

## ASSOCIATION OF ULTRA-PROCESSED FOOD CONSUMPTION WITH ENDOTHELIAL FUNCTION AND ARTERIAL STIFFNESS

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### ABSTRACT

**Objective:** The objective of the study was to assess whether the consumption of ultra-processed foods is associated with endothelial dysfunction and induction of arterial stiffness in eutrophic and overweight individuals. **Methods and Results:** Cross-sectional study in adults (>18 years), with body mass index (BMI) between 18.5 and 30 kg/m<sup>2</sup>, and low to intermediate cardiovascular risk. Endothelial function was measured using the flow-mediated dilation (FMD) technique, and arterial stiffness (PWV, Alx@75, and central blood pressure) was assessed using a standardized oscillometric method. The eating habits of three months were collected with three 24-hour recalls, and the classification for ultra-processed foods was performed according to NOVA and categorized into tertiles for statistical assessment. Thirty-three individuals were assessed, with a mean age of 38.6±10.0 years, 82% female, 85% white, 52% single, 88% individuals with more than 12 years of schooling, and 46% had a formal job. The mean consumption of ultra-processed foods was 700 Kcal/day, and total calorie consumption was 1631 Kcal/day. There was no statistical difference between the groups of consumption of ultra-processed foods and PWV (p=0.538), Alx@75 (p=0.780), central systolic blood pressure (p=0.718), central diastolic blood pressure (p=0.864), and %FMD (p=0.246). **Conclusion:** In eutrophic and overweight adults with low to intermediate cardiovascular risk, consuming ultra-processed foods was not associated with endothelial function as measured by FMD or arterial stiffness.

**Key words:** Food processing. Coronary disease. Vascular endothelium. Vascular Stiffness. Nutrition.

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### RESUMO

**Associação do consumo de alimentos ultraprocessados com função endotelial e rigidez arterial**

**Objetivo:** Avaliar a associação do consumo de alimentos ultraprocessados na função endotelial e na rigidez arterial em indivíduos eutróficos e com excesso de peso. **Métodos e Resultados:** Estudo transversal em adultos (>18 anos), com índice de massa corporal (IMC) entre 18,5 e 30 kg/m<sup>2</sup> e risco cardiovascular baixo a intermediário. A função endotelial foi medida pela técnica de dilatação mediada por fluxo (FMD), e a rigidez arterial (VOP, Alx@75 e pressão arterial central) foi avaliada por meio de método oscilométrico padronizado. Os hábitos alimentares de três meses foram coletados por meio de três recordatórios de 24 horas, e a classificação dos alimentos ultraprocessados foi realizada segundo ANOVA e categorizados em tercís para avaliação estatística. Foram avaliados 33 indivíduos, com idade média de 38,6±10,0 anos, 82% do sexo feminino, 85% brancos, 52% solteiros, 88% indivíduos com mais de 12 anos de escolaridade e 46% tinham emprego formal. O consumo médio de alimentos ultraprocessados foi de 700 Kcal/dia e o consumo calórico total foi de 1.631 Kcal/dia. Não houve diferença estatística entre os grupos de consumo de alimentos ultraprocessados e VOP (p=0,538), Alx@75 (p=0,780), pressão arterial sistólica central (p=0,718), pressão arterial diastólica central (p=0,864) e %FA (p=0,246). **Conclusão:** Em adultos eutróficos e com sobrepeso, com risco cardiovascular baixo a intermediário, o consumo de alimentos ultraprocessados não foi associado à função endotelial medida pela DMF ou à rigidez arterial.

**Palavras-chave:** Processamento de alimentos. Doença cardíaca coronária. Endotélio vascular. Rigidez Vascular. Nutrição.

## INTRODUCTION

Cardiovascular diseases (CVD) are important causes of mortality worldwide (Ribeiro and collaborators, 2016; Nascimento and collaborators, 2018).

Among the main clinical manifestations of CVD are acute myocardial infarction (AMI) and ischemic stroke, both having atherosclerosis as the underlying cause. Atherosclerosis is initiated by endothelial dysfunction (ED) that causes vascular changes including arterial stiffness (AS) (Mozaffarian and collaborators, 2015; Smekal and Vaclavik, 2017).

The vascular endothelium is considered an active and dynamic tissue essential in maintaining blood circulation, regulating vascular tone (control of local dilation and contraction), microvascular permeability, vascular signaling and inflammation (Kiseleva and collaborators, 2018).

