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Effect of kefir and soy yogurt consumption on serum IGF-1 levels in young healthy women

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ABSTRACT

Background: Milk and dairy product intake are associated with higher IGF-1 concentrations, a well-known factor promoting adverse events such as carcinogenesis. Different associations with high levels of IGF-I were found for dairy protein such as milk and derivatives, and soy protein. In this contest, fermented milk product (kefir) exhibits a growing number of health-promoting effects including stimulation of the immune system, and antimutagenic and anticarcinogenic activity, but there is a lack of data on healthy humans.

Objectives: We aimed to determine the serum IGF-1 profiles of young healthy volunteers of the female sex after kefir or soy yogurt consumption during a Mediterranean diet.

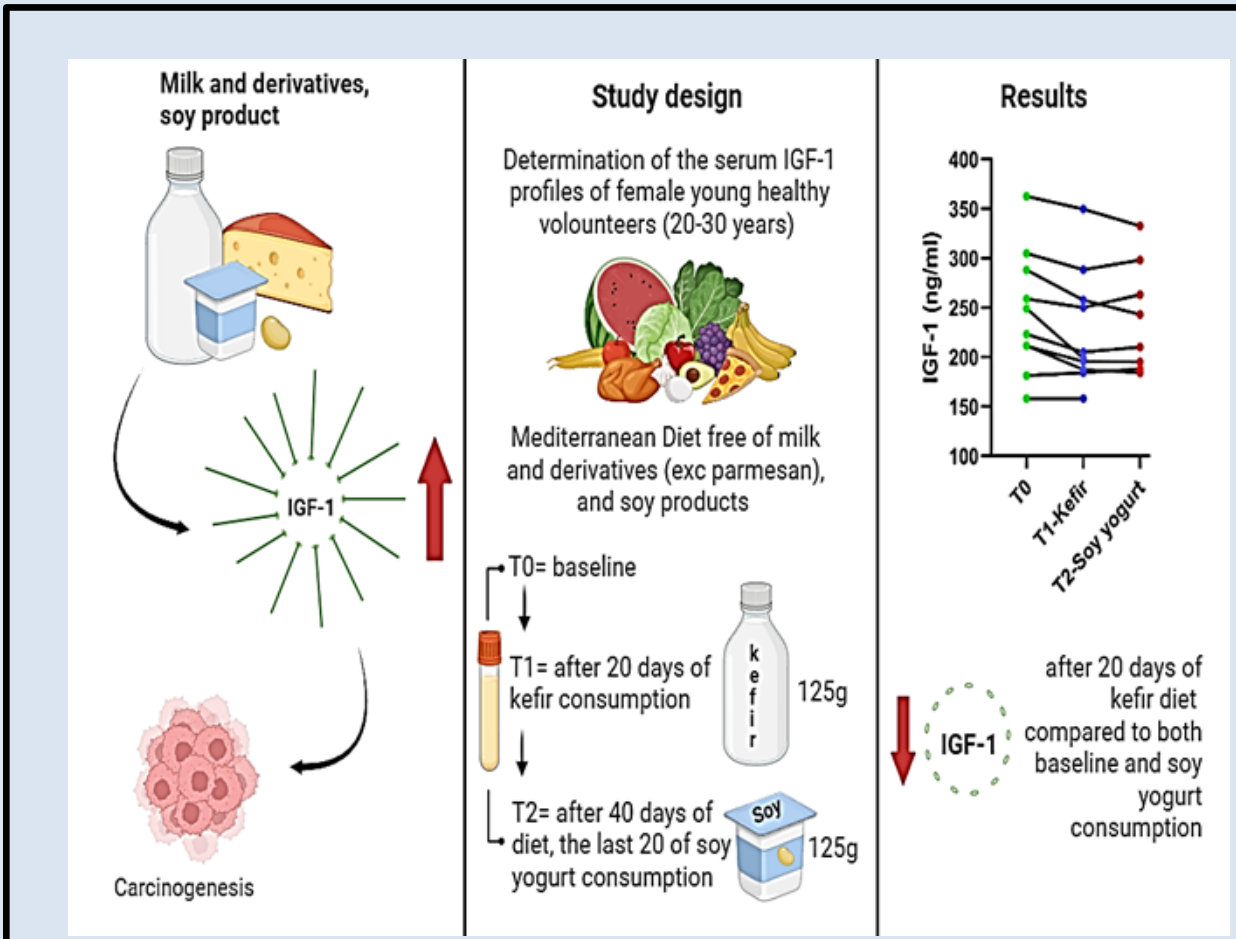
Materials and Methods: The study was conducted by monitoring the serum IGF-1 levels of female participants, following a normocaloric and normoproteic Mediterranean Diet, at the baseline (T0) and after 40 days of which the first 20 days (T1) consuming 125g of kefir, and the last 20 days (T2) consuming 125g of soy yogurt.

