The Effect of Caffeinated and Decaffeinated Coffee Consumption on Biochemical and Cardiac Parameters among Brazilians with Type 2 Diabetes

Danielly Mesquita Figueiredo[1], Carlos José Pimenta[1], José Luís Contado[1], Maria Do Livramento De Paula[2], Roberto Wagner Júnior Freire De Freitas[3] and Márcio Flávio Moura De Araújo[4*]

[1]Federal University of Lavras (UFLA), Lavras, Brazil

[2]Federal University of Maranhao (UFMA), Sao Luis, Brazil

[3]Oswaldo Cruz Foundation (FIOCRUZ), Eusebio, Ceara, Brazil

[4]University for International Integration of the Afro Brazilian Lusophony (UNILAB), Redencao, Brazil

Research Article

ABSTRACT

Aim: To analyze the effect of consuming caffeinated and decaffeinated coffee (coffea arabica) on biochemical and cardiac parameters among Brazilians with type 2 diabetes.

Method: A random sample of 42 volunteers, in good cardiovascular condition, was divided into three groups: caffeinated coffee, decaffeinated coffee, and non-consumers.

Results: After 6 months of monitoring, a reduction in glycemia ($p<0.05$) was observed in the caffeinated coffee group, and of triglycerides, among the moderate consumers ($p<0.05$). Among coffee consumers, independent of the type, there was reduction in platelets ($p<0.05$) and glycosuria. Both at baseline and at the end of the study, the active participants with moderate coffee consumption presented lower values of thyroxine ($p<0.01$). On the other hand, those who did not consume coffee presented higher values in miles walked ($p<0.05$) and in the volume of oxygen consumed per minute ($p<0.01$) at the end of the study. We also observed that coffee consumers, independent of type, presented lower metabolic equivalent values ($p<0.01$).

Conclusion: Among the consumers of caffeinated coffee, there was improvement in the serum levels of glycemia, triglycerides and platelets. Among non-consumers, however, there was improvement of some cardiac indicators, such as miles walked and volume of oxygen consumed per minute.

INTRODUCTION

In the last 20 to 30 years, many researchers have validated the use of phytotherapeutic substances in the management of type 2 diabetes (DM2) in human beings and animals. In the United States, for example, around one third (34%) of adult patients with DM2, equivalent to 3.6 million people, use alternative and/or complementary medicine for

this purpose [1]. The single or combined use of these products with drugs has shown benefits such as modulation in the metabolism of carbohydrates, recovery of function of pancreatic beta cells, and in insulin resistance. Furthermore, antioxidant properties and reduction in cardiovascular risk have been ascertained [2-5].

Coffee, for example, is one of the main natural products triggering debates regarding its effects on human health. It is one of the drinks consumed most worldwide, particularly in South America; in Brazil, for example, the estimated consumption is of 81 L/inhabitant/year [6,7].

Besides its stimulant property, due to the presence of caffeine, coffee contributes through the ingestion of bioactive compounds such as the phenolic agents (especially chlorogenic acid [caffeoylquinic acid]). These are related to many of the effects which benefit human health: antioxidant, anti-mutagenic, chemopreventive, antiatherogenic and hepatoprotective action [8]. In the cardiovascular system, caffeine and the coffee diterpenes (cafestol and kahweol) help in issues such as arterial hypertension, endothelial inflammation, dyslipidemias, ischemias, arrhythmias, coronary diseases and neurovascular diseases [6,7].

Regarding the issue of DM2, this drink has given rise to major debates on this question. Recent meta-analyses consulted indicate that coffee consumption is positive in the prevention of DM2 [9-11]. The consumption of at least two cups of caffeinated or decaffeinated coffee per day (each cup containing approximately 50 ml) reduces the risk of developing DM2 by 12% and 11% respectively [10]. In both versions, the relative risk for DM2 is smaller [9]. There is also an inverse relation between coffee consumption and metabolic syndrome (prediabetes) [11].