Endothelial cells synthesize and release factors that lead to contraction or relaxation of vascular smooth muscle cells (Persson, 2015).

Endothelial dysfunction is an early marker for the development and progression of atherogenic plaques. ED is characterized by a reduction in the bioavailability of endothelium-derived vasodilators, such as nitric oxide, and a relative increase in the bioavailability of vasoconstrictors. This imbalance impairs endothelium-dependent vasodilation (Pennathur and Heinecker, 2007).

AS is characterized by changes in the physical properties of the arterial wall, such as distensibility, compliance, and elasticity. AS affects arterial adaptation to pressure and blood flow in each heartbeat.

Thus, AS increases the risk of arterial block due to hemodynamic stress associated to flow pattern changes in the elastic arteries (Townsend and collaborators, 2015).

Arterial hypertension and dietary factors are among the most frequent risk factors contributing to CVD (Nascimento and collaborators, 2018; Virani and collaborators, 2020).

The consumption of ultra-processed foods (UPF) has become a concern because of its potential contribution to the development and aggravation of hypertension, dyslipidemia, obesity, diabetes mellitus, metabolic syndrome, and cardiovascular diseases (CVD). UPF consumption has been associated with all-

cause mortality (Bonaccio and collaborators, 2020; Nardocci, Polsky and Moubarac, 2020; Donat-Vargas and collaborators, 2021; Lima and collaborators, 2020; Ivancovsky-Wajcman and collaborators, 2021). Nevertheless, it is not known whether UPFs induce early changes in endothelial function and arterial stiffness.

The concern with consuming UPFs is also due to its low nutritional quality. As defined by the NOVA food classification system, UPFs are industrial formulations manufactured with little or no natural food stuffs in their original form, that are composed of refined flours, simple sugars, saturated fats, and typically various types of additives derived from coal or petroleum (Monteiro and collaborators, 2017).

They are attractive for their low price and convenience and are highly palatable; in addition, information on available UPFs is disseminated with aggressive marketing strategies (Moodie and collaborators, 2013).

Knowing the negative impact of the consumption of UPFs and their influence on cardiovascular health (Brasil, 2014; Srouf and collaborators, 2019), we hypothesize that these foods could be significantly associated with early changes in endothelial function and induce arterial stiffness.

Thus, this study aimed to assess whether the consumption of ultra-processed foods is associated with changes in endothelial function and arterial stiffness of eutrophic and overweight individuals with low to intermediate cardiovascular risk.

## MATERIALS AND METHODS

### Study design and population

Cross-sectional study with 33 eutrophic and overweight individuals. The study was conducted at the Vascular Laboratory of the Heart Institute of Santa Maria (ICor), Brazil, from February to September 2019.

### Inclusion criteria

This study included individuals aged between 18 years and 60 years, with Body Mass Index (BMI) between 18.5 Kg/m<sup>2</sup> and 30 Kg/m<sup>2</sup> (eutrophic and overweight) and Global Risk Score (GRS) from low to intermediate cardiovascular risk.

### Exclusion criteria

Subjects who did not undergo lipid profile examination in the previous year, with a diagnosis of moderate or severe liver cirrhosis (CHILD score B or C), severe chronic obstructive pulmonary disease (GOLD score C or D), coronary artery disease (angina pectoris, or positive functional test, or catheterization with lesions > 70% in at least one coronary artery, or signs of previous myocardial infarction), heart failure (EF < 50%) or prior hospitalization for heart failure, persistent or permanent atrial fibrillation, severe peripheral arterial failure (intermittent claudication, or previous revascularization or limb amputation), neurological disease (previous stroke or TIA), active or treated infectious diseases in the last 30 days, Diabetes Mellitus, smokers and history of hospitalization in the two months before the study were excluded from the study.

### Variables studied

This study assessed data on demographics, food intake, laboratory tests, endothelial function, and arterial stiffness.

### Demographics

Study subjects responded to a questionnaire structured by the researchers to assess age, gender, self-reported ethnicity (white, brown, black, or others), marital status (single, married, widowed, divorced, or others), education level (<4 years of study, between 4 and 8 years of study, 9 to 12 years of study, and >12 years of study) and profession (employment with a formal contract, employee without a formal contract, self-employed, homemaker, and retired).