Results: A total of 10 female participants were enrolled in the study (age=26.1± 2.9 years). The IGF-1 level (ng/ml) was in the range of normality for all the participants except for one participant (T0=245 ± 61, T1=227 ± 58, T2= 239 ± 55). The mixed-model analysis revealed statistically significant differences in IGF-1 levels by diet ($p=0.014$; $\eta 2p=0.49$). In particular, post-hoc

analysis revealed a lower value after 20 days of kefir diet compared to both baseline (p= 0.014) and 40 days of diet (p=0.163).

Conclusion: Caloric and protein intake have been suggested to influence circulating IGF-I, promoting carcinogenesis. Kefir consumption could improve the IGF-1 levels. Our data suggest that the inclusion of whole milk kefir in a normocaloric and normoprotein diet promotes blood IGF-1 levels in healthy young women as compared to soy yogurt consumption, reinforcing the beneficial effect of fermented milk on metabolic disorders. The interpretation of this result will need to be better investigated in further studies on large sample sizes.

Keywords: IGF-1, Kefir, normocaloric diet, soy yogurt



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INTRODUCTION

Kefir can be obtained from various raw materials such as water and milk and for this reason there are water kefir and milk kefir on the market today. From a nutritional point of view, the richest is milk kefir. The components that transform milk into kefir are kefir grains, a mix of

bacteria and yeast colonies living in a substrate of proteins, fat, and polysaccharides, having a white-colored granular, filamentous gelatinous appearance. Kefiran, its most characteristic component, is a water-soluble heteropolysaccharide, widely studied for its health benefits [1]. Kefir contains a complex microbiota of around 50 different types of microorganisms which is an example of a symbiotic community in which they cooperate by sharing their bioproducts as a source of energy and growth factors; the microbic population is mostly represented by lactic acid bacteria, yeasts, streptococci, and lactococci, in a symbiosis that allows the stability of the microbiological profile to be maintained throughout the entire fermentation cycle [2]. In the last years, many countries have approached Kefir consumption, mostly Asia, America, and Eastern Europe [3-4]. The interest in the therapeutic properties of probiotic products is growing and numerous investigations to date have been accomplished in the field of probiotic products and of kefir.

Many published studies attribute a series of beneficial effects on health to the regular consumption of kefir such as reduction of LDL cholesterol, lowering of blood glucose levels, and antagonistic action against various pathogens, while more recent discoveries support the beneficial role brought by the non-microbial fraction (especially some metabolites of microorganisms such as lactate and organic acids) of kefir in modulating and strengthening the immune system, also through antiviral activities. The kefir consumption has only recently gained popularity even if it has been consumed for thousands of years, because consumers are opting for foods with functional properties. In fact, in addition to the benefits already mentioned, the list of kefir's supposed health benefits can be extended by considering further positive effects that can improve the consumer's well-being: improved digestion, better tolerance to lactose, gut microbiome modulation, improvement of the metabolic dysregulation occurring in obesity, anti-inflammatory effects, and resizing of the cardiac and renal hypertrophy; furthermore, anti-oxidant and anti-allergenic activity [5-7], and anticarcinogenic and antimutagenic activity[8-9], are all improving effects attributed to this interesting functional food. The ever-growing interest in functional foods makes it increasingly necessary to define them as precisely as possible to make them easily identifiable by consumers and at the same time easily usable by producers. Thus, FFC's scientists are working with USA governmental representatives to improve the current definition of Functional foods to be properly termed. According to FFC and its most recent proposed definition (2021) a Functional food can be defined as "natural or processed foods that contain biologically-active compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms" [10] Kefir, based on the studies available to date, appears to adequately satisfy this definition.

Probably, the kefir activity is emphasized by the release of antioxidants micronutrients (vitamins E, B3, B6, and B12, and minerals Se, Fe, Zu, and Mn), organic acids, amino acids, and antioxidant enzymes (glutathione peroxidase, catalase, and superoxide dismutase) formed during the fermentation process [11-12]. Figure 1 summarizes the chemical and nutritional composition of kefir.

