The Glycemic Response to Infant Formulas: a Randomized Clinical Trial

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Research Article

Abstract

Objectives: Commercial infant formulas attempt to imitate the unique composition of human milk, which contributes to its distinctive influence on glycemic and insulinemic responses. However, lactose-free and milk protein-free formulas are often recommended due to medical reasons or chosen due to personal preferences (e.g., veganism). The aim of this study was to determine the glycemic and insulinemic indices of a variety of infant formulas.

Methods: We conducted a three-arm, randomized, double-blind, crossover study. The participants were healthy adult volunteers aged 25-40 years. Each participant randomly drank three commercially available infant formulas (cow's milk protein-based ["standard"], soy protein-based, and lactose-free). Glycemic and insulinemic responses and glucose and insulin blood levels were determined and compared between the three formulas.

Results: Twenty subjects were enrolled (11 females/9 males, mean age 32.8 ± 2.9 years). No significant difference was found in the glycemic index between the three formulas (21.5, 29.1, and 21.5 for the standard, soy protein-based, and lactose-free formulas, respectively, $p = 0.21$). However, maximal glucose levels were significantly higher for the soy protein-based formula compared to both the standard and lactose-free formulas (111.5 mg/dL compared to 101.8 mg/dL and 105.8 mg/dL, respectively, $p = 0.001$).

Conclusion: A cow's milk protein-based formula, a lactose-free formula, and a soy protein-based formula elicited similar glycemic index. However, soy protein-based formula produced a significantly higher increase in postprandial glucose levels. The implication and the biological significance of these results has yet to be determined.

Summary

What is Known

* Lactose and milk protein are often replaced in infant's formulas by substitutes. The metabolic response to these various infant formulas is still under investigation.

* Low glycemic diet is beneficial and desirable, and further evaluation of infant formula metabolic response will offer valuable insight into the metabolic programming aspects.

What is New

* In our study, a cow's milk protein-based formula containing lactose, a lactose-free formula, and a soy protein-based formula elicited similar glycemic index.

* Postprandial blood glucose peak was significantly higher following soy protein-based formula consumption.

Introduction

Human milk is recommended as the sole source of nutrition for term infants up to the age of 6 months and supplemented with solid foods for up to two years or beyond, as mutually desired by mother and child [1–3]. Most commercial infant formulas try to imitate its composition, not only in terms of calorie distribution between carbohydrates, fats, and proteins, but also in terms of its unique composition of amino and fatty acids. After water, carbohydrates are the most prevalent nutrient in human milk, in the form of lactose (with an average concentration of 70 g/l) and oligosaccharides. Lactose is readily digested by nearly all infants, whereas oligosaccharides are non-digestible and play a number of functional roles in infants [4]. The two types of milk proteins, whey and casein, differ in their solubility in an acidic environment. About 70% of breast milk protein is acid soluble (whey) and about 30% is insoluble (casein) [5].

Both lactose and milk protein contribute to milk's distinctive character of having a low glycemic index (GI) and a high insulinemic index [6, 7]. Low glycemic carbohydrates are a desirable component of nutrition in the modern age, and epidemiological evidence suggests many benefits to following a low glycemic index diet [8, 9]. Recently, Jenkins et al. demonstrated that a diet with a high glycemic index was associated with an increased risk of cardiovascular disease and death [10]. However, both lactose and milk protein are often replaced in infant formulas by substitutes due to medical reasons, such as metabolic diseases (e.g., galactosemia) and cow's milk protein allergy [11, 12], as well as due to personal preference (e.g., religion, veganism). The main alternatives of carbohydrates in infant formulas are sucrose, corn syrup, and tapioca or corn starch. One of the alternatives to milk protein is a soy protein-based formula.

It is agreed upon, that if certain stimuli occur during the sensitive and critical period of the first 1000 days from the time of fertilization to the age of two years, they can lead to adaptive changes, known as "metabolic programming" [13, 14]. These changes have been shown to influence obesity and metabolic morbidity later in life [15, 16]. This highlights the importance of assessing the specific glycemic response that is elicited by consuming various types of infant formula during this critical period.

