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Brazil nut consumption reduces trimethylamine-n-oxide (TMAO) and inflammation in a patient with cardiorenal syndrome: a brief communication

*Consumo de Castanha-do-Brasil reduz o N-óxido de
trimetilamina (TMAO) e a inflamação em um paciente com
síndrome cardiorrenal: uma comunicação breve*

Abstract

Introduction: Gut dysbiosis is a common feature in cardiorenal syndrome, and it is linked to increased uremic toxins, like trimethylamine-n-oxide (TMAO), which are involved with inflammation and cardiovascular mortality. Brazil nut (typical Brazilian seed) has anti-inflammatory and antioxidant properties, but there is no evidence of the effects of gut microbiota modulation and reduction of uremic toxins. **Objective:** To assess the impact of Brazil nut consumption on TMAO levels and inflammation markers in a patient with cardiorenal syndrome. **Methods:** A coronary artery disease patient (66 years and BMI, 26 kg/m²), stage-3 of CKD (eGFR 36 mL/min), receive done Brazil nut per day for three months. **Results:** TMAO plasma levels and NF-κB mRNA expression were reduced, and glutathione peroxidase (GPx) activity increased after this intervention. **Conclusion:** Brazil nut prescription may be a promising strategy to mitigate complications related to the cardiorenal syndrome. This case supports the concept of "Food as medicine" targeting the uremic phenotype in cardiorenal syndrome.

Keywords: Cardiorenal syndrome. Trimethylamine-n-oxide. Inflammation. Brazil Nut.

Resumo

Introdução: A disbiose intestinal é uma característica comum na síndrome cardiorrenal e está associada ao aumento de toxinas urêmicas, como o N-óxido de trimetilamina (TMAO), que estão envolvidas com a inflamação e mortalidade cardiovascular. A castanha-do-Brasil (semente típica brasileira) possui propriedades anti-inflamatórias e antioxidantes, mas não há evidências dos seus efeitos na modulação da microbiota intestinal e redução de toxinas urêmicas. **Objetivo:** Avaliar o impacto do consumo de castanha-do-Brasil nos níveis de TMAO e marcadores de inflamação em um paciente com síndrome cardiorrenal. **Métodos:** Um paciente com doença arterial coronariana (66 anos e IMC, 26 kg/m²), estágio 3 da DRC (TFGe 36 mL/min), recebeu uma castanha-do-Brasil por dia durante três meses. **Resultados:** Os níveis plasmáticos de TMAO e a expressão de mRNA de NF-κB foram reduzidos e a atividade da glutatona peroxidase (GPx) aumentou após esta intervenção. **Conclusão:** A prescrição de castanha-do-Brasil pode ser uma estratégia promissora para mitigar as complicações relacionadas à síndrome cardiorrenal. Este caso apoia o conceito de "alimento como remédio" visando o fenótipo urêmico na síndrome cardiorrenal.

Palavras-chave: Síndrome cardiorrenal. N-óxido de Trimetilamina. Inflamação. Castanha-do-Brasil.

INTRODUCTION

Cardiovascular and kidney diseases are closely associated, and this heart–kidney interaction involves several regulatory hormones, inflammatory molecules, oxidative stress, and gut dysbiosis. It has been reported as a cardiorenal syndrome.¹ Gut dysbiosis is associated with increased uremic toxins, mainly contributing to the cardiorenal syndrome. In addition, gut dysbiosis is a common complication in chronic kidney disease (CKD), and impaired renal function is associated with accumulating these toxins, which promotes adverse cardiac effects.^{1,2}

Trimethylamine-N-oxide (TMAO) is a uremic toxin produced by the fermentation of choline, carnitine, and betaine from food such as red meat, fish, eggs, and spinach.^{3,4} TMAO is considered a cardiovascular biomarker, and as such, it is associated with mortality and atherosclerosis plaque formation in CKD.^{5–7} TMAO can be associated with vascular calcification via the activation of inflammatory pathways, such as the nuclear factor kappa B (NF- κ B) pathway, and consequently with the progression of the cardiorenal syndrome.⁸ In this context, dietary interventions rich in bioactive compounds and nutrients have been considered an excellent strategy to modulate gut microbiota and prevent TMAO-induced disorders.⁹

Brazil nut is the source of selenium, magnesium, copper, zinc, unsaturated fatty acids, and fiber and also polyphenols, such as flavonoids and phenolic compounds.^{10,11} Brazil nuts can mitigate oxidative stress and inflammation in patients with CKD via the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway.^{12–14} Here, we described a case of a cardiorenal patient who received a Brazil nut supplementation for three months.