The interest in the potential properties of kefir in the field of carcinogenesis dates back to several years ago. In fact, in 1982 Shiomi et al. established the activity of a water-soluble polysaccharide separated from kefir grains (KGF-C) on tumor cells the first publication about the antitumoral activity of a water-soluble

polysaccharide (KGF-C) separated from kefir grains was published in 1982 by Shiomi et al. The study demonstrated that KGF-C has a strong ability to inhibit the proliferation of tumor cells of the Erlich ascitic lineage or sarcoma 180 after oral or peritoneally administration [13-14]. Subsequent studies have shown that the KGF-C could delay the tumor development through an immunomodulatory activity on T cells which does not seem to involve B cells [15] in a more incisive way than Dahi, a yogurt enriched with probiotics not too dissimilar to kefir with positive data in colorectal cancer [16]. Moreover, following studies showed the same activity on Lewis lung carcinoma after oral administration of kefir [17].

Milk and its derivatives are currently considered foods that can induce an increase in IGF-1 levels. This is because there are observational and intervention studies that have shown an association between consumption of milk and dairy products and increased concentrations of IGF-1 (insulin-like growth factor-1); even if the results have not always been consistent, this belief is widespread among those involved in nutrition. The dietary regulation of IGF-I deserves elucidation. Studies on fasting carried out more than twenty years ago showed a decrease in the plasma concentration of IGF-1 after a few days of fasting [18]. Furthermore, some studies on mice have strengthened these results by demonstrating that moderate but prolonged caloric restriction reduced IGF-I concentrations by 20-40% ([19-20], mechanism mediated by the development of resistance to the growth hormone (GH). Several subsequent studies, however, including one recent randomized trial [21] have failed to show any reduction of IGF-I in humans after long-term caloric restriction. Rather, in humans, caloric restriction seems to significantly reduce IGF-I along with restriction in protein intake [21]. Among the different proteins coming from animal sources, those coming from milk and derivatives seem to have a more significant effect on the increase in IGF-1, but they do not all act in the same way. An interesting recent observational analysis conducted by the UK Biobank showed that some dairy products can cause more significant increases in IGF-1 levels than other products. Yogurt proteins have been positively associated with increased circulating concentrations of IGF-q 1 while proteins derived from cheeses appear to not to have this property. Therefore, the source of milk proteins is crucial in positively influencing the circulating concentration of IGF-I [22].

Regardless of the source of origin of the proteins, it seems to be quite certain that there is a positive association effect between the total intake of proteins, fibers, and starch from whole grains and circulating concentrations of IGF-I [25]. There are also no great certainties regarding the effects of soy proteins as the existing data is not homogeneous. The positive association would be confirmed following the intake of large quantities of soy protein (>25 g/day) which appears to modestly increase circulating levels of IGF-1 compared to the control protein [22]; however, this modulation has been suggested to be beneficial for muscle protein synthesis and prevention of sarcopenia in postmenopausal women [26]. According to those analyses, different associations with the IGF-I levels and the dietary impact depending on the source of dairy protein warrant further investigation due to the differences in protein sources may prove to be potentially important and warrant further investigation.

Considering the lack of data in the field, we aimed to determine the serum IGF-1 profiles of young healthy volunteers of the female sex after kefir or soy yogurt consumption during a Mediterranean diet.

Figure 1. The chemical composition and nutritional values of kefir [23-24]

Components	100 g	Components	100 g
Energy	65 kcal	**Mineral content (g)**	
Fat (%)	3.5	Calcium	0.12
Protein (%)	3.3	Phosphor	0.10
Lactose (%)	4.0	Magnesium	12
Water (%)	87.5	Potassium	0.15
Milk acid (g)	0.8	Sodium	0.05
Ethyl alcohol (g)	0.9	Chloride	0.10
Lactic acid (g)	1		
Cholesterol (mg)	13	**Trace elements**	
Phosphatateds (mg)	40	Iron (mg)	0.05
		Copper (µg)	12
Essential amino acids (g)		Molybdenum (µg)	5.5
Tryptophan	0.05	Manganese (µg)	5
Phenylalanin+tyrosine	0.35	Zinc (mg)	0.36
Leucine	0.34		
Isoleucine	0.21		
Threonine	0.17	**Aromatic compounds**	
Methionine+cystine	0.12	Acetaldehyde	
Lysine	0.27	Diacetyl	
Valine	0.22	Acetoin	
Vitamins (mg)		**Vitamins (mg)**	
A	0.06	B12	0.5
Carotene	0.02	Niacin	0.09
B_1	0.04	C	1
B_2	0.17	D	0.08
B_6	0.05	E	0.11

