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Dairy consumption and inflammatory profile: a cross-sectional population-based study, São Paulo, Brazil.

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The authors declare no conflict of interest. Tábata Natal Gadotti designed and conceived the work that led to the submission and drafted the manuscript. Marina Maintinguer Norde played an important role in interpreting the results. Marcelo Macedo Rogero acquired data and revised the manuscript. Mauro Fisberg revised the manuscript. Regina Mara Fisberg and Erica Oki acquired data. Lígia Araújo Martini approved the final version.

Abstract

Objectives: To investigate the association between dairy products consumption and plasma inflammatory biomarkers levels among a representative sample of Brazilian adults from São Paulo City.

Subjects/Methods: The data come from a cross-sectional population-based study, *Health Survey for São Paulo*. All individuals aged 20 to 59 with complete food consumption information (24-hour dietary recall and Food Frequency Questionnaire) and blood sampling analysis were included, totalizing a sample of 259 subjects. Sample was separated into two groups according to their systemic inflammatory pattern considering plasma levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), soluble intracellular adhesion molecule (sICAM-1), soluble vascular cell adhesion molecule (sVCAM-1), monocyte chemoattractant protein (MCP-1), interleukins (IL)-1β, 6, 8, 10, 12, adiponectin, leptin, and homocysteine. Multiple logistic regression tests were conducted to estimate the odds ratio (OR) for the inflammatory cluster (INF) across tertiles of dairy consumption.

Results: When adjusted by age, smoking status and energy intake the OR for INF group in the highest tertile of yogurt consumption was 0.34 [95% confidence interval (CI): (0.14 – 0.81)] relative to the reference tertile, demonstrating also a linear effect (P trend=0.015). Cheese consumption exhibited an OR of 2.49 [95% CI: (1.09 – 5.75)] relative to the reference.

Conclusions: Increasing yogurt consumption might have a protective effect on inflammation, while cheese consumption seems to be associated with a pro-inflammatory status. The results of the present study aggregate a new perspective on existent evidence demonstrating the importance to assess dairy products contribution on diet and its impact on the development of non-communicable diseases and associated risk factors.

Key words: Dairy products; Inflammation; Biomarkers; Yogurt; Health Survey for São Paulo; Cardiovascular health.

Introduction

Dairy products are recognized as diet best source of calcium based on its content and bioavailability[1]. This food group also provides high-quality protein due to its complete amino acids profile, which appears to exert a favorable influence on body composition changes in weight loss and lean mass retention[2]. Moreover, milk, cheese, and yogurt are considered high-nutrient dense foods, enabling a significant improvement to other essential nutrient intakes, such as magnesium, potassium, phosphorous, zinc and vitamin B, what clearly supports their association with a better diet quality[3,4].

Besides the recognized importance on bone health due it's calcium and nutrtients content, it's role in inflammation derived diseases development, as such cardiovascular diseases, emerges as a focus of several investigations,[2,5]. Indeed, dairy complex fatty acid profile and its interaction with other components, considering the combination of long and short chain saturated fatty acids, still instigate researchers in order to establish a consensus on possible beneficial effects on health[6,7,8].

In the last five years, the volume of publications inversely correlating dairy products to cardiovascular diseases risk factors has increased drastically (9,-13). Robust cohort studies demonstrate an inverse association between dairy consumption and type 2 diabetes risk, highlighting the effect of fermented dairy products[9,10] and specifically of yogurt[11,12]. In addition, individuals with higher dairy product consumption were revealed to be less likely to smoke and more likely to be physically active, besides having a better cholesterol profile[11,12]. Results considering the inverse relation with hypertension and body mass index were likewise observed[13,14.]

Although mechanisms by which dairy products may act are not completely elucidated, some studies have pointed to the modulation of the inflammatory profile as the path by which diet might take part in the role of cardiovascular diseases [13, 15]. Chronic low-grade systemic inflammation, an inherent condition of obesity status, related to the increase of proinflammatory cytokines, as such tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), contributes to the pathophysiology of numerous metabolic disorders, such as obesity, non-alcoholic fatty liver disease, insulin resistance, dyslipidemias, hypertension, and cancer [16,17].