The process which clarifies the prevention of DM2 based on coffee consumption presents multiple mechanisms which have been widely disseminated in the literature. Even so, it remains uncertain whether people with diabetes can use coffee as a therapeutic tool against the progression of this pathology [12].

This may be partly explained by the fact that most publications investigating the effect of coffee consumption focus, rather, on its role in the prevention or risk of DM. To the best of our knowledge, at the time of writing no data have been published regarding the biochemical and cardiac effects in people with DM2 using caffeinated or decaffeinated coffee, or indeed those who consume neither.

Furthermore, many health professionals, such as endocrinologists, nurses and biologists emphasize the need for further studies with natural products, with rigorous methodological designs, the aim being to list evidence regarding these products' clinical efficacy, safety, and mechanism of action [1,2]. This study's objective, therefore, was to analyze the effects of the consumption of caffeinated and decaffeinated coffee on biochemical and cardiac parameters in a sample of people with DM2 in Brazil.

MATERIALS AND METHODS

Study Design

This is an experimental study undertaken with patients with DM2, in four primary health care services in the cities of Lavras and Bom Sucesso, in the Brazilian state of Minas Gerais. The study respected the principles of the Helsinki Declaration, and was approved by the committee for ethics in research with human beings of the Federal University of Lavras (UFLA), under protocol number: 108589.

All the participants signed the terms of free and informed consent prior to the holding of the study. At the end of the study, all of the clinical and laboratory results were made available to the patients free of charge.

Population and Sample

The study population was made up of adult patients with DM2, of both sexes. Approximately 100 patients were recruited, through interviews held on local television and radio stations, as well as seminars on the use of coffee in health provided in the above-mentioned health services. The following inclusion criteria were established: to be aged ≥ 18 years old, not to be insulin-dependent, to have good cognitive capacity (not to suffer from mental problems or dementia, or to use psychotropic substances), to have had DM2 for at least six months and to be in good cardiovascular condition (a cardiologist's report was required, indicating good physical aptitude and absence of coronary diseases, valvular heart diseases, arrhythmias or ischemias).

The patients underwent a physical examination, cardiovascular evaluation (ergometric test monitored by a cardiologist) and analysis of their medical records in order to check that they complied with the eligibility criteria.

Those patients who did not participate in all the stages of the study were removed from the study. As a result, the sample culminated in 42 eligible persons, allocated randomly in the following way: 18 individuals consuming caffeinated coffee, 18 consuming decaffeinated coffee, and six individuals' not consuming coffee.

The sample was mainly composed of patients with DM2 who were female (54.7%), hypertensives (83.3%), overweight (42.8%), non-smokers (90.3%), and aged between 42 and 77 years old (mean of 59.3 ± 9.1 years old). Regarding waist circumference, 57.2% and 42.8% of the men and women, respectively, had high values.

Measurements

At the start of the study, the participants were classified according to level of physical activity and consumption, or not, of coffee. Participants who undertook physical activity fewer than three times a week were considered sedentary. Coffee consumption level, in its turn, was established as low (up to two cups a day), moderate (3 to 4 cups a day) and high (>4 cups a day).

Variables related to the metabolic control of DM2 (plasma glycine [PG], total cholesterol [TC], low density lipoprotein-cholesterol [LDL-c], very low density lipoprotein-cholesterol [VLDL-c], high density lipoprotein-cholesterol [HDL-c], triglycerides (TG), systolic arterial pressure [SAP], diastolic arterial pressure [DAP], waist circumference [WC] and body mass index [BMI]), cardiovascular evaluation (ergometric test) and biochemical evaluation (blood count, urine examination and thyroid hormones) were measured. The anthropometric variables were measured every two months, while the others were measured at baseline and six months later.

Data Collection

The clinical and anthropometric evaluation were carried out in the health services, while the cardiological evaluation and laboratory tests took place in a cardiology clinic and biochemical analysis laboratory on a separate occasion.