MATERIALS AND METHOD

Study design and recruitment: The study was conducted by monitoring participants on the serum IGF-1 levels at the baseline and after forty days of which the first twenty days of kefir consumption, and the last twenty days of soy yogurt consumption instead of kefir. Twenty-nine Caucasian young healthy participants aged between twenty and thirty years were screened for enrolment in the study. Eligible participants had to meet the following criteria: age between 20 and 30 years, no acute or chronic diseases, no gastrointestinal diseases or endocrine disorders, no drug use, no antibiotics, no

sports activities before and during the study, not smokers, not pregnant, and not lactating. Participants were screened according to their food habits in terms of adherence to a balanced diet in line with the Mediterranean model [27]. A total of 10 participants fulfilled the eligibility criteria to participate. Before the beginning of the study, the participants signed an informed consent for the blood sampling. Participants compiled a food diary [28] which was checked by the expert field worker to evaluate the adherence to the Mediterranean model.

Characteristics of the diet: Participants were instructed about the food quality and the storage method, to maximize the diet uniformity. Macronutrients were distributed on average as follows: protein= 19% of the Dietary Recommended Intake (DRI), carbohydrates= 43% of the DRI, fat= 39% of the DRI. The proteins were distributed at 1g/kg of body weight and were equally divided between animal and plant sources. Table 1 shows the average protein intake from the different food groups. The diet was free of milk and derivatives, except for parmesan. Participants consumed 125g of Kefir available on the market at breakfast in the first 20 days. After that, they substituted Kefir with 125g of Soy yogurt available on the market for a further 20 days.

Table 1. Sources of dietary proteins

Animal proteins (mean)	Plant proteins (mean)
Parmesan 25g	Cereals 52g
Meat 57g	Vegetables 47g
Eggs 30g	Legumes 19g
Fish 42g	Fresch fruit 16g
Meat 57g	Nuts 20g

Anthropometrics: Anthropometry was conducted by measuring the height to the nearest 0.1 cm, using the Seca 213 portable stadiometer (Seca GmBH & Co Kg, Hamburg, Germany), and the weight to the nearest 0.1 kg accuracy, using the Tanita BC-730 digital weighing scales (Tanita Corporation, Tokyo, Japan) every week. The Body Mass Index (BMI) was calculated as weight (kg) divided by height (m) squared.

Blood sample collection: Circulating IGF-1 was measured in the serum of the blood samples using a chemiluminescent immunoassay with the Liaison XL platform (DiaSorin Ltd, Italy) before beginning the study, and after 20 and 40 days of monitoring.

Statistical analysis: Statistical analyses were performed in GraphPad Prism (version 8.4.3, GraphPad Software Inc., San Diego, CA, USA). Data are expressed as mean ± standard deviation (SD). After testing for normality (Shapiro-Wilk test and Q-Q plot), a mixed-model analysis (diet as fixed factor, participants as random factor, Geisser-Greenhouse's correction for sphericity) was used to estimate significant differences among the experimental results with posthoc Tukey's correction for multiple comparisons. Differences were considered statistically significant at $p < 0.05$.

RESULTS

A total of 10 female participants were enrolled in the study (age=26.1± 2.9). The mean BMI was 25 kg/m^2. Table 2 shows the IGF-1 quantification at the baseline (T0), after 20 days (T1) of kefir consumption, and 40 days (T2) of a diet of which the last 20 days by consuming soy

yogurt instead of kefir. IGF-1 was in the range of normality for all the participants except for one participant. Two participants did not provide IGF-1 quantification at T2. Table 3 shows descriptive statistics.

Table 2. IGF-1 quantification at baseline and after 20 (T1) and 40 (T2) days of diet.

		IGF-1 levels			
ID	Age (years)	T0 (ng/ml)	T1 – kefir (ng/ml)	T2 - Soy yogurt (ng/ml)	Reference value (ng/ml)
1	29	181.4	184	188	107.8-246.7
2	29	249	198.6		107.8-246.7
3	22	288.1	257.6	243.2	149.1- 332.3
4	21	211.5	187.4	184.2	149.1- 332.3
5	26	362.5	349.6	332.7	107.8-246.7
6	30	158	158		107.8-246.7
7	26	258.8	250.2	263	107.8-246.7
8	25	304.9	288.3	298.2	149.1- 332.3
9	27	211	195.6	195	107.8-246.7
10	26	223.2	205	210	107.8-246.7

IGF-1 (Insulin Growth Factor – 1) levels were quantified on blood samples. ID= Identification number; T0= baseline quantification; T1= quantification after 20 days of kefir consumption; T2= quantification after 40 days of diet of which the last 20 days by consuming soy yogurt instead of kefir. Empty lines correspond to missing values.