### Food consumption

To determine food habits and food consumption according to the processing level (NOVA), three 24-hour dietary recalls (24hDR) were collected from the study individuals. The first was performed at the beginning of the study, the second after 1.5 months, and the last at the end of the study (after three months). The volunteers reported the quantities, in homemade measures, and the form of preparation of the food consumed. The quantification of the foods listed in each 24hDR was transformed into grams or milliliters.

Subsequently, the amount of each food was converted into kilocalories of energy and grams or milligrams of nutrients in the CalcNut Spreadsheet, based on the food composition table (TACO) (Costa, 2011; NEPA, 2014).

For foods not included in the TACO, the table of the nutritional composition of foods consumed in Brazil (IBGE, 2011) or computed from food labels was used. The foods reported were classified according to NOVA: fresh or minimally processed foods, processed foods, and ultra-processed foods (Monteiro and collaborators, 2017; Brasil, 2014; Louzada and collaborators, 2015). To assess the volunteers eating habits, the mean of each category of NOVA and the total calories of the three 24hDR were calculated. The food consumption pattern was divided into terciles based on the amount of ultra-processed foods.

### Laboratory Exams

Biochemical parameters were measured at the end of the study (the third month of follow-up). Volunteers were asked to fast for 6 hours and venous blood was collected. The lipid profile was obtained using commercial kits with colorimetric methodologies (Bioclin®, Brazil), and the Low-Density Lipoprotein (LDL) was calculated from the Friedewald formula (Faludi and collaborators, 2017). The dosage of nitric oxide (NOx) was performed by the modified Griess method in an automated biochemical analyzer (model BS 380(R) Mindray, Shenzhen, China).

### Endothelial function

Endothelial function was assessed by flow-mediated dilation (FMD) (Pauca, O'rourke and Kon, 2001) 90 days after the initiation of the study. Brachial artery images were obtained using high-resolution ultrasound (PureWare HD15, Philips® with a linear transducer of 7 to 12 Hz). With the patient lying in dorsal decubitus, FMD was measured in the region above the anterior cubital fossa of the right arm and in the longitudinal plane. After placing the pressure cuff on the forearm, it was inflated to 50 mmHg above the systolic blood pressure, and ischemia was maintained for five minutes to cause reactive hyperemia. Arterial imaging was obtained one minute after cuff deflation. All images were obtained at the beginning of the R wave of the electrocardiogram, coinciding with the final period of diastole. Three

measurements were performed to determine the arterial diameter, and the value was validated only when the measurement showed less than 10% variation. The vasodilation response was expressed as a percent change in diameter (%FMD) (Corretti and collaborators, 2002).

The volunteers were instructed not to consume beverages containing caffeine, berries, cocoa, or dark chocolate, supplements with antioxidant activity, and alcoholic beverages for 72 hours before the test. They were also instructed to maintain a regular diet, avoid consuming high-fat foods, and not perform physical activity on the assessment day. Also, the volunteers attended the study site with a 6-hour fast (Corretti and collaborators, 2002).

### Arterial stiffness

Arterial stiffness was measured using an oscillometric device Dyna-MAPA AOP (Cardios®, São Paulo, Brazil). This test is based on obtaining blood pressure in the brachial artery using a cuff and the oscillometric method (Barroso, Barbosa and Mota-Gome, 2020). Central systolic blood pressure (SBP) and central diastolic blood pressure (DBP), amplification index (Alx@75), and pulse wave velocity (PWV) values were obtained (Hametner and collaborators, 2013).

The assessment was performed with the patient sitting comfortably and quietly, using a blood pressure cuff connected to the oscillometric device.

The AS tests were performed before the assessment of endothelial function, and a cardiologist supervised the entire protocol of the present study.

### Ethical aspects

The study followed the rules of Resolution No. 466/12, which regulates

research involving human beings, approved by the Ethics Committee on Research with Human Beings of the Federal University of Santa Maria (CAAE 02246818.2.0000.5346, opinion 3.143.338).

### Statistical Analysis

Data were stored in an Excel spreadsheet and analyzed using the Statistical Package for the Social Sciences – SPSS version 21.0. The normality of the distribution of the quantitative data was verified with the Kolmogorov-Smirnov test, and its description was in the form of mean and standard deviation or median and interquartile range, depending on the distribution. Absolute and relative values described categorical variables. To compare the measurements between the collection times, the Generalized Estimation Equations model was used. The comparison of quantitative measures according to the NOVA classification in tertiles was made with ANOVA and Kruskal Wallis test. Analyses with  $P < 0.05$  were considered significant.

