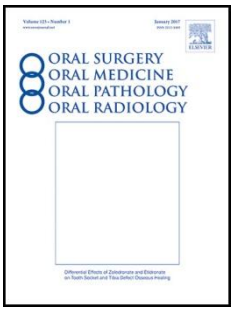
Accepted Manuscript



Title: Occurrence and associated factors of carotid artery calcification detected by digital panoramic radiography in chronic kidney disease patients undergoing hemodialysis

Author: Paulo R.L. Maia, Ana M.C. Medeiros, Hallissa S.G. Pereira, Kenio C. Lima, Patrícia T. Oliveira

PII: S2212-4403(18)30903-9
DOI: https://doi.org/10.1016/j.oooo.2018.04.005
Reference: OOOO 1999

To appear in: *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*

Received date: 10-10-2017
Revised date: 1-4-2018
Accepted date: 13-4-2018

Please cite this article as: Paulo R.L. Maia, Ana M.C. Medeiros, Hallissa S.G. Pereira, Kenio C. Lima, Patrícia T. Oliveira, Occurrence and associated factors of carotid artery calcification detected by digital panoramic radiography in chronic kidney disease patients undergoing hemodialysis, *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* (2018), https://doi.org/10.1016/j.oooo.2018.04.005.

OCCURRENCE AND ASSOCIATED FACTORS OF CAROTID ARTERY CALCIFICATION DETECTED BY DIGITAL PANORAMIC RADIOGRAPHY IN CHRONIC KIDNEY DISEASE PATIENTS UNDERGOING HEMODIALYSIS

Authors:

Paulo R L Maia – Oral and Maxillofacial Radiologist, Masters, Department of Dentistry, Federal University of Rio Grande do Norte, Av. Sen. Salgado Filho, 1787, Natal - RN, 59056-000, Brazil.

Ana M C Medeiros – Doctor, Department of Dentistry, Federal University of Rio Grande do Norte, Av. Sen. Salgado Filho, 1787, Natal - RN, 59056-000, Brazil.

Hallissa S G Pereira – Doctor, Department of Dentistry, Federal University of Rio Grande do Norte, Av. Sen. Salgado Filho, 1787, Natal - RN, 59056-000, Brazil.

Kenio C Lima – Doctor, Department of Dentistry, Federal University of Rio Grande do Norte, Av. Sen. Salgado Filho, 1787, Natal - RN, 59056-000, Brazil.

Patrícia T Oliveira – Doctor, Department of Dentistry, Federal University of Rio Grande do Norte, Av. Sen. Salgado Filho, 1787, Natal - RN, 59056-000, Brazil.

Corresponding author: Paulo Raphael Leite Maia

Av. Capitão Mor-Gouveia, 2488, Cidade da Esperança, Natal-RN, Brazil.

E-mail: paulo.raphael@ig.com.br

Phone: 55 84 994140075

Formatting of funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Word count for the abstract = 175

Complete manuscript word count = 3099

Number of references= 36

Number of figures = 1

Number of tables = 4

Statement of clinical relevance: The high occurrence of CAC detected by panoramic digital radiography in patients with CKD undergoing hemodialysis reinforces the importance of a careful interpretation of these examinations and the correct management of these patients by dental surgeons.

ABSTRACT

Objectives: To investigate the occurrence and associated factors of carotid artery calcification (CAC) in chronic kidney disease (CKD) patients undergoing hemodialysis.

Study Design: A total of 309 panoramic radiographs of CKD patients (180 men and 129 women with a mean age of 43.7 years) undergoing hemodialysis were evaluated by a single radiologist to evaluate the frequency of CAC. An evaluation of the associated factors of age, gender, time spent in hemodialysis, arterial hypertension, diabetes mellitus, biochemical parameters, and other systemic diseases was also performed.

Results: The occurrence of CAC detected by the panoramic radiographs of these patients was 15.9% The chi-squared test found that there was a statistically significant association between age, gender, and diabetes mellitus and the presence of CAC ($p<0.05$). Multivariate analysis demonstrated that time spent in hemodialysis was significantly associated with the occurrence of CAC.

Conclusion: There was a significant presence of CAC detected on digital panoramic radiographs in CKD patients undergoing hemodialysis. Calcification was more frequent in older patients, women, individuals with diabetes mellitus, and patients who had undergone hemodialysis for longer periods.

Keywords: Panoramic radiography; Atherosclerosis; Carotid artery calcification; Hemodialysis.