There is little information on the metabolic response to breast milk consumption, and on whether it differs among various formulas. To the best of our knowledge, only one study [17] demonstrated a similar glycemic and insulinemic responses in adults who consumed breast milk and cow's milk protein ("standard") formula, but a wide range of responses to other formulas in a different cohort.

The aim of the present study was to investigate the glycemic and insulinemic responses to several common commercially available types of formulas, containing carbohydrate or protein substitutes, in comparison to those of a standard formula based on cow's milk protein and containing lactose. We hypothesized that the glycemic and insulinemic responses to a soy protein-based formula and a lactose-free formula will be different from those following the ingestion of the standard formula.

Materials And Methods

Patient Population

The study was conducted from March 2018 to December 2019 at the Tel Aviv Sourasky Medical Center. Due to ethical considerations and practical reasons (e.g., consuming different types of infant formulas in defined quantities and taking repeated blood samples), the study could not be conducted on infants. Therefore, the participants were healthy young adults volunteers aged 25–40 years, with normal body mass index (BMI) values. Candidates were excluded if they had chronic illnesses or metabolic morbidities (e.g., diabetes, insulin resistance, or abnormal fasting glucose values), if they were overweight (BMI > 25), if they had taken any medication on a regular base, and if they had a soy allergy or lactose sensitivity or avoided dairy products for any reason (e.g., veganism). Pregnant women were also excluded. Each subject served as his/her own control.

Study design

This pilot study is a three-arm, double-blind, randomized, crossover trial. Upon study inclusion, anthropometric (weight, height, BMI) and demographic data (age, sex) were recorded for each participant. The study design followed the standardized method for the determination of the glycemic index of foods [18]. Each participant completed a total of four sessions: 50g of glucose dissolved in water (reference food) was consumed in the first session, and three different kinds of formulas were randomly consumed in the next three sessions. The three formulas included a "standard" formula, which was a cow milk protein-based ("Nestlé, Materna Extra Care Stage 1") containing lactose, a soy protein-based formula ("Nestlé, Materna Soya"), and a lactose-free formula ("Nestlé, Materna Extra Care Comfort"). All formulas contained 50g of carbohydrates and 9g of proteins in a total volume of 200ml each. Table 1 depicts the formulas' carbohydrate and protein compositions.

Table 1
Carbohydrate and protein content of infant formulas

Formula brand	Carbohydrate composition*	Protein composition*
Cow's milk protein-based formula (Materna Extra Care Stage 1)	Lactose (100%)	Whey (60%), casein (40%)
Soy protein-based formula (Materna Soya)	Glucose syrup solids (100%)	Soy (100%)
Lactose-free formula (Materna Extra Care Comfort)	Glucose syrup solids (100%)	Whey (60%), Casein (40%)
Values taken from nutritional information on product labels.		

At each of the sessions, each participant had an intravenous line placed, and underwent a blood test for fasting glucose and insulin (at time 0). In the first session, blood samples for liver enzymes, lipid profile,

and HbA1C were taken in order to rule out unknown morbidity that could affect glycemic or insulinemic responses. Each participant then consumed 200ml of concentrated glucose solution containing 50g of glucose. Blood glucose and insulin levels were measured at defined time points over a two-hour period: glucose levels were taken at seven time points (fasting (baseline)) and 15, 30, 45, 60, 90, and 120 minutes after drinking the solution), and insulin levels at three time points (fasting (baseline) and 60 and 120 minutes after drinking the solution). These glucose and insulin values were taken as references of the glycemic and insulinemic responses for each participant, as defined elsewhere [18].

After a washout period, each volunteer participated in three additional sessions, in each one he was randomly assigned one of the three formulas above. An independent medical team member was responsible for randomization (performed by a computer software), and formulas preparation (prepared by mixing powder into water), so that both the participant and the researcher providing the formulas and taking the blood samples were blinded to the formula the participant was receiving at each session. There was a 48-hour or longer break between sessions, and each trial was conducted after a 10-hour night fast. Blood samples were taken as described above in each of these three sessions. The participants neither ate nor drank and remained seated during each session, which lasted approximately 120 minutes.