MATERIALS AND METHODS

Diagnosis and medical treatment

In July 2015, a 66-year-old, married, sedentary Brazilian man was admitted to the Nuclear Medicine Section at Hospital Universitário Antônio Pedro. Initial evaluation revealed a coronary artery disease (ischemia and fibrosis) confirmed during myocardial perfusion scintigraphy. A secondary evaluation showed hypertension and overweight (BMI 26 kg/m² and waist circumference 106.5 cm) as well as stage 3 of CKD with eGFR of 36 mL/min/1.73 m². The current medications were atenolol, furosemide, and clonidine hydrochloride. He quit smoking 42 years ago and denied alcoholic drinks and illicit drugs. The patient obtained full informed consent to report his case in writing. This patient was enrolled in the study on Brazilian nut consumption's effects on the expression of factors that regulate inflammation in patients with coronary artery disease (Brazil trial registration number: RBR-5MZZD4). The Faculty of Medicine Ethics Committee approved the study protocol at Fluminense Federal University (n° 3.223.250).¹⁵ He was excluded for not according to the inclusion criteria (stage 3 of CKD).

Nutritional assessment

Food intake was attained using a 24-h food recall and analyzed by DietWin® software. Betaine intake was determined by the United States Department of Agriculture Database (USDA) and carnitine following the database of Rebouche & Engel.¹⁶ He did not receive any nutritional prescriptions, and his diet was a breakfast of whole-grain bread, white cheese, bananas, coffee with milk and sweetener (around 18 drops), lunch, and dinner of rice, beans, red meat, and salads. He used to drink coffee, milk, water, juice, and soft drinks. His dietary assessments were approximately 1600 kcal/day, 1.16 g/day of protein, 62% of carbohydrate, 17% of lipids, 27.8g of total fiber, 85.0 µg/day of selenium, 315 mg/day of choline, 193.1 mg/day of betaine, and 639.0 mg/day of carnitine.

Brazil nut intervention

A nutritionist prescribed Brazil nuts daily for three months, and he was advised to continue his ordinary eating habits and not consume other nuts during this period. The dose and time of the prescribed nut were based on previous studies in patients with CKD and coronary artery disease.^{12-15,17-19} One Brazil nut contained 36.7 kcal, 0.8g of protein, 0.5g of carbohydrates, 3.5g of lipids and 291µg of selenium¹⁷ which fulfils the recommendation of selenium dietary reference intake (DRI).²⁰

Biochemical analyses

The routine biochemical parameters including lipids profile, glucose, C-reactive protein (CRP), Castelli's index I and II, urea, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined by Bioclin® kits. Low-density lipoprotein (LDL) was calculated by the Friedwald equation.²¹ GPx activity was measured by ELISA kits (Cayman Chemical, Ann Arbor, MI, USA, no 703102-96). NF-kB mRNA expression was evaluated from peripheral blood mononuclear cells using quantitative real-time polymerase chain reaction.¹² Determination of TMAO, choline, and betaine levels was performed by LC-MS/MS, according to Missailidis et al.²²

RESULTS

Routine biochemical parameters results are shown in Table 1. The lipid profile was improved after intervention, and choline levels were decreased.

Table 1. Biochemical parameters before and after three months of Brazil nut supplementation in a cardiorenal patient from Niterói, Rio de Janeiro in 2015.

Parameters	Before	After
Total Cholesterol (mg/dL)	191.0	126.0
High-density lipoprotein (mg/dL)	39.0	44.0
Low-density lipoprotein (mg/dL)	100.6	49.8
Triglycerides (mg/dL)	257.0	161.0
Castelli Index I (mg/dL)	4.9	2.9
Castelli Index II (mg/dL)	2.6	1.1
Urea (mg/dL)	69.0	78.0
Creatinine (mg/dL)	2.0	2.2
Glomerular filtration rate (mL/min)	35.7	31.9
Aspartate aminotransferase (mg/dL)	14.0	11.0
Alanine aminotransferase (mg/dL)	9.0	5.0
Choline (ng/µL)	11.0	9.6
Betaine (ng/µL)	7.8	7.5

Table 2 shows the values regarding uremic toxin, inflammation markers, and antioxidant enzymes. CRP levels were reduced by 75%, NF- κ B gene expression decreased by 28% and TMAO plasma levels were reduced by 47% after consumption of Brazil nut intervention. Also, GPx activity increased by 30% after supplementation.