INTRODUCTION

Chronic kidney disease (CKD) is defined as disorders in renal structure or function that last for a period of more than three months and negatively affect the health of the individual. The condition is progressive and irreversible and hemodialysis is required when it evolves to its final stage (1).

Cardiovascular diseases are the most common comorbidity and leading cause of death in patients with CKD (1). Studies have found that patients with CKD have a greater risk of developing cardiovascular events than the general population, although the mechanisms of this association are not fully understood (3,4).

The presence of traditional risk factors such as hypertension, diabetes mellitus, smoking, a sedentary lifestyle, and hyperlipidemia do not fully explain the high rate of cardiovascular diseases in these patients. Non-traditional factors inherent to the disease or its treatment may contribute to the high prevalence of the condition and subsequently to the higher rates of morbidity and mortality related to cardiovascular events (4–6).

Atherosclerotic disease is one such event and is characterized by the formation and accumulation of plaques containing fat, cholesterol, fibrous tissue, and macrophages, which are susceptible to calcification, in the intimal layer of the medium-caliber arteries. This is particularly significant as it can lead to the complete obliteration of the lumen of these vessels (7). The association of calcified atherosclerotic plaques in the carotid artery and ischemic cardiovascular events in patients undergoing hemodialysis has been described by previous studies (8,9).

Panoramic radiographs are widely used in dental practice and may be useful for the identification of carotid artery calcification (CAC) (10–12). Previous studies (13,14) have evaluated the occurrence of CAC in patients with CKD as detected on panoramic radiographs. However, the samples were small and included patients with different

disease stages, making it difficult to analyze individuals undergoing hemodialysis, who have the most severe forms of kidney disease and the greatest chance of developing complications.

Due to the high prevalence of cardiovascular problems in patients with CKD, the aim of the present study was to investigate the occurrence of CAC in patients in the terminal stage of the disease who were undergoing hemodialysis and to evaluate significant correlations between these calcifications and possible factors associated with this condition as age, gender, time undergoing hemodialysis, arterial hypertension, diabetes mellitus, and biochemical parameters. The null hypothesis stated that there was no significant association between any of the variables and the presence of CAC.

MATERIALS AND METHODS

A cross-sectional association-based study was carried out. A margin of error of 5% was used to calculate the sample size and the percentage of patients studied who had CAC (15.9%) was taken as the prevalence. A further 15% was added to adjust the sample size to the associations (15), resulting in a minimum *n* of 235 participants. The sample was made up of individuals with CKD undergoing hemodialysis who received treatment at the Nephrology Department of the Hospital Universitário Onofre Lopes from January 2013 to December 2016.

At our institution, patients are routinely referred to the dental surgeon for the elimination of infectious foci before renal transplantation. Thus, for this dental evaluation, panoramic radiography is always requested as part of a pre-transplant examination protocol. The panoramic radiographs used in the study were carried out at the Image Service of the Department of Dentistry as part of the protocol of multi-professional exams prior to renal transplantation, using a Carestream® KODAK 8000C device (Carestream Health Corporation, Rochester, NY, USA) with exposure parameters of 70-74 kVp and 4-6.3 mA. The sample comprised patients who agreed to participate in the study by signing a free and informed consent form, who had filled out medical records, and whose panoramic radiographs provided an adequate bilateral visualization of the region adjacent to the spine. All others were excluded. During the study period, 461 patients referred for panoramic radiographs were considered, and after applying the inclusion and exclusion criteria, the n value was 309 participants.

The CAC evaluation was performed by a single oral and maxillofacial radiologist with 6 years of experience, who evaluated the images on two different dates 20 days apart, using the Carestream® Kodak Dental Software program on a 15-inch LED monitor under low light. The level of agreement between examination sessions was calculated (kappa = 0.839).

The diagnosis of CAC was performed as described by other authors (12,15–17). Irregular and heterogeneous vertical-linear radiopacities observed on the lateral panoramic radiographs at the level of the C3 and C4 vertebrae below the angle of the jaw were considered suggestive of CAC (Figure 1).

Clinical data including age, gender, time spent in hemodialysis, arterial hypertension, diabetes mellitus, biochemical parameters (extracted from the

examination prior to the date of the survey), and the presence of other systemic diseases were obtained from the medical records of these patients.