All the participants fasted for 12 h prior to venipuncture. Furthermore, they were also advised to avoid the consumption of coffee for 72 h prior to the taking of the blood sample. In the assessment of the biochemical parameters and the parameters related to control of DM2, commercial kits were used, sold by the company Labtest Diagnystica S/A®, using standardized techniques based in enzymatic and colorimetric methods through the use of spectrophotometry, following the manufacturer's recommendations. The concentrations were determined using the automatic biochemical analyzer, while the findings for LDL-c were calculated using Friedewald's formula.

During the ergometric test, the Ellestad Protocol was adopted. The test was interrupted when the patient presented intense physical tiredness and submaximal cardiac frequency (CF) was reached, a marked increase in SAP and absence of vasodilator effects in relation to DAP. The data obtained after the subjects' ergometric tests were: test duration; distance walked; volume of oxygen consumed per min (VO2); Metabolic Equivalent (MET); CF; SAP and DAP.

The individuals were weighed on digital scales accurate to 0.1 kg, of the Welmy® brand, with an attached anthropometer, with a capacity of up to 200 kg, with their shoes off and wearing light clothes. BMI was established using the calculation of weight (kilograms)/(height) [2] in meters. Measurement of WC was undertaken at the level of the navel using a flexible tape measure without compressing the tissues.

The reference values used in the analysis of the laboratory and anthropometric data were based in the Guidelines of the Brazilian Society of Diabetes (SBD) 2015-2016 [13].

Experiment

Following the division of the volunteers, these participated in seminars on the type and appropriate preparation of their coffee. In this way, the guidance was to use three measures of coffee, using a specific measuring spoon (each measure equivalent to 1 teaspoon–15 mls or 12 g) per 500 mls of hot water, and to filter the coffee using filter paper. Those who wished to have their drinks sweetened were advised to use up to 5 drops of sweetener.

The participants in the 'normal' coffee group (caffeinated) received "*coffea Arabica*", produced in the vegetable products laboratory of the Department of Food Sciences of the UFLA. The other group was provided with a product of the same type of coffee, decaffeinated, of the Melita® brand. In both cases, the coffee made available for six months was from the same lot and had the seal of purity of the Brazilian Coffee Roasters Association (ABIC).

The participants were advised to consume one dose of their type of coffee at least twice a day. They were also advised not to consume other products containing caffeine (chocolate, cola type soft drinks, mate tea and tea) during the course of the study, so that there would be no interference in the results.

Statistical Analysis

The experiment followed an entirely randomized design, in a factorial design, with additional factors and treatments. The factors included were: (1) level of activity (2) (Active; Sedentary), level of coffee consumption (3) (low, moderate and high) and type of coffee (2) (normal and decaffeinated). The treatments included were active person not consuming coffee and sedentary person not consuming coffee.

In each period of the experiment (time 0 and time 6 months), tests were run on the study participants, the experiment being undertaken using 14 treatments; each treatment was applied on three different individuals with DM2, that is to say, three repetitions, making a total of 42 individuals.

Due to the need for the presence of a control group, considered as an additional treatment, and of the data which did not fit into a conventional analysis structure, the *"non-consumer of coffee, (sedentary and active)"* was adopted as additional treatment. In order to analyze the additional treatment, a contrast was used of the individuals who do not consume coffee versus factorial. The statistical model was as shown below:

$Yijk = \mu + Ti + Aj + Nk + TAij + TNik + ANjk + TANijk + eijk$

Where i=1,2 (types of coffee), j=1,2 (levels of physical activity), k=1,2,3 (levels of coffee consumption), with y_{ijk} being the value observed referent to the interaction between types of coffee, levels of coffee consumption, and levels of physical activity; μ was a constant, inherent to each observation, and e_{ijk} was the experimental error.

The data obtained were processed using the free software program, Sisvar (developed by UFLA). Measurements of central tendency were calculated, and the Tukey test and Student t tests were used in the analysis of the hypotheses. In all the analyses, a confidence interval of 95% was used.