Statistical analyses

The SPSS software was used for all statistical analysis (IBM SPSS statistic for Windows, version 25, IBM corp., Armonk, NY, 2017). Categorical variables were reported as frequency and percentage. Normality was assessed by Kolmogorov-Smirnov test and with a histogram. Continuous variables were presented with medians and interquartile ranges (IQR) or mean ± standard deviation (SD) as appropriate. Chi-squared tests or Fisher's exact test were used for categorical variables as appropriate. GI variations between the formulas were evaluated by Kruskal-Wallis Test. Because each of the tested formulas was given to each participant, the Friedman test and the Wilcoxon test were applied to compare postprandial glucose and insulin levels between the different solutions.

The Glycemic Index was calculated using the area under the curve over the baseline, excluding the area beneath the baseline (incremental area under the curve [IAUC]), as recommended by the Food and Agriculture Organization, which was assessed as the sum of trapezius, relative to the IAUC after reference food consumption (glucose solution) [18]. All statistical tests were two-tailed, and a P value < 0.05 was considered significant.

Ethical considerations

The study protocol was approved by the institutional review board of the Tel Aviv Sourasky Medical Center (0760-16-TLV). Written informed consent was obtained from all participants.

Results

A total of 31 volunteers were originally recruited to the study. Eleven of them were excluded because they failed to meet the inclusion criteria. The study cohort consisted of 20 healthy adults. Nine of them were males (45%) and 11 were females (55%), their mean ± SD age was 32.8 ± 2.9 years, and their median (IQR) BMI was 21.1 (19.7−23.4). Their lipid profile and liver function test results were all within normal limits, and their median HbA1C was 5.3% (5.1−5.6) (normal range 4.6−5.7%) (Table 2).

Table 2
Demographic and clinical characteristics

		Participants (*n* = 20)
Sex		
	Male	11 (55%)
	Female	9 (45%)
Age, year (range)		32.8 ± 2.9
Anthropometric data		
	Height (m)	1.7 (1.6−1.8)
	Weight (kg)	61.5 (58.0-73.8)
	BMI (range)	21.1 (19.7−23.4)
Laboratory data		
	AST (U/L)	21.5 (18.0-25.8)
	ALT (U/L)	21.0 (13.3−25.0)
	TG (mg/dL)	74.0 (55.8−91.8)
	Total cholesterol (mg/dL)	172.0 (158.3-193.5)
	HDL (mg/dL)	56.6 (44.9−64.0)
	LDL (mg/dL)	103.0 (81.3-113.3)
	HbA1C (%)	5.3 (5.1−5.6)
Data are presented as n (%), mean ± SD, or median (Q1-Q3).		
BMI - body mass index, AST - aspartate transaminase, ALT - alanine transaminase, TG - triglycerides, HDL - high-density lipoprotein, LDL - low-density lipoprotein, HbA1c - hemoglobin A1c		

The participants completed the four test sessions with no adverse events. Figures 1 and 2 depict the 2-hour glucose and insulin response curves for the three infant formulas. There was no significant difference in the calculated glycemic index between the three formulas (21.5 ± 21.7, 29.1 ± 17.2, 21.5 ± 14.5 for the standard formula, soy protein-based formula, and lactose-free formula, respectively, p = 0.21,

Fig. 1 and Table 3). However, the calculated mean of peak glucose levels reached by the participants during the two-hour period was significantly higher for the soy protein-based formula than for the cow`s milk protein-based or lactose-free formulas (111.5 mg/dL vs 101.8 mg/dL and 105.8 mg/dL, respectively, p = 0.001, Table 3). Moreover, the maximum increase in glucose levels after formula consumption relative to baseline was also significantly higher for the soy protein-based formula than for the standard or lactose-free formulas (21.7 mg/dL vs 13.1 mg/dL and 16.3 mg/dL, respectively, p = 0.006, Table 3). No significant difference was found for the minimum glucose levels between the formulas (78.7 mg/dL, 75.1 mg/dL, and 79.2 mg/dL for the standard formula, soy protein-based formula, and lactose-free formula, respectively, p = 0.47, Fig. 1).