Table 2. TMAO levels, inflammatory and antioxidant parameters before and after three months of Brazil nut supplementation in a cardiorenal patient from Niterói, Rio de Janeiro in 2015.

Parameters	Before	After
C-reactive protein (mg/dL)	3.00	0.76
Transcription factor- κ B mRNA expression	0.71	0.51
Trimethylamine N-oxide (ng/ μ L)	0.45	0.24
Glutathione peroxidase (mg/dL)	50.90	68.70

DISCUSSION

This case report demonstrated that Brazil nut consumption might be a simple and essential strategy to mitigate inflammation and reduce levels of uremic toxins produced by the gut microbiota. Brazil nut consumption for three months decreased TMAO and CRP levels, NF- κ B mRNA expression, and increased GPx activity.

TMAO is a uremic toxin and constitutes a cardiovascular risk factor that accumulates in plasma when renal function declines and increased TMAO levels can predict mortality.^{5,23-27} It has been demonstrated that TMAO promotes foam cell formation, atherosclerosis, and aortic lesions and stimulates platelet activity, favoring thrombus formation.²⁸⁻³⁰ TMAO also promotes vascular inflammation through the signaling of Mitogen-Activated Protein Kinase and the NF- κ B pathway.³¹ Thus, several studies have aimed to modulate TMAO levels with bioactive compounds and nutrients to reduce cardiovascular risk.³²⁻³⁵ However, research concerning dietary patterns or bioactive nutrients on TMAO production in patients with the cardiorenal syndrome is limited.

One of the pathways proposed to reduce the generation of TMAO would be the modulation of gut microbiota and inhibiting Trimethylamine-producing bacteria.³⁴ Indeed, several studies observed a reduction in TMAO levels through gut microbiota modulation after dietary intervention.³²⁻³⁴ Another pathway proposed is via polyphenols that can have antioxidant effects and donate electrons to TMAO, leading to its transformation into Trimethylamine (TMA) again.³³ In this context, Brazil nuts are rich in phenolic compounds and a great source of selenium, related to gut microbiota modulation and antioxidant effects.³⁶⁻³⁹ Thus, the beneficial effects of Brazil nut on TMAO levels were possibly due to gut microbiota modulation and the antioxidant capacity of this nut that may have contributed to donating electrons to TMAO. Indeed, this antioxidant effect was observed with the increase of GPx activity, an antioxidant enzyme associated with reducing free radicals.⁴⁰ Several other studies have shown that Brazil nut supplementation increased GPx activity.^{13,14}

Moreover, previous studies have suggested that TMAO is involved in the NF- κ B pathway activation.^{8,31} This case study also explored the potential effect of Brazil nut consumption in this pathway. The results

showed a beneficial effect after intake of Brazil nut, which corroborates a previous study, which showed a reduction in NF- κ B mRNA expression after three months of Brazil nut supplementation.¹² Brazil Nut promoted several benefits for this patient. Thus, Brazil nuts may be a potential nutritional strategy to mitigate complications in patients with cardiorenal syndrome. This case illustrates the possibility of using “Food as medicine” to target the uremic phenotype in cardiorenal syndrome.

We should note that our findings concerning a single case that preclude any firm conclusions regarding the general effect of Brazil nuts in patients with cardiorenal syndrome. However, it is essential to note that the patient's eating habits did not change during the supplementation period, and his medications remained the same before and after Brazil nut consumption; this may suggest that these parameters did not influence the observed effects.

CONCLUSION

In this individual, Brazil nut intake for three months reduced TMAO levels, mitigate the NF- κ B-response, and increased the total antioxidant activity by increasing GPx- activity.

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Contributors

Coutinho-Wolino KS and Stockler-Pinto MB participated in the idealization of the study design, data collection, analysis and interpretation, study writing and final review, and approval of the manuscript for submission. Cruz BO, Cardozo LFME, Mesquita CT, and Mafra D participated in the collection, analysis, and interpretation of data, in the writing of the study and final review, and in the approval of the manuscript for submission.

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