RESULTS

At the end of the experiment, the group that consumed caffeinated coffee exhibited lower fasting plasma glycemic values than the group that consumed decaffeinated coffee ($p < 0.05$). The difference between these groups in regards to the glycemic values was approximately 40% ($p < 0.05$). In addition, in the group that consumed decaffeinated coffee, glycemic indexes increased over the course of the study (Table 1). However, there were no significant statistical differences in relation to the level of coffee consumption (low, moderate or high) and the participants' PG ($p > 0.05$).

Table 1: Means of glucose, by type of coffee and non-consumption of coffee, at the beginning and at the end of the experiment. Note: CV-Coefficient of Variation, *Comparisons of the coefficient of variation of values on the columns express statistically significant difference ($p < 0.05$), **Comparisons of the coefficient of variation of values on the columns do not express statistically significant difference ($p > 0.05$).

	Glucose (mg/dL)		p-value
Type of Coffee	Baseline	6 months	
Caffeinated	157.00	148.22	> 0.05
Decaffeinated	162.39	166.44	<0.05
CV (%)	34.65**	39.77 *	
Past consumption of coffee			
Yes	159.64	157.33	>0.05
CV (%)	34.65**	39.77**	
No	133.00	135.67	>0.05
CV (%)	17.38**	23.34**	
Non-consumers of coffee			
Active	125.67	124.67	>0.05
Sedentary	140.33	146.67	>0.05
CV (%)	17.38**	23.34**	

Both at the beginning and at the end of the intervention, active people exhibited lower fasting plasma glycemic values than sedentary participants ($p < 0.05$).

Glycemic values were compared according with confusing variables (past consumption of coffee and physical activity between the non-consumers of coffee). The fasting plasma glycemic values did not present statistically significant differences in relation to these comparisons (Table 1).

At the end of the study, those who consumed coffee presented a reduction in their serum levels of TC (182.44–181.97 mg/dL), differing from the non-consumers, whose values rose (212.33–215.33 mg/dL) ($p<0.01$). The active participants who consumed coffee presented low levels of TC before and after the study in relation to active non-consumers ($p<0.01$).

Coffee consumers exhibited lower LDL-c values at both the baseline and the end of the experiment. The variations between these two time-points reached approximately 37% ($p<0.05$) (Table 2).

Table 2: Comparison between variation coefficient mean of LDL-c and HDL-c according to consumers and non-consumers of coffee at the beginning and at the end of the experiment.

Participants	LDL-c		HDL-c	
Coffee	Baseline	6 months	Baseline	6 months
Consumes	102.92	107.07	41.64	41.62
Does not consume	128.30	123.93	44.00	44.00
CV (%)	39.73	36.63	29.23	29.23
p-value	<0.05	<0.05	>0.05	>0.05

At the end of this study, the V-LDL mean serum level of the active participants with moderate consumption of caffeinated coffee (33.07 mg/dL) was practically half in relation to the levels of the sedentary consumers with moderate consumption of caffeinated coffee (60.20 mg/dL) ($p<0.05$).

Before the experiment, the participants with higher levels of TG were those who were sedentary, with moderate consumption of caffeinated coffee, and high consumption of decaffeinated coffee. At the end of the treatment, there was a statistically significant reduction only among the sedentary participants with moderate consumption of caffeinated coffee ($p<0.05$) (Table 3).

Table 3: Means of the level of coffee consumption within each type of coffee and situation of physical activity at the beginning and at the end of the experiment, by the variable of triglycerides. Note: CV-Coefficient of variation, LC–Low Consumption, MC–Moderate Consumption, HC–High Consumption, [*]Turkey Test.