Table 3
Post-prandial differences in glucose and insulin levels per formula

	Cow's milk protein formula	Soy protein-based formula	Lactose-free formula	P value
Glycemic index	21.5 ± 21.7	29.1 ± 17.2	21.5 ± 14.5	0.21
Peak glucose level (mg/dL)	101.8 ± 9.1	111.5 ± 13.7	105.8 ± 12.1	0.001 *
Glucose change from baseline (mg/dL)	13.1 ± 7.2	21.7 ± 11.5	16.3 ± 10.3	0.006 *
Peak insulin level (mU/ml)	12.1 ± 6.5	12.1 ± 7.0	10.8 ± 5.5	0.45
Insulin change from baseline (mU/ml)	5.0 ± 5.7	5.0 ± 5.2	3.4 ± 6.4	0.52
Values are expressed as mean ± standard deviation.				
*Difference between soy-based formula to both cow`s milk protein based- and lactose-free formulas.				

The postprandial insulinemic response, during the two-hour period, was similar for all three formulas used. The maximum insulin levels and the maximum insulin increase from baseline for the standard formula, soy protein-based formula, and lactose-free formula, were 12.1 mU/ml, 12.1 mU/ml, and 10.8 mU/ml (P = 0.45, Fig. 2), and 5.0 mU/ml, 5.0 mU/ml, and 3.4 mU/ml (p = 0.52, Table 3), respectively.

Discussion

In this randomized, double-blind controlled study, we aimed to assess the glycemic and insulinemic responses to three main types of formula. We found no differences in the glycemic index between the standard (cow's milk protein-based containing lactose), the lactose-free, and the soy protein-based formula. However, peak blood glucose levels were significantly higher after consumption of a soy protein-based formula.

Epidemiological evidence suggests that a diet based on low glycemic carbohydrates has many benefits, especially in an era when obesity is becoming a global epidemic [8, 9, 19]. Several studies have examined and demonstrated the effect of certain carbohydrates and amino acids on post-prandial glycemia and insulinemia [6, 20–25], but there is little information on the differences in metabolic response to various infant formulas. Wright et al. [17] compared glycemic and insulinemic responses to breast milk and standard infant formula among 10 healthy breastfeeding mothers, and found no differences between them. In that part of their study, similarly to ours, each volunteer consumed both her own breast milk and infant formula. In the second part of their study, 11 formulas that differed in carbohydrate and protein composition were tested among 10 healthy young adult volunteers, and a wide range of responses was demonstrated. It is well known that the metabolic response differs among people, and it is possible that this also affected the differences observed by Wright et al. Our current double-blind study, which included almost twice as many volunteers, compared the glycemic and insulinemic responses to different kinds of infant formula, but did so while eliminating the variability in metabolic responses between different individuals, since each subject served as his/her own control.

To the best of our knowledge, our study is the first to compare glycemia and insulinemia as the result of consuming standard formula with formulas containing carbohydrate or protein substitutes in healthy adults. Our findings might be clinically relevant because high postprandial glucose levels, especially during the growth period and metabolic programming in infancy, might have long-term adverse effects. The present study showed that standard cow's milk formula, lactose-free formula, and soy protein based-formula had similar glycemic index despite their different compositions. However, our findings demonstrated that the consumption of a soy protein-based formula resulted in a significantly higher increase in postprandial peak glucose levels. The implications of similar glycemic indexes but different peak glucose levels have yet to be explored, but they may indicate rapid changes in blood glucose concentrations following consumption of soy protein-based formula. These fluctuations in glucose levels may increase hunger levels, cause rebound hypoglycemia, and impair the body's ability to maintain stable blood glucose levels over time [19]. Noteworthy, although postprandial peak glucose levels were significantly higher for the soy-based formula, it did not meet the criteria for hyperglycemia.

Despite the increase in peak glucose levels following the consumption of a soy protein-based formula, the maximum increase in insulin levels was similar for all tested formulas. The fact that we only had three insulin measurements throughout the two-hour period in each session, as opposed to seven glucose tests, may have reduced accuracy in the assessment of the insulin response.