### RESULTS

Thirty-three individuals with a mean age of  $38.6 \pm 10.0$  years (range 25 to 57 years) were assessed; most were female (81.8%), caucasian (84.8%), single (51.5%), and with more than 12 years of schooling (87.9%). Most of the participants had a formal job (45.5%), presented a low risk for cardiovascular events, according to the Global Risk Score (84.8%), stated that they had no family history of cardiovascular disease (66.7%) or smoking (87.9%), and reported alcohol consumption (84.8%). Patients who were former smokers ( $n=4$ ) smoked for approximately 16.5 years. Participants had, on average, a normal BMI ( $24.9 \pm 2.6$  kg/m<sup>2</sup>), practiced physical activity (78.8%), mostly for more than 150 minutes per week (60.6%) (Table 1).

**Table 1** - Sample characteristics regarding identification, health, and lifestyle data, at baseline.

DEMOGRAPHICS	n (%)
Gender	
Female	27 (81.8)
Male	6 (18.2)
Ethnicity	
White	28 (84.8)
Black	1 (3.0)
Brown	4 (12.1)
Marital status	
Single	17 (51.5)
Married	14 (42.4)
Separated	1 (3.0)
Divorced	1 (3.0)
Educational level	
Literate	1 (3.0)
4 to 8 years	1 (3.0)
9 to 12 years	2 (6.1)
More than 12 years	29 (87.9)
Occupation	
Formal employment	15 (45.5)
Informal employment	11 (33.3)
Homemaker	2 (6.1)
Retired	1 (3.0)
Student	4 (12.1)
Weight status	
Eutrophic	50%
Overweight	50%
Health	
Global Risk Score	
Low cardiovascular risk	28 (84.8)
Intermediate cardiovascular risk	5 (15.2)
Family history of cardiovascular disease	
No	22 (66.7)
Yes	9 (27.3)
Does not know	2 (6.1)
Lifestyle	
Former smoker	4 (12.1)
Smoking time in years (mean±SD)	16.5±7.0
Consumes alcoholic beverages	28 (84.8)
Physical activity practitioner	26 (78.8)
Physical activity time <150 minutes/week	6 (18.2)
	20 (60.6)

Note. Data are mean ± SD or number (%) of patients.

Food consumption according to processing level is presented in Table 2, and

the variables showed no statistical difference over the study time.

**Table 2** - Food consumption according to processing level, at baseline, after 1.5 months, and 3 months of patients with low to intermediate cardiovascular risk, eutrophic and overweight.

Nutrients	Baseline	After	After	p
	(Mean±SD)	1.5 months (Mean±SD)	3 months (Mean±SD)	
Fresh and minimally processed (kcal)	793.2±72.0	836.8±79.0	859.2±73.4	0.706
Fresh and minimally processed (%)	51.8±3.3	50.1±3.9	55.7±3.8	0.431
Processed (kcal)	112.5±28.4	100.4±31.4	91.4±18.7	0.832
Processed (%)	6.5±1.7	5.4±1.3	6.3±1.5	0.852
Ultra-processed (kcal)	668.3±75.4	792.1±101.7	640.1±91.1	0.407
Ultra-processed (%)	42.0±3.5	44.5±4.0	38.0±3.5	0.414
Total Kcal	1,574.1±1111.7	1,729.2±112.7	1,590.6±112.5	0.493

Note. Data are mean ± SD. P: Generalized Estimation Equation Model.

The consumption of UPFs stratified according to intake tertiles showed no statistical difference over time on biochemical parameters tested, central diastolic blood

pressure, central systolic blood pressure, AIX@75-amplification index, PWV, %FMD, and anthropometric data (Table 3).

**Table 3** - Biochemical variables, arterial stiffness, and endothelial function according to tertiles of kcal consumption of ultra-processed foods.