Coffee/Sedentary	Baseline			
				p-value
Caffeinated	LC	MC	HC	
Active	148.00	148.67	127.67	> 0.05
Sedentary	143.33	327.33	133.33	> 0.05
Decaffeinated	LC	MC	HC	
Active	110.00	278.00	91.00	<0.05
Sedentary	93.00	143.00	288.33	<0.05
6 months				
Caffeinated				p-value
	LC	MC	HC	
Active	163.67	165.33	169.67	>0.05
Sedentary	129.00	301.00	139.33	<0.05
Decaffeinated	LC	MC	HC	
Active	123.67	240.00	97.67	>0.05

Sedentary	113.33	153.67	197.67	>0.05

In regards to the level of coffee consumption (low, moderate and high), no significant differences were found in the correlations between this variable and LDL-c or HDL-c values (p>0.05). However, we observed that the V-LDL values were lower in active participants with high consumption level of decaffeinated coffee (p<0.05).

After the experiment there were no statistically significant differences among the variables of SAP, DAP, WC and BMI in relation to the factors studied (coffee consumption, type of coffee, and level of physical activity and of coffee consumption) (p>0.05).

It was possible to observe that, at the end of the study, those who consumed coffee (225.94 mg/dL), regardless of the type, presented a lower mean in the platelet count in comparison with non-consumers (245.50 mg/dL) (p<0.05).

Statistically significant differences were not found, at the end of the study, in the uric acid levels in the groups evaluated (p>0.05). In both the study's periods (basal and final), the active participants with moderate consumption of caffeinated coffee (3-4 cups) presented lower thyroxine values (T4) (p<0.05) in comparison with the consumers of the decaffeinated drink.

From the baseline to the end of the study, the coffee consumers exhibited a decrease on the glycosuria incidence rates (from 41.7% to 27.8%). On the other hand, non-consumers of coffee exhibited no changes on glycosuria incidence over the course of the study (incidence rates remained around 16.6%).

The maximum CF in the basal period (150.4 bpm) and final period (147.4 bpm) of the study was below that calculated for the participants at the start of the study (160.5 bpm) (p<0.01), independently of the consumption or type of coffee, or even level of activity. It was also observed that those who consumed coffee (regardless of the type) had lower MET values at the end of the study (p<0.01).

The mean values of the double product (cardiac frequency vs. systolic arterial pressure) and duration of the test during the ergometric test (min/sec) did not differ statistically in relation to the variables of coffee consumption, type of coffee, level of activity and coffee consumption in both groups (p>0.05). On the other hand, those who did not consume coffee presented higher means in the item of 'miles walked' in the study's basal period and final period (p<0.05). The participants who did not consume coffee also, at the end of the study, presented higher mean values for VO2max in relation to those who did consume coffee (p<0.01).

DISCUSSION

At the end of the experiment, those who consumed normal coffee (caffeinated) presented lower values for plasma glycine. In relation to the basal value, this reduction was of 5%. To the authors' knowledge, there is a vast number of publications in the medical literature evidencing an inverse relationship between coffee consumption and glycemia in healthy persons [9-11,14,15].

In the present study, this event was repeated, but this time among diabetic people, whose insulin sensitivity was already impaired. As a result, it is possible to hypothesize that coffee's anti-diabetic effect may assist not only in reducing the incidence, but also in the metabolic control, of cases of DM2 which are already in place.

It is a fact that one limitation of this study was to have adopted PG (current value) as a therapeutic outcome, instead of glycated hemoglobin (HbA1c) which reflects the previous glycemic control (mean glycemia over the last 120 days). However, PG is the more traditional test, is less expensive, and is one of the more accurate for assessing glycemic control, and is stipulated by the American Diabetes Association (ADA) and by the SBD. Furthermore, according to comparison scales between HbA1c and PG proposed by these bodies, it is possible to establish that the final glycemic values of those who consumed normal coffee in this study remained at 7% (the target therapeutic goal among the diabetic people) [16,17].

If the use of caffeinated coffee was able to contribute to glycemic control, it is also possible to infer that it acts in the control and/or prevention of micro- and macrovascular complications resulting from DM2. It is a fact that in this study, the levels of proteinuria and glycosuria of the patients using coffee, regardless of the type, also showed a reduction in relation to those of the non-consumers. These findings reveal an improvement in these patients' renal function during the course of the study. In principle, this fact cannot be attributed to glycemic improvement, as the phenomenon also occurred among those without statistically significant reduction of PG. It may perhaps be the case that some compound present in coffee – apart from caffeine – is related to this phenomenon.