Lactose is the principal carbohydrate in breast milk, and its many benefits are well known. For example, it enhances calcium absorption (thus contributing to bone mineralization) as well as the absorption of other minerals, such as magnesium, zinc, and iron [26–28]. In addition, some of its derivatives and fermentation process products have a prebiotic potential, and are utilized by the gut bacteria from probiotic strains thus encouraging their growth. Furthermore, galactose, a monosaccharide that is one component of lactose, plays an important role in the brain and nervous system development, and is a vital source of energy for the brain, especially in neonates [29–31]. Therefore, regardless of its glycemic

index, the removal of lactose from the infant's diet should be carefully considered if done without a compelling medical cause.

The soy protein-based formula is medically recommended for infants suffering from galactosemia (a rare hereditary metabolic disorder) or lactase deficiency (hereditary or acquired). However, it is otherwise not recommended for use during the first 6 months of life [32]. Soy is recognized as being one of the richest sources of phytoestrogens, which are plant ingredients similar in composition to mammalian estrogens [33, 34]. In addition, soy products are relatively rich in phytate, which binds calcium and impairs its absorption, and a soy-based formula contains significantly more aluminum than other formulas [35, 36]. Our present study may rise another reason to refrain from using a soy protein-based formula without justified medical indication.

The main limitation of our study is that the participants were adults and not infants who are the formula consumers and the research target. Unfortunately, this is unavoidable due to obvious ethical and practical reasons. We are well aware of the differences between the metabolism of infants and that of adults and the age-related differences in the enzymatic activity in the digestive system, which can affect the glycemic and insulinemic responses. However, it is reasonable to assume that infant will respond to these various formulas in a similar manner, if not in a more pronounced way. Another limitation lies in the assessment of the insulinemic response; its accuracy may have been hampered by budgetary constraint, because only 3 insulin tests per participant in each session were performed. A major strength of this study is that each subject served as his/her own control for the evaluation of each formula.

In conclusion, the hypothesis that formulas containing carbohydrate or protein substitutes would have different glycemic indexes than a typical formula was not supported by this study. Instead, this current study revealed a significant increase in blood glucose levels after consumption of soy protein-based formula when compared to standard and lactose-free formulas. The implication and clinical significance of these results have yet to be determined; however, we believe that these findings are of concern in the decision making process for pediatricians considering endorsing a soy protein-based formula without specific medical justification.

List Of Abbreviations

BMI - body mass index

GI - glycemic index

IAUC - incremental area under the curve

IQR - interquartile range

SD- standard deviation

Declarations

Conflicts of interest: The authors declare no conflict of interest.

Availability of data and material: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable.

Authors' contributions: AA, HML, DR, and RL designed the study, participated in data analysis, drafted the manuscript and approved the final version to be submitted. AA was also undertook participants' recruitment and obtaining informed consent, ensured their compliance with the study protocol, and verified that the study was conducted in accordance with the permits granted. In addition, she conducted the clinical trial, and was responsible for data acquisition, IV line placement, and blood samples' collection and transference to the endocrinological laboratory for analysis. NS was the study initiator, participated in its design and revised the manuscript. AO and LM participated in the study design and revised the manuscript. MP was responsible for randomizing and formula preparation

Ethics approval: This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the Helsinki ethics committee. Written informed consent was obtained from all participants.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: N/A.