Variables	Consumption of ultra-processed foods (kcal)			p <sup>a</sup>
	Tertile 1 N=11 (Mean±SD)	Tertile 2 N=11 (Mean±SD)	Tertile 3 N=11 (Mean±SD)	
<b>Biochemistry</b>				
Total Cholesterol (mg/dL)	218.8±39.8	211.6±33.0	202.4±42.7	0.612
Triglycerides (mg/dL)	90.4±56.4	94.5±34.5	106.9±33.4	0.645
LDL (mg/dL)	130.5±29.4	127.6±31.5	112.0±34.6	0.355
HDL (mg/dL)	70.3±20.8	65.2±20.0	69.2±14.3	0.797
NOx (µmol/L)	151.9±82.1	143.7±77.3	138.5±34.1	0.897
<b>Arterial stiffness</b>				
Central systolic blood pressure (mmHg)	105.7±8.0	102.6±9.4	102.2±8.0	0.718
Central diastolic blood pressure (mmHg)	72.6±7.4	74.9±9.0	73.3±9.4	0.864
AIX@75-Amplification Index (%)	19.6±11.9	23.7±10.4	21.4±12.1	0.780
Pulse wave velocity (m/s)	6.1±0.7	5.6±0.8	5.7±1.1	0.538
<b>Endothelial function</b>				
%FMD (median and IR)	3.72 (-0.32 and 5.11)	3.22 (1.81 and 7.51)	1.08 (-0.26 and 5.35)	0.246 <sup>b</sup>
<b>Anthropometrics</b>				
Weight (kg)	64.5±8.7	69.4±7.2	65.5±7.8	0.324
BMI(kg/m <sup>2</sup> )	24.5±2.2	26.3±2.2	24.3±3.0	0.127

**Legend:** BMI: Body Mass Index; SD: standard deviation; IR: interquartile range; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NOx: nitric oxide; FMD: flow-mediated dilation. P: a: ANOVA test; b: Kruskal-Wallis test. Intertertile ranges of ultra-processed foods: Tertile 1 = 263.46 to 468.59 kcal; Tertile 2 = 468.60 to 860.41 kcal; Tertile 3 = 860.42 to 1,593.22 kcal. Note: the missing data were 10 for central systolic and diastolic blood pressure; reflection coefficient; AIX@75; pulse wave velocity.

## DISCUSSION

In this study, we have investigated whether the consumption of UPFs was associated to FMD-endothelial dysfunction and arterial stiffness in individuals with low to intermediate risk for cardiovascular events and who were eutrophic or overweight. Interestingly no association was found between consuming up to 40% of daily caloric intake from UPFs and endothelial function or arterial stiffness.

To the best of our knowledge, this is the first study assessing the association between the consumption of UPFs and endothelial function in humans. In our study, the changes in FMD did not indicate an association with the consumption of 40% of calories of the diet as UPF.

It is known that nutrient intake can help improve or impair endothelial function. Thus, the concern of diet interaction with endothelial dysfunction has been a relevant subject of study, because diet studies have shown physiological effects of the vascular endothelium. Indeed, effects that are independent predictors of cardiovascular risk, such as reduction of vasodilation and induction of pro-inflammatory or prothrombotic state, have been reported (Persson, 2015; Rajendran and collaborators, 2013). In the study by Davis and collaborators, 2017, consuming the Mediterranean diet was associated with an improved endothelial function (measured by the %FMD).

The Mediterranean diet, based on the consumption of fresh or minimally processed foods, was associated with improved endothelial function and with a greater balance of vascular homeostasis in individuals with coronary heart disease, even with severe endothelial dysfunction (Yubero-Serrano and collaborators, 2020). The benefits of polyphenol-rich diets on the prevention of CVD, including inhibition of endothelial dysfunction and promotion of vascular relaxation have also been reported (Yamagata, 2019).

We did not find an association between the consumption of UPFs and endothelial function. However, a relationship between higher consumption of UPFs and the occurrence of cardiovascular health problems has been recently reported. The study by Srour and collaborators, 2019, showed that the higher consumption of UPFs was related to higher risks of developing cardiovascular, coronary, and cerebrovascular diseases. Blanco-Rojo

and collaborators, 2019 and Kim, A Hu, and Rebholz, (2019), observed that a frequent intake of UPFs is associated with an increased risk of all-cause mortality.

The continuous consumption of ultra-processed foods can also cause, over the years, an increase in peripheral blood pressure, a higher incidence of diabetes mellitus, obesity, metabolic syndrome, as well as an increase in total cholesterol and LDL cholesterol (Nardocci, Polsky and Moubarac, 2020; Mendonça and collaborators, 2016; Poti, Braga and Qin, 2017; Rauber and collaborators, 2020).