The authors are not aware of the above-mentioned association, among people with diabetes, being mentioned in the literature. However, among healthy people, the habitual consumption of coffee is related to increase in the glomerular filtration rate. The association between proteinuria and caffeine consumption is not yet clear, as a result of which, there

is as yet no robust evidence contraindicating the consumption of coffee or drugs containing caffeine in healthy persons or persons with renal problems [18,19]. On the other hand, not consuming coffee with caffeine seems to improve symptoms such as urinary frequency and urgency [17].

The participants who consumed coffee, especially the active ones, presented better levels of LDL-c, V-LDL and triglycerides. In this case, the function of the coffee could be contested due to two questions: the regular practice of physical activity improves the lipid profile, and patients using hypolipidemic drugs were not excluded from the sample. Another two points of the present study, however, incorporate our findings: the study duration (demonstrating the relationship of casuality) and the way the drink was prepared (using filter paper and without boiling).

The detection of lower V-LDL values on active participants with high consumption level of decaffeinated coffee could be related to substances in the coffee, other than caffeine. This should be investigated in further researches.

Nevertheless, according to a meta-analysis consulted, coffee consumption is associated with a rise in the levels of TC, LDL-c and TG of 8.1 mg/dL, 5.4 mg/dL and 12.6 mg/dL, respectively, above all among those who do not filter the drink. Not boiling the coffee helps in a lower liberation of the lipid fractions of the coffee, which end up being retained in the filter paper [20].

People with moderate consumption of normal coffee, and who are active, presented a reduction in the levels of T4. Only one publication was found which similarly ascertained a reduction in the absorption of T4 in healthy women who consumed coffee [21]. In this case, it is important to emphasize that during the study, the T4 values always indicated a situation with normal laboratory values, and that DM2 itself can contribute to reduction in thyroid function. There are also reports in the health literature that caffeine, and not necessarily coffee, can protect against thyroid cancer [22,23]. As a result, we can infer that coffee consumption (of both types) did not alter the thyroid hormones.

It was possible to infer that coffee consumption was safe in relation to CF and platelet aggregation among the subjects as, in both groups, there was reduction of these parameters at the end of the experiment. On the other hand, those who did not consume coffee obtained better performance in some items of the ergometric test (VO2, MET, miles walked). As a result, we can deduce that individuals with diabetes who did not consume coffee obtained an improvement in physical fitness.

Indeed, the ergogenic effect of caffeine in exercises with long duration is questionable. There are controversies due to the lack of standardization of the methodologies used in the experiments (type of experiment, intensity and duration, doses of caffeine and tolerance). Furthermore, this type of analysis is hindered by the fact that caffeine affects nearly all the tissues of the body, making it difficult to observe the mechanisms of action [24]. Another point which deserves consideration is caffeine's interaction with substances already present in the organism which promote–or do not–the development of metabolic changes [25].

Some researchers argument that caffeine favors vessel injury and thrombus formation [26]. Thus, the reduction of platelets that coffee consumers exhibit throughout this study could be an important finding. This reinforces the argument that the effects of caffeine on the blood vessels is still not fully understood and other clinical trials are necessary.

In the light of this study's findings, it is important to note that the American Diabetes Association (ADA) accepts the use of natural products in controlling DM2 so long as they are recommended and/or used under the supervision of a health professional, who must check these products' safety and efficacy prior to indicating them to the patients [2,16]. It is believed that the data from the present study add positive evidence in regard to this. However, prior to accepting the habit of consuming coffee as a therapeutic option, it is believed that it is important to observe the findings among people with DM 2 in different regions of the world, and with larger samples.

CONCLUSION

It was possible to conclude in the sample evaluated that among consumers of caffeinated coffee, there was improvement in the serum levels of glycemia, triglycerides and platelets. However, among those who did not consume coffee, there was improvement of some cardiac indicators, such as miles walked and the volume of oxygen consumed per minute.