Age (≤35 years, 36-50 years, > 50 years) and time spent in hemodialysis (≤1 year, 1-3 years, >3 years) were divided into terciles following distribution analysis. The categorization of the creatinine (<8mg/dL, 8-11mg/dL, >11mg/dL) and urea (<115mg/dL, 115-155mg/dL, >155mg/dL) variables was also performed in terciles based on distribution analysis, as the blood levels of these parameters in the patients in the study are above those considered normal. Statistical categorization was based on the respective reference values for the following biochemical parameters: glycemia (up to and including 99mg/dL and over 99mg/dL), potassium (up to and including 5mmol/dL and over 5mmol/dL), total cholesterol (up to and including 200mg/dL and over 200mg/dL), LDL cholesterol (up to and including 129mg/dL and over 129mg/dL), HDL cholesterol (up to and including 60mg/dL and over 60mg/dL), triglycerides (up to and including 150mg/dL and over 150mg/dL), calcium (up to and including 10mg/dL and over 10mg/dL) and phosphorus (up to and including 4.5mg/dL and over 4.5mg/dL). Gender and the presence of systemic diseases (arterial hypertension, diabetes mellitus, and other diseases) are listed as percentages of the population.

The construction of the research database and the statistical analyses were performed on the SPSS® software platform version 22.0 (Statistical Package for Social Sciences, IBM Corp., Armonk, NY). Bivariate analysis was used to calculate the *p*-value with the chi-squared and Fisher's exact tests and two binary logistic regression models were applied. The Hosmer-Lemeshow test was performed to measure the goodness of fit of the logistic regression. The prevalence ratios (PR) and 95% confidence intervals (CI) were calculated for each analysis.

This study was approved by the Research Ethics Committee of the Hospital Universitário Onofre Lopes – CEP/HUOL under opinion number 1.663.957/2016.

RESULTS

The sample of 309 patients evaluated was predominantly composed of younger male adults. The occurrence of CAC detected in the panoramic radiographs of these patients was 15.9% (CI 95%: 11.9 - 19.9). The sample size for some analyzes of the associated factors was lower than that used to calculate the occurrence of CAC.

Table I shows the characterization of the sample for the variables of age, gender, time spent in hemodialysis, arterial hypertension, diabetes mellitus, and biochemical parameters of systemic diseases.

In the bivariate analysis, there was a statistically significant association between the variables of age, gender, and diabetes and the presence of CAC, as shown in Table II. The prevalence ratio revealed a 71% higher occurrence of CAC in women than men, and a 393% greater prevalence in those aged over 50 compared with those aged 35 or under.

After testing the multicollinearity between variables whose *p* value was less than or equal to 0.20, two binary logistic regression models were applied, grouping the variables of age and gender (Table III), and time spent in hemodialysis and diabetes mellitus (Table IV). Multivariate analysis revealed that, regardless of the other variables, age, gender, time spent in hemodialysis, and diabetes mellitus were significantly associated with the presence of CAC. The null hypothesis was rejected for the effects of age, gender, diabetes mellitus, and time spent in hemodialysis.

DISCUSSION

Few studies have evaluated the presence of CAC in CKD patients undergoing hemodialysis. The present study marks the first use of digital panoramic radiographs to detect calcification in these patients, and with a larger sample than was used in previous works.

The occurrence of CAC observed in the digital panoramic radiographs of CKD patients undergoing hemodialysis was 15.9%. This is significantly higher than the frequency of this disorder in the general population, which varies from 0.43% to 9.9%, as shown in previous research (10,12,19–23). Kansu et al. (13) and Lee et al. (22), who identified an occurrence of CAC of 17.6% and 21.8%, respectively, also found a high frequency of CAC in patients undergoing hemodialysis, although these studies used smaller samples.

The higher prevalence of CAC in CKD patients is still not fully understood. As the risk factors traditionally associated with the development of such calcification in the general population, such as dyslipidemia, hypertension, diabetes, smoking, and obesity, do not sufficiently explain the greater occurrence in CKD patients (25), it is thought that factors inherent to CKD itself may be associated with elevated occurrence (5). Among these, the chronic inflammation regularly observed in CKD patients has been associated with the development of atherosclerosis. It is believed that elevated levels of inflammatory markers such as cytokines, adhesion molecules, chemokines, and reactive oxygen species may favor the formation of atherosclerotic plaques and consequently CAC (5,7,24,25).

Elevated levels of urea in the bloodstream, increased toxins not filtered by hemodialysis, and factors related to dialysis, such as the biocompatibility of the membrane of the equipment and the use of catheters, may also be involved in the development of chronic inflammation, thus contributing to the emergence of CAC (4,26).