In a systematic review of cohort studies in children and adolescents, at least one association was found between ultra-processed foods and components of the metabolic syndrome (Frías and collaborators, 2023).

In our study, a diet with a 40% caloric intake from UPFs shared with intakes with other healthy food sources, such fresh and minimally processed foods (see Table 2), does not affect endothelial function.

In our study central systolic blood pressure and central diastolic blood pressure, Alx@75, and PWV did not show a significant association with the consumption of ultra-processed foods.

Our findings align with a study in 40 young normotensive adults, that reported no association between UPFs consumption and PWV or Aix (Smiljanec and collaborators, 2020).

Arterial stiffness is characterized by changes in the physical properties of the arterial wall, such as distensibility, compliance, and elasticity.

Distinguishing changes in the arterial wall have functional implications since they affect how arteries adapt to the pressure and blood flow in each heartbeat (Townsend and collaborators, 2015).

An increase in arterial stiffness is a main factor in aging and diseases associated with the cardiovascular system, such as diabetes, atherosclerosis, and chronic kidney disease (Townsend and collaborators, 2015; Fowkes and collaborators, 2013; Mozos and collaborators, 2017; Avolio, 2013).

Some studies have shown a relationship between consuming certain nutrients, bioactive compounds, or foods and central blood pressure levels. Central arterial pressure, as well as PWV and Alx@75 are well-established markers of central hemodynamics and arterial stiffness (Palatini and collaborators,

2011; Sun and collaborators, 2018). A study by Jennings and collaborators, (2012), examined the association between flavonoid intake and arterial stiffness, central blood pressure, and atherosclerosis, to find that anthocyanins had a protective effect on central blood pressure.

The lipid profile of the participants' serum was not changed according to the consumption of UPFs.

In a national study conducted with 327 high school adolescents, followed for two months, a direct association was found between the consumption of UPFs and levels of triglycerides and dyslipidemia; that is, UPFs consumption led to a worsening in the biochemical parameter profile of young people (Lima and collaborators, 2020).

Indeed, total cholesterol and LDL levels were found associated with the consumption of UPFs (Poti, Braga and Qin, 2017). However, the low number of prospective studies prevents strong conclusions (Poti, Braga and Qin, 2017).

The NOx levels of the study subjects were not associated with UPF. NOx is a free radical, second messenger that measures several physiological functions, including vasodilation, inhibition of platelet aggregation, neurotransmission, learning and memory formation, microbial and antitumor activity (Dusse and collaborators, 2005).

The reduction in the bioavailability of nitric oxide, observed in the physiology of aging and atherosclerosis, is also a factor promoting increased vascular tone and reduced vascular contractility (Brozovich and collaborators, 2016). However, no association between NOx and UPFs consumption was found in the literature.

The limitations of our study include a small sample size and a short follow-up that reached three months. Larger studies and diets with higher amounts of UPF content are needed to establish the relationship of UPFs with early vascular dysfunction.

## CONCLUSION

In individuals with low to intermediate cardiovascular risk, eutrophic and overweight, we found no association between consuming a diet with up to 40% of caloric content derived from UPFs and endothelial function or arterial stiffness.

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## DECLARATION OF COMPETING INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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## AUTHOR CONTRIBUTION

Gabriele F.S. Costa: drafting of manuscript, and critical revision and approval of the final version; Diego Chemello: conception of the research, interpretation of data, drafting of manuscript, and critical revision and approval of the final version; Arielen Ferigollo: conception of the research, data collection, and critical revision and approval of the final version; Tábata Pavão: data collection, critical revision and approval of the final version; Jamile Ceolin: analysis and interpretation of data, critical revision and approval of the final version; Joana Rodrigues: data collection, and critical revision and approval of the final version; Marco A.L. Saffi: analysis and interpretation of data, critical revision and approval of the final version; Ângela G. Batista: critical revision and approval of the final version; Carolina S. Stein: biochemical analyses, critical revision and approval of the final version; Rafael N. Moresco: biochemical analyses, critical revision and approval of the final version; Luis U. Signori: critical revision and approval of the final version; Vera E. Closs: analysis and interpretation of data, critical revision and approval of the final version; Lina Badimon: drafting of manuscript, critical revision and approval of the final version; Patrícia Chagas: conception of the research, interpretation of data, drafting of manuscript, and critical revision and approval of the final version.



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