Despite being scarce in literature, some studies report a consistent relationship between dairy consumption and inflammatory biomarkers. In this context, when evaluating Mediterranean-type diet, Arouca et al[18] found that a higher consumption of dairy products was associated with lower levels of IL-1,IL-5, IL-6, IL-10 and TGF-β. Similarly, results from a cross-sectional study demonstrate that individuals in the highest category of low-fat dairy consumption had the lowest plasma VCAM-1 levels [19]. In addition, analysis of a sample of adults in the cohort The ATTICA study evidence an inverse association between dairy consumption and plasma CRP, IL-6 and TNF-α levels, which were even more significant in those who consumed more than 14 dairy servings per week[20]. Indeed, a recent case-control was able to observe a reduction on IL-1 and IL-6 gene expression from peripheral blood mononuclear cells in the group of participants who consumed three low-fat dairy servings a day when compared to those on a carbohydrate-based control [21]. On the other hand, systematic reviews do not reach to conclusive outcomes[22,23], indicating the need for further research.

The aim of the present study is to investigate the association between dairy products consumption and plasma inflammatory biomarkers levels among a representative sample of Brazilian adults from São Paulo City.

Methods and materials

Subjects and study design

The data came from Health Survey for São Paulo (HS-SP), a cross-sectional population-based study about health and living conditions among a representative sample of urban area residents of São Paulo city, Brazil. HS-SP sample was obtained by a two-stage cluster sampling: census tracts and households. In the first stage, 70 census sectors were randomly raffled among the 267 sectors of the city of São Paulo urban area. In the second stage, private households were selected in each sector by simple random raffle, allowing general and dietary data collection from approximately 1661 men and women aged more than 12 years. Of these individuals, 701 were interviewed again to obtain the second measure of food intake as well as blood sampling and anthropometric measurement. For the present study, all individuals whose aged >19y and <60y, from both sexes were selected. The use of anti-inflammatory medication, fat absorption inhibitors, or antiretroviral therapy, outliers with values _99th for each inflammation biomarkers

(n= 39) and without complete dietary information (n=3) were considered exclusion criteria. The final sample was composed of 259 individuals.

The study was approved by the local ethics committee, and all individuals signed the consent form.

Data collection and processing

A structured questionnaire to assess demographic (sex, age, race), socioeconomic (per capita household income, head of the household's education level) and lifestyle (alcohol consumption, smoking habits, physical activity – International Physical Activity Questionnaire - IPAC) characteristics was applied to the sample during the first home visit by trained interviewers.

Anthropometric variables

Body weight and height were taken on second home visit by trained research assistants, being measured in duplicate with the individual barefoot and wearing light clothing, in accordance with procedures recommended by the World Health Organization[24]. Weight was measured in kilograms by a calibrated digital scale, platform type (Tanita, Model HD-313, maximum capacity of 150 kg, accuracy of 100 grams) and height in centimeters using a portable stadiometer fixed in flat and without baseboard wall (Seca, Model 208, maximum measuring 200 cm, accuracy 0.1 cm). BMI was calculated by height and weight values based on the formula kg/m^2 and individuals classified as underweight, eutrophic, overweight and obese according to cutoffs proposed by World Health Organization for adults.

Dietary Data

The food consumption data were collected by the application of 2 nonconsecutive 24-hour dietary recall (R24h). The first measure was held by personal interview and the second one by telephone interview together with the application of a Food Frequency Questionnaire (FFQ). To structure the collection thought R24h, interviewers were instructed to follow the procedures described in the Multiple Pass Method (MPM), a 5-step data collection method developed by the Department of Agriculture[25] with the objective to guide the interviewer on assisting individuals to recall in details foods and beverages consumed in the previous day, therefore minimizing

collection errors. Regarding the second R24h, interviewers followed Automated Multiple-Pass Method (AMPM) procedures, the automated version of MPM, which incorporates the program Nutrition Data System for Research (NDS-R) (2007 version, Nutrition Coordinating Center, University of Minnesota, Minneapolis, U.S.). Consumption information obtained by both R24h underwent to critical analysis for the identification and correction of errors as well as for the conversion of traditional measures in grams and milliliters to standardized cooking measures[26,27], which was necessary to the use of NDS-R.

The applied FFQ was designed and validated for São Paulo population[28], consisting of a 38 food items list with frequencies ranging from 0 (never) to 10 times, and time units that included day, week, month and year. The use of FFQ allowed obtaining more accurate data on food episodically consumed, what was particularly useful for this study considering the low frequency of consumption of dairy products, especially yogurt.

Dairy consumption was adjusted by the interpersonal consumption variance through the statistical modeling technique Multiple Source Method (MSM), that estimates in individual-level the regular dietary intake combining information obtained from the R24h (quantities consumed) and FFQ (frequency of consumption)[29].

For the present analysis, only milk, cheese and yogurt were included as dairy products, and then following products excluded: soy milk, chocolate milk (ready), condensed milk and all kinds of chocolate. Cheese was divided in regular and light based on fat content.