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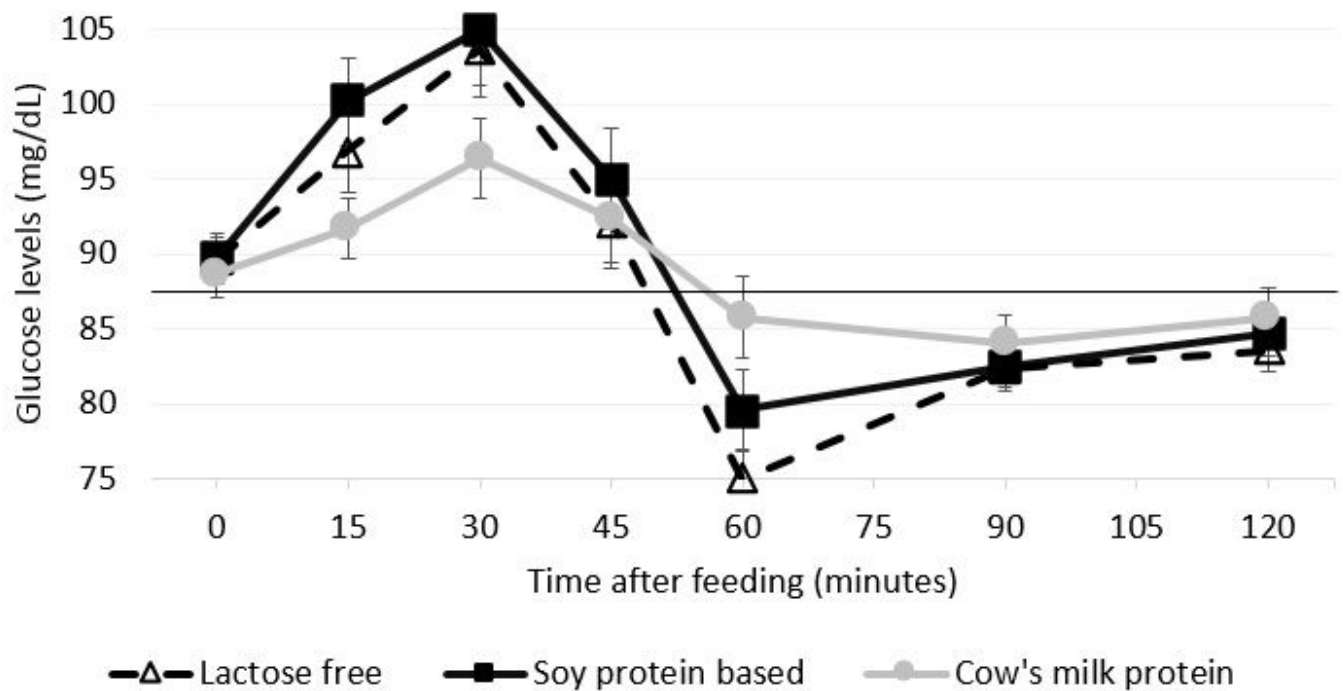
Figures

Figure 1

Post-prandial plasma glucose level per infant formula (mean ± SEM (standard error of the mean)), and horizontal plain line drawn at baseline value.
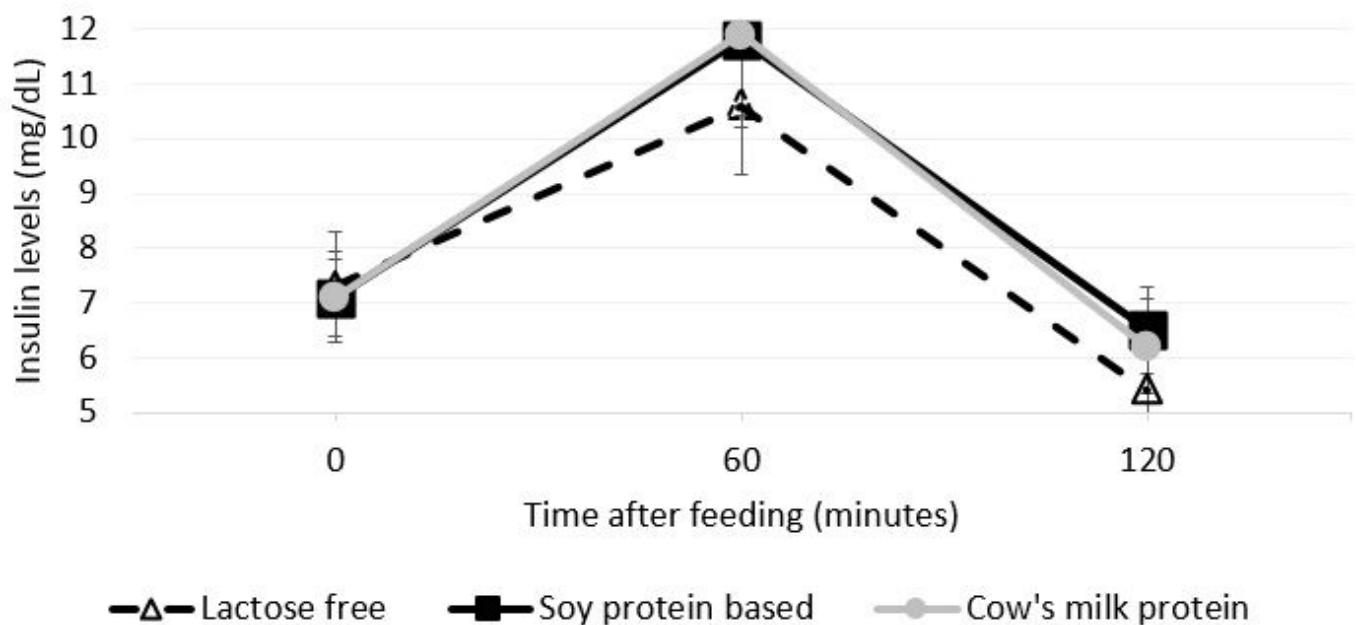
Figure 2