Table 3. Descriptive statistics of mixed-effect analysis.

Time	Mean ± SD (IGF-1 ng/ml)	95% CI	
		Lower bound	Upper bound
T0 (n=10)	245 ± 61	201	289
T1-Kefir (n=10)	227 ± 58	186	269
T2-Soy yogurt (n=8)	239 ± 55	1193	285

IGF-1= Insulin Growth Factor – 1; T0= baseline; T1= quantification after 20 days of kefir consumption; T2= quantification after 40 days of diet of which the last 20 days by consuming soy yogurt instead of kefir. CI= Confidence interval for differences.

The mixed-model analysis revealed statistically significant differences in IGF-1 levels by diet (p=0.014; η^2_p=0.49). In particular, post-hoc analysis revealed a lower value after 20 days of kefir diet compared to both baseline (*p*= 0.014) and 40 days of diet (*p*=0.163). Results are shown in Figure 2.

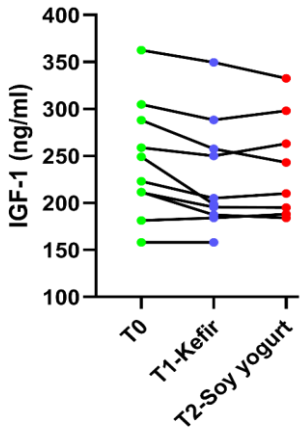

Figure 2. Multiple comparisons of IGF-1 levels at the three times of diet: IGF-1= Insulin Growth Factor–1 (ng/ml); T0= baseline; T1= quantification after 20 days of kefir consumption; T2= quantification after 40 days of diet of which the last 20 days by consuming soy yogurt instead of kefir. CI = Confidence interval for differences.

DISCUSSION

Kefir consumption has been growing in recent times, raising interest in its historically beneficial effect, supported in the last years by several scientific studies. *In vitro,* or animal model studies confirmed the association of kefir consumption with improved digestion and food tolerance, control of plasma glucose, blood pressure, inflammation processes, antioxidant, and anti-carcinogenic activity, and more [5-7]. Some studies demonstrated that plain kefir consumption improved lactose digestion probably thanks to the high level of β-galactosidase activity which is higher than plain yogurt. The microbial production of, organic acids, peroxides, acetaldehyde, carbon dioxide, kefiran and bacteriocines and antibacterial peptide could counteract pathogenic infections [29].

A randomized controlled clinical trial in type -2 diabetic patients who received 600 mL fermented milk (kefir) twice a day, versus a control group who received 600 mL conventional fermented milk twice daily for eight weeks of intervention, showed that the serum level of insulin, homocysteine, and BMI, changed improving the HOMA-IR, which decreased significantly in probiotic group after intervention [13]. Homocysteine serum levels in both groups decreased after the intervention, suggesting the potential role of kefir in the modulation of cancer-related dysmetabolism, too. [30-31]. This may also account for one of the envisaged protective mechanisms against prostate cancer in diabetics using kefir, as suggested a few years ago [32]. As among metabolic IGF-1 functions are included the maintenance of normal insulin sensitivity and glucose uptake increase a good strategy in managing some metabolic disorders could be to regulate blood glucose and IGF-1 levels through supplementation with functional food like kefir, to prevent several diseases and enhance the care in others including cancer. Aldona Kasprzak described in a recent review about the role of IGF-1 in glucose metabolism in physiology and colorectal carcinogenesis IGF- 1 regulates directly or indirectly a multiplicity of processes such as activation of signaling pathways (e.g., PI3K/Akt/mTORC, TGF-β/PI3K/Akt/mTOR, and Raf/MAPK), activation of glucose transporters (mainly GLUT1), and key glycolytic enzymes (e.g., LDHA, LDH5, HK II, and PFKFB3), aberrant expression of oncogenes (e.g., MYC, and KRAS) and overexpression of signaling proteins (e.g., HIF-1α and HIF-1β, TGF-β1, PI3K, ERK, Akt, and mTOR). Most of just mentioned processes are indirectly or directly regulated by IGF-1 makes the hypothesis regarding the consumption of functional foods, such as

kefir, to improve the prevention and management of diseases stronger and more necessary for further investigation [33].