REFERENCES

1. Dham S, et al. The role of complementary and alternative medicine in diabetes. Curr Diab Rep. 2006;6:251-258.

2. Birdee GS and Yeh G. Complementary and alternative medicine therapies for diabetes: a clinical review. Clinical Diabetes. 2010;28:147-150.

3. Pandey A, et al. Alternative therapies useful in the management of diabetes: a systematic review. J Pharm Bioallied Sci. 2011;3:504-512.

4. Franz MJ, et al. Evidence-based diabetes nutrition therapy recommendations are effective: the key is individualization. Diabetes, Metab Syndr Obes. 2014;7:65-72.

5. Marikkar MJ, et al. Evaluation of banana (Musa sp.) owers of selected varieties for their. antioxidative and anti-hyperglycemic potentials. Int Food Res. 2016;23:1988-1995.

6. Lima FA, et al. Coffee and human health: a focus on the substances of the beverage related to cardiovascular disease. Rev Nutr. 2016;23:1063-1073.

7. Encarnaзго RO and Lima DR. O cafe e a saude humana. Embrapa Cafe, Brasнlia. 2003.

8. Canela MD, et al. Consumption of stimulant drinks and consequent ingestion of phenolic compounds and caffeine. Nutrire Rev Soc Bras Aliment Nutr. 2009;34:143-157.

9. Ding M, et al. Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis. Diabetes Care. 2014;37:569-586.

10. Jiang X, et al. Coffee and caffeine intake and incidence of type 2 diabetes mellitus: a meta-analysis of prospective studies. Eur J Nutr. 2014;53:25-38.

11. Shang F, et al. Coffee consumption and risk of the metabolic syndrome: a meta-analysis. Diabetes Metab. 2016;42:80-87.

12. Akash MS, et al. Effects of coffee on type 2 diabetes mellitus. Nutrition. 2014;30:755-763.

13. Sociedade Brasileira de Diabetes. Diretrizes da Sociedade Brasileira de Diabetes 2015-2016. AC Farmaceutica, Sao Paulo.

14. Reunanen A, et al. Coffee consumption and risk of type 2 diabetes mellitus. Lancet. 2003;361:702-703.

15. Saremi A, et al. Coffee consumption and the incidence of type 2 diabetes. Diabetes Care. 2003;26:2211-2003.

16. American Diabetes Association. Standards of medical care in diabetes-2015. Diabetes Care. 2015;38:S1-S2.

17. Staack A, et al. Prospective study on the effects of regular and decaffeinated coffee on urinary symptoms in young and healthy volunteers. Neurol Urodyn. 2015;36:432-437.

18. Bolignano D, et al. Caffeine and the kidney: what evidence right now? J Ren Nutr. 2007;17:225-234.

19. Nakajima K, et al. Association between habitual coffee consumption and normal or increased estimated glomerular filtration rate in apparently healthy adults. Br J Nutr. 2010;103:149-152.

20. Cai L, et al. The effect of coffee consumption on serum lipids: a meta-analysis of randomized controlled trials. Eur J Clin Nutr. 2012;66:872-877.

21. Benvenga S, et al. Altered intestinal absorption of L-thyroxine caused by coffee. Thyroid. 2008;18:293-301.

22. Garattini S. Caffeine, coffee and health. Raven Press, Milan. 1992.

23. Nascimento-Saba CCA, et al. Pituitary-thyroid axis in short- and long-term experimental diabetes mellitus. Braz J Med Bio Res. 1997;30:269-274.

24. Silva MS. Os efeitos da cafeнna relacionados a atividade fнsica: uma revisгo. Rev Digital. 2003;9:1-8.

25. Cappelletti S, et al. Caffeine: Cognitive and physical performance enhancer or psychoactive drug? Curr Neuropharmacol. 2015;13:77-88.

26. McEwen BJ. The influence of diet and nutrients on platelet function. Semin Thromb Hemost. 2014;40:214-226.