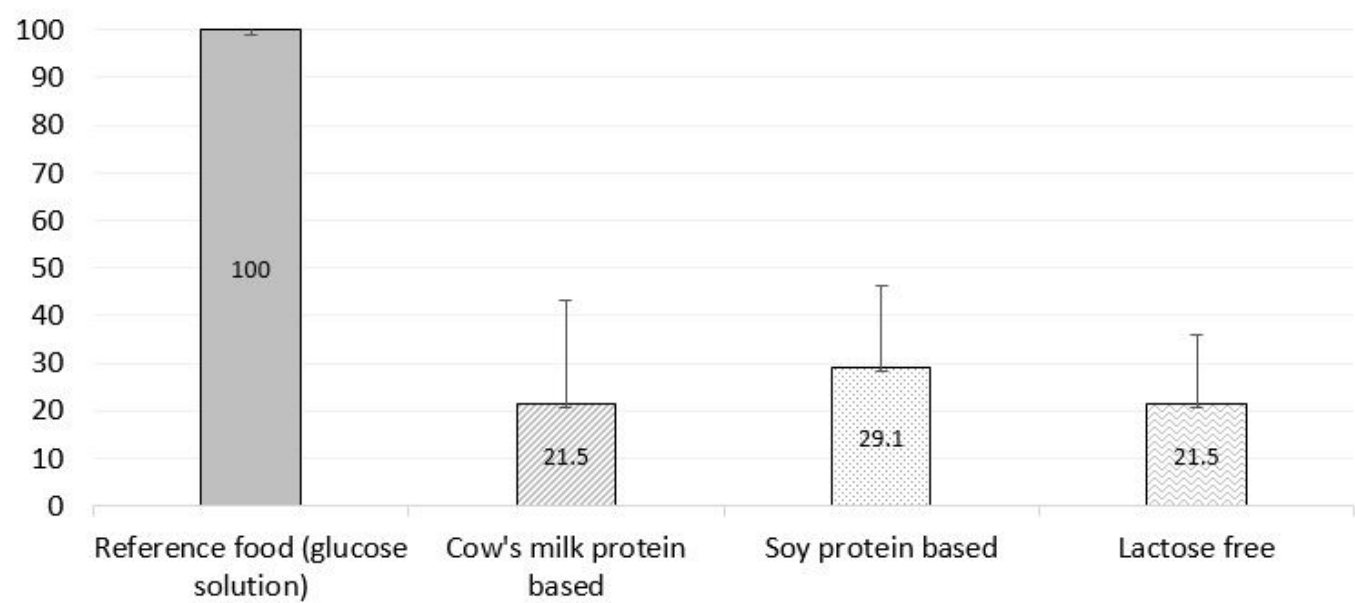Post-prandial plasma insulin level per infant formula (mean ± SEM)

Figure 3

Glycemic index per infant formula (mean ± SD).