Biochemical Measurements

Approximately 20 mL of blood sample was collected in dry tubes with EDTA (ethylene diamine tetra acetic acid) by venipuncture after 12-hour overnight fasting. Immediately, the tubes were stored in thermic boxes and transported to the laboratory where samples were centrifuged, aliquoted and stored in a freezer at -80ºC for further analysis. Plasma high sensitivity C-reactive protein (CPR) levels were measured with the nephelometric method by using Beckman IMMAGE hsCRP reagent. Plasma TNF-α, soluble intercellular adhesion molecule (sICAM-1), soluble vascular cell adhesion molecule (sVCAM-1), MCP-1, IL-1β, IL-6, IL-8, IL-10 and IL-12, adiponectin, leptin, and homocysteine concentration were measured by Multiplex immunoassay. Plasma total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol and triglyceride levels were determined by enzymatic colorimetric assay.

182

183 *Statistical Analysis*

184 Continuous variables with normal distribution were expressed as a mean and standard
185 deviation or alternatively as a median and interquartile range. Categorical variables were
186 expressed as absolute frequency and percentage. Subjects that presented plasma inflammatory
187 biomarker levels exceeding the 99th percentile were considered as having outlier values and
188 excluded from the analyses.

189 A multivariate cluster analysis (K-means) was performed on the normalized data and
190 used to group individuals who had no outlier values for any variable (n=262) according to 11
191 plasma inflammatory biomarker levels. Distances were sorted and observations taken at constant
192 intervals. Patients were separated into two Clusters, representing non-inflammatory (NINF;
193 n=169) and Inflammatory (INF; n=93) clusters.

194 Dairy consumption differences between clusters were analyzed with Somers' D test. The
195 association between dairy consumption (total dairy and specifically milk, yogurt, and cheese)
196 and inflammatory patterns were calculated using the odds ratio of the INF cluster, considering
197 tertiles of dairy consumption, and taking the lowest tertile as the reference category. To test for
198 trend, the tertiles of dairy consumption were considered as continuous in the logistic model.

199 Multiple logistic regression was used to estimate adjusted odds ratio (OR) for
200 independent associations between dairy consumption and INF cluster by adding the confounder
201 variables as covariates. The confounder variables selected for adjustment were age (categorized
202 into 10-year intervals), smoking status and total dietary calorie. All tests were considered
203 significant when $p<0.05$ and were performed using Stata SE version 13 (StataCorp, Texas, USA)
204 and STATISTICA version 9.0 (StatSoft, Inc., Tulsa, USA). All the analyses were conducted with
205 the "survey" option in Stata to account for complex sampling effects.

206

207 **Results**

208

209 *Characteristics of studied population*

210 The mean age of the individuals evaluated was 37.4 years-old. It was mainly composed
211 of males (51%), non-smokers, with more than nine years of education of household heads. Mean
212 *per capita* family income was about USD 212. The prevalence of overweight and obese

individuals were 30.1% and 18.9%, respectively. Approximately 90% of subjects reported insufficient practice of physical activity (Table 1).

Dairy consumption and association with biochemical variables

The median intake of total dairy products was 146.7 g/day. Considering food groups separated, median intake values of milk, cheese and yogurt were 118.8, 10.7 and 10.0 g/day, respectively. Types of most consumed cheese in a descending order, was mozzarella, *queijo prato* (Brazilian kind) cream cheese and parmesan. Most of individuals consumed plain yogurt fruit flavored

When differences in dairy consumption medians were tested among inflammation clusters, NINF exhibited a higher yogurt consumption when compared to INF group. On the other hand, cheese consumption was significantly higher in INF group (Table 2).

In multiple logistic regression model, the OR for INF group in highest tertile of yogurt consumption was 0.28 [95% confidence interval (CI): 0.13 – 0.63] relative to the reference tertile and remained significantly after adjustment for age, smoking status and dietary calorie [OR= (95% CI): 0.34 (0.14 – 0.81)]. Data also pointed to a linear effect (P trend = 0.015), indicating that the chances of finding individuals with a lower inflammatory status increase with yogurt consumption. By the other hand, a significantly higher OR for INF group was observed for middle and highest tertiles of cheese consumption when compared to reference tertile, remaining significantly only for the middle tertile after adjustments (Table 3).