Another important factor that can explain the greater occurrence of atherosclerosis and consequently CAC in CKD patients is the oxidative stress caused by the increase in circulating free radicals and the reduction of antioxidant levels observed in patients undergoing hemodialysis for long periods (24,27,28). Thus, patients in the final stage of CKD who are in hemodialysis, as in the sample of the present study, are more exposed to oxidative stress and chronic inflammation, factors that favor the development of

atherosclerosis. These findings could explain the association between the time spent in hemodialysis and the presence of CAC found in this study, in which patients who had undergone hemodialysis for longer periods had a greater incidence of CAC.

Mineral metabolism imbalance has also been related to a higher occurrence of CAC in CKD patients undergoing hemodialysis. Some authors argue that altered levels of parathyroid hormone, vitamin D, serum calcium, and especially phosphate play an important role in favoring the vascular calcification process (29,30). Although the present study did not evaluate parathyroid hormone or vitamin D, calcium and phosphorus levels were analyzed. These were not, however, significantly associated with CAC, agreeing with the study by Lee et al. (22).

A significantly greater occurrence of CAC was found in women and in individuals aged over 50. The chronic and progressive nature of atherosclerosis and the increase in prevalence with age may explain this association. In addition, the higher occurrence of CAC in women may be related to the post-menopausal reduction in estrogen levels, which favors the development of calcification (31).

It was found that 69% of the sample of the present study reported at least one other systemic disease, such as diabetes mellitus, arterial hypertension, or systemic lupus erythematosus. However, only diabetes mellitus demonstrated a significant association with the presence of CAC, unlike the findings of a similar study by Lee et al. (22). Another investigation revealed a greater prevalence of CAC in the panoramic radiographs of patients with type 2 diabetes than in a group without the disease (32). Constantin et al. (33) concluded in their study that diabetes, regardless of serum cholesterol levels, significantly increases the predisposition of individuals to the development of atherosclerosis. According to Amarante et al. (34) this phenomenon occurs because the metabolic changes characteristic of diabetics, such as hyperglycemia, increased free fatty acids, and insulin resistance, activate molecular mechanisms that provoke oxidative stress and reduce the bioavailability of nitric oxide, leading to a lower endothelial smooth muscle response to relaxation factors and platelet dysregulation with increases in prothrombotic factors. Additionally, in diabetic patients, the non-enzymatic glycosylation end products of the vessel wall proteins contribute to the development of vascular lesions (35).

There is no consensus in the medical literature on the pathophysiological mechanisms involved in the increased risk of cardiovascular events in patients with CKD. Herrington et al. (36) concluded that there is a lack of reliable evidence for the

recommendation of strategies for the prevention and treatment of cardiovascular complications such as strokes in CKD patients undergoing dialysis. However, in a prospective 6-year follow-up study, Collado et al. (8) found that the presence of atheromatous plaques, especially when calcified, are predictors of new cardiovascular events and mortality in hemodialysis patients. In this context, we consider that the early diagnosis of signs of cardiovascular impairment, prompt referral for medical evaluation, and the early initiation of preventive measures are extremely important.

We acknowledge that the present study has certain limitations such as the fact that it is a retrospective analysis, features only a single examiner, and lacks a reference exam for the interpretation criteria.

Patients with CKD undergoing hemodialysis are candidates for renal transplantation, and panoramic radiography is one of the exams that form part of the pre-transplantation protocol in our institution. These examinations are inexpensive, present a minimum biological risk, and can be an important tool for the detection of CAC in chronic kidney patients. Careful analysis of panoramic radiographs can allow dental surgeons to broaden their evaluations, which are often directed solely towards identifying infectious dental foci, in order to detect CAC and can serve as an important indicative exam for the order of other more precise diagnostic methods for the identification of CAC, such as carotid Doppler ultrasonography (US).

In conclusion, CKD patients undergoing hemodialysis exhibited a significant occurrence of CAC as detected by digital panoramic radiography. Advanced age, female gender, longer periods of hemodialysis, and diabetes mellitus were associated with a higher frequency of CAC. A careful interpretation of panoramic radiographs may lead to early diagnosis. When CAC is detected, patients may be referred for Doppler ultrasonographic examination of the carotid artery in association with the US usually performed to check visceral and peripheral arteries, preventing more serious cardiovascular complications in this high-risk group. It is therefore worth emphasizing the importance of the continuous search for knowledge regarding the