* 2012;11:44.
46. Drewnowski A, Krahn DD, Demitrack MA, Nairn K, Gosnell BA: Taste responses and preferences for sweet high-fat foods: Evidence for opioid involvement. *Physiol Behav* 1992;51:371–379.
47. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T: Very-low-carbohydrate ketogenic diet v. Low-fat diet for long-term weight loss: A meta-analysis of randomised controlled trials. *Br J Nutr* 2013;110:1178–1187.
48. Shai I, Schwarzfuchs D, Henkin Y, *et al.*: Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008;359:229–241.
49. McVay MA, Voils CI, Coffman CJ, *et al.*: Factors associated with choice of a low-fat or low-carbohydrate diet during a behavioral weight loss intervention. *Appetite* 2014;83:117–124.
50. Paoli A, Cenci L, Fancelli M, *et al.*: Ketogenic diet and phytoextracts comparison of the efficacy of Mediterranean, zone and tisanoreica diet on some health risk factors. *Agro Food Ind Hi-Tech* 2010;21:24–29.
51. Schwingshackl L, Hoffmann G: Long-term effects of low glycemic index/load vs. high glycemic index/load diets on parameters of obesity and obesity-associated risks: A systematic review and meta-analysis. *Nutr Metab Cardiovasc Dis* 2013;23:699–706.
52. Maki KC, Phillips AK: Dietary substitutions for refined carbohydrate that show promise for reducing risk of type 2 diabetes in men and women. *J Nutr* 2015;145:159S–163S.
53. Reinehr T: Type 2 diabetes mellitus in children and adolescents. *World J Diabetes* 2013;4:270–281.
54. Tay J, Thompson CH, Brinkworth GD: Glycemic variability: Assessing glycemia differently and the implications for dietary management of diabetes. *Annu Rev Nutr* 2015;35:389–424.
55. Brownlee M, Hirsch IB: Glycemic variability: A hemoglobin A1c-independent risk factor for diabetic complications. *JAMA* 2006;295:1707–1708.
56. Forbes JM, Cooper ME: Mechanisms of diabetic complications. *Physiol Rev* 2013;93:137–188.
57. Bonora E: Postprandial peaks as a risk factor for cardiovascular disease: Epidemiological perspectives. *Int J Clin Pract Suppl* 2002:5–11.
58. Pradeepa R, Mohan V: Postprandial glycaemic excursions and cardiovascular risk. *J Indian Med Assoc* 2011;109:912, 917–920.
59. Feinman RD, Pogozelski WK, Astrup A, *et al.*: Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base. *Nutrition* 2015;31:1–13.
60. Dashty M: A quick look at biochemistry: Carbohydrate metabolism. *Clin Biochem* 2013;46:1339–1352.
61. Layman DK, Baum JI: Dietary protein impact on glycemic control during weight loss. *J Nutr* 2004;134:968S–973S.
62. Verreijen AM, Verlaan S, Engberink MF, Swinkels S, de Vogel-van den Bosch J, Weijs PJ: A high whey protein-, leucine-, and vitamin D-enriched supplement preserves muscle mass during intentional weight loss in obese older adults: A double-blind randomized controlled trial. *Am J Clin Nutr* 2015;101:279–286.
63. Pasiakos SM: Metabolic advantages of higher protein diets and benefits of dairy foods on weight management, glycemic regulation, and bone. *J Food Sci* 2015;80(Suppl 1):A2–A7.
64. Pal S, Ellis V: The acute effects of four protein meals on insulin, glucose, appetite and energy intake in lean men. *Br J Nutr* 2010;104:1241–1248.
65. Luhovyy BL, Akhavan T, Anderson GH: Whey proteins in the regulation of food intake and satiety. *J Am Coll Nutr* 2007;26:704S–712S.
66. Brown RJ, Rother KI: Non-nutritive sweeteners and their role in the gastrointestinal tract. *J Clin Endocrinol Metab* 2012;97:2597–2605.
67. Yang Q: Gain weight by ''going diet?'' Artificial sweeteners and the neurobiology of sugar cravings: Neuroscience 2010. *Yale J Biol Med* 2010;83:101–108.
68. Swithers SE, Martin AA, Davidson TL: High-intensity sweeteners and energy balance. *Physiol Behav* 2010;100:55–62.
69. Ludwig DS: Artificially sweetened beverages: Cause for concern. *JAMA* 2009;302:2477–2478.
70. Rogers PJ, Hogenkamp PS, de Graaf C, *et al.*: Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including meta-analyses, of the evidence from human and animal studies. *Int J Obes (Lond)* 2016;40:381–394.
71. Low YQ, Lacy K, Keast R: The role of sweet taste in satiation and satiety. *Nutrients* 2014;6:3431–3450.
72. Anders S, Schroeter C: Diabetes, diet-health behavior, and obesity. *Front Endocrinol (Lausanne)* 2015;6:33.
73. Mulvaney SA, Schlundt DG, Mudasiru E, *et al.*: Parent perceptions of caring for adolescents with type 2 diabetes. *Diabetes Care* 2006;29:993–997.