Discussion

The relationship between dairy products and inflammation has been observed in individuals with chronic diseases as obesity, type 2 diabetes, hypertension and cardiovascular diseases. However, in Brazil, where the dairy products consumption is considered low, such relationship was not investigated. The lasted nationally representative Brazilian Household Budget Survey[30] reported the total amount of daily dairy intake is around 1 dairy portion, considered insufficient in comparison to National and International Dietary Guidelines recommendation of 3 dairy portions a day.

By using data from a populational based study, with a proposed sample clusterization into two groups according to their systemic inflammatory pattern [31,32] the overall analysis demonstrated that an increase in yogurt consumption could have a linearly protective effect on inflammation. Otherwise, people who consume cheese seems to have an increased chance to present elevated levels of pro-inflammatory biomarkers. The difference in nature of these associations suggests that despite cheese and yogurt being both considered dairy products, the specificities of each sub-group composition might have a direct effect on inflammatory status, therefore on health.

In this sense, considering the major role that fatty acids play on inflammation is through biomarkers expression modulation, the observed results could be explained based on dairy products fat content. In fact, a significantly positive association between saturated fatty acids, which generally represent around 70% of dairy total fat content and pro-inflammatory biomarkers was been reported [33.] So when comparing a yogurt that has approximately 3% of total fat to a mozzarella or parmesan cheese, which contains about 25-30% and proportionally more saturated fatty acids, their consumption could act most favorable to a pro-inflammatory status. On the basis of food and inflammation, these findings are in compliance with other studies, where a beneficial effect on low-grade systemic inflammation was particularly associated with low-fat dairy[19,34] or specific dietary patterns that these products with a limited content of fat were present[35,36].

It is important to notice that mechanisms regarding the effects of dairy fat content on cardiovascular diseases and mortality, still inconclusive[37,38]. Nevertheless, there is robust evidence demonstrating that lauric, myristic and palmitic fatty acids increase LDL-c[39] levels, which is in accordance with international dietary guidelines recommendations to minimize consumption of saturated fat and stimulate the preference for low-fat dairy products[40,41,42.] In opposition, a recent systemtic review and meta-analysis of butter consumption, a high saturated dairy food, on risk of cardiovascular disases, diabetes and total mortality, suggest a relative small or neutral averall association with the investigated conditions[43]. In addition, recent publications highlight the beneficial effects of yogurt regular consumption on risk factors linked to cardiovascular diseases[44,45,11], including long-term reduced weight gain, what could also indirectly contribute to reaching a lower inflammatory status.

The probable mechanisms by which dairy products may affect low-grade systemic inflammation are not been fully elucidated. The benefits of an adequate dairy consumption are often attributed to the nutrient composition of bovine milk, such as fatty acids, proteins, and micronutrients. Actually, Da Silva and Rudkowska (2015) [46] in a review of dairy nutrients on inflammatory response, suggested that the beneficial effects could be related to specific chain of saturated fatty acids, *trans* –fatty acids and milk proteins, which could have a synergistic effect with micronutrients.

A considerable hypothesis is the potential effect of specific fatty acids, such as the butyric, on attenuating the activity of transcription factor NF-κB47, that regulates gene expression of key inflammatory biomarkers like TNF-α, IL-1β, and IL-6. On the other side, myristic, palmitic and palmitoleic acids may exert the contrary effect up-regulating NF-κB31. Lactoferrin is an additional component of interest to be studied in the scope of immunity regulation, since it is possible that dietary lactoferrin mimic the protective and immune-modulating properties of host lactoferrin supporting the hypothesis that lactoferrin may directly influence immune cells[48].

Moreover, the action of hypotensive peptides from dairy when inhibiting angiotensin-I-converting enzyme leads to a reduced synthesis of angiotensin II that can also promote a less inflammatory status. In this context, angiotensin II has been shown to modulate inflammatory response such as the increase of vascular permeability and expression of cell adhesion molecules[49]. Apparently, dairy calcium content does not exert a direct effect on inflammatory status[19.] On the other hand, high intakes of calcium might be able to stimulate lipolysis[50], therefore inducing favorable changes in adiposity indexes and consequently adipocyte pro-inflammatory activity, which found out to be strictly correlated to biomarkers levels[15]

Few pieces of evidence on literature have studied the relation between dairy consumption and inflammation and none of them had evaluated this correlation focusing specifically on each dairy group. Therefore, the results of the present study aggregate a new perspective on existent evidences and may contribute to explains why current results still inconclusive on this topic as long as an isolated effect of individual dairy food groups, such as yogurt, is probably attenuated when assessed together with other dairy derivatives producing a negative or neutral impact on inflammatory status regulation.