On the other hand, past studies have investigated the relationship between the consumption of dairy products and the level of IGF-1 in serum, showing a positive association between the intake of dairy products, milk, yogurt, and IGF-1 levels, denying this association with cheeses [34]. The effect of kefir on situations prone to metabolic syndrome is corroborated by specific studies [34-35] and makes this compound susceptible to endotoxin-associated diseases such as obesity and liver disease [36]. The Insulin-like growth factors (IGFs) are peptides that act as humoral mediators of growth hormone action [37]. Within the IGF family, the molecular structure of IGF-1 closely resembles that of insulin as it has an A and a B chain connected by three disulfide bonds [38]. Since the molecular architecture of IGF-1 is so like that of insulin, IGF-1 can bind, albeit with low affinity, to the insulin receptor [39]. Thanks to these structural characteristics, IGF-1 plays an important role in cellular glucose metabolism, amino acid absorption, glycogen synthesis, mitogenesis and lipogenesis at the cellular level [39]. The majority of the IGFs found in serum exist in a 150-kDa complex, which includes the IGF molecule, the acid labile subunit, and IGF binding protein 3. This complex enhances the half-life of serum IGFs and facilitates their endocrine actions [40].

IGF-1, being a polypeptide hormone plays an important role in the growth-promoting process that is essential for normal growth and development. Its role in protein, glucose and lipid metabolism is now well characterized [41]. Some studies suggest that dietary intake, especially the total amount of proteins in their origin, can influence the concentration of circulating IGF-1 [41-42]. Evidence from observational studies and randomized controlled trials suggested that increased intake of protein [43-44] and dairy products [13], likely due to their protein content (44), may increase IGF-1 concentrations. However, the associations of circulating IGF-1 concentrations with different sources of protein and other nutrients have not been yet well characterized. In our study, we examined the relationship between daily kefir consumption, and circulating IGF-1 concentrations in young women in apparent good health. Our results showed that a normal-protein diet, which fits the Mediterranean model in terms of quality and recommended portions of food, and includes a daily portion of kefir, appears to reduce the blood concentration of IGF-1. On the other hand, the reduction of IGF-1 levels by kefir consumption was confirmed compared to soy yogurt consumption.

Our results showed a tendency to increase IGF-1 by replacing kefir with soy yogurt, although the values remain within the range of normality. Soy protein was shown to increase the IGF-1 levels, depending on the amount and duration of the ingestion, and on the health status of the participants. The potential positive role of kefir consumption in the IGF-1 modulation of healthy young women compared to soy yogurt consumption that we found in our results suggests the beneficial effect of fermented milk on metabolic disorders markers [13], shoring up the role of kefir as functional milk beverage to be introduced in a dietary pattern. Although in our study we did not analyze memory/cognition parameters, it can't be without reminding that, within the overall benefit kefir may provide to human health, it has been shown its capacity to ameliorate the gut-brain axis dysfunction [45]. This can also be reconciled with its interplay with IGF-1 whose relevant role in brain aging has significant scientific evidence [46]. Moreover, either metabolic impairment or IGF-1 resistance has been reported in brain degenerative disease [47]. Thus, one cannot rule out the capacity of kefir to indirectly exert beneficial neuroprotection by endocrine modulation, as shown with some phytonutrients [48]. It would also be

very interesting to investigate the different impacts on serum levels of IGF-1 and the other parameters mentioned above, following the consumption of an authentic kefir obtained from kefir grains cultured in milk compared to the industrially produced kefir used in this work. There is a study on mice that demonstrates how the effects induced by authentic kefir on immunomodulation are better than those obtained with the administration of industrially kefir, prepared with an initial culture such as that which people can purchase in the store [49].

CONCLUSIONS

In conclusion, our data suggest that the inclusion of whole milk kefir in a normocaloric and normoprotein diet leads to beneficial effects on blood IGF-1 concentrations. The interpretation of this result will need to be better investigated with further studies.

Abbreviations: IGF-1: Insulin Growth Factor – 1; GH: Growth Hormone; DRI: Dietary Recommended Intake

Competing Interests: The authors have no financial interests or conflicts of interest.

Author Contributions: C.A.: conceptualization, methodology, formal analysis, investigation, resources, writing—original draft preparation, visualization, and project administration; C.S.: conceptualization, methodology, formal analysis, investigation, writing—original draft preparation, and visualization; T.P.: writing—review and editing, and supervision; L.H.: writing—review and editing; L.F.O.: writing—review and editing; F.M.: writing—review and editing, and supervision. All authors have read and agreed to the published version of the manuscript.

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