Strengths of the present analysis include the use of a representative sample of adults residents of São Paulo city, dietary data collection through two complementary instruments following strict standard procedures and interpersonal consumption variance adjustment. The limitations of the study are the cross-sectional design that does not allow inferring causality on relationships as well the high prevalence of overweight and obese individuals.

In addition, low dairy consumption by Brazilian population might also have interfered on correlations effect, reducing its strength, which can be further explored by future supplementation studies.

Conclusion

Increasing yogurt consumption might have a protective effect on inflammation, while cheese consumption seems to be associated with a pro-inflammatory status. The results of the present study aggregate a new perspective on existent evidence demonstrating the importance to assess dairy products contribution on diet and its impact on the development of non-communicable diseases and associated risk factors.

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Conflict of Interest

The authors declare no conflict of interest.

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489 *Tables*

490

491 **Table 1**. Characteristics of the study population. Health-Survey of Sao Paulo, 2008.

Variables	N	%
Sex		
Famale	127	49.0%
Male	132	51.0%
*Per capita family income**		
Up to a minimum wage per capita/month	96	37.1%
More than a minimum wage per capita/month	163	62.9%
Household head education		
10 or more years	153	59.1%
0-9 years	106	40.9%
Alcohol consumption		
Yes	146	56.4%
No	113	43.6%
Smoking habits		
Yes/ex-smoker	62	24.0%
No	197	76.0%
Nutritional status		
Underweight	6	2.3%
Eutrophic	126	48.7%
Overweight	78	30.1%
Obese	49	18.9%
Practice of moderate physical activity		
Sufficiently	32	12.4%
Insufficiently	227	87.6%
Inflammatory clusters		
Inflammatory (INF)	95	36.7%
Non-inflammatory (NINF)	164	63.3%

Sample size: n=259. *Amount of minimum wage per capita in 2008 was USD 120.26

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Table 2. Differences in dairy consumption among clusters

Diary consumption	NINF (n=164)	INF (n=95)	p value
Yogurt (g/day)	11.8 (0 – 82.2)	7.7 (0 – 96.3)	**0.004**
Milk (g/day)	114.3 (0 – 378.6)	128.3 (0 – 566.6)	0.981
Cheese (g/day)	9.11 (0 – 51.5)	11.3 (0 – 67.6)	**0.023**
Total dairy (g/day)	141.5 (0 – 402.7)	148.3 (0 – 584.1)	0.950

Values are expressed in median (min-ax).Values in bold are statistically significant ($p<0.05$).

513 **Table 3**. Odds ratio (OR) for INF cluster among tertiles of dairy consumption

Tertiles of dairy consumption	OR (95%CI)	p trend	Adjusted OR (95%CI)	Adjusted p trend
Yogurt		**0.002**		**0.015**
1st tertile (0g – 4.8g)	Ref.		Ref.	
2nd tertile (9.4g – 15.1g)	0.58 (0.31 – 1.1)		0.70 (0.37 – 1.30)	
3rd tertile (23.3g – 96.3g)	**0.28 (0.13 – 0.63)**		**0.34 (0.14 – 0.81)**	
Milk		0.549		0.838
1st tertile (0g – 73.7g)	Ref.		Ref.	
2nd tertile (74.7g – 166g)	1.02 (0.57 – 1.84)		1.12 (0.61 – 2.08)	
3rd tertile (166.1g – 566.6g)	0.80 (0.39 – 1.65)		0.92 (0.42 – 1.98)	
Cheese		0.060		0.052
1st tertile (0g – 7g)	Ref.		Ref.	
2nd tertile (7.1g – 13.7g)	**2.39 (1.09 – 5.24)**		**2.49 (1.09 – 5.75)**	
3rd tertile (13.8g – 67.6g)	**2.00 (1.01 – 3.97)**		2.04 (1.00 – 4.15)	
Total dairy		0.823		0.804
1st tertile (0g – 102g)	Ref.		Ref.	
2nd tertile (103g – 193g)	0.83 (0.45 – 1.56)		0.87 (0.45 – 1.67)	
3rd tertile (193g – 584g)	0.93 (0.47 – 1.84)		1.11 (0.52 – 2.35)	

514 Adjusted logistic models were conducted with age, smoking status and total dietary calorie as
515 covariates. Values in bold are statistically significant ($p<0.05$).

Highlights:

- The relationship between dairy consumption and inflammatory biomarkers is proposed

- The probable mechanisms relies on nutrient content in dairy products

- Yogurt consumption might have a protective effect on inflammation

- Cheese consumption seems to be associated with pro-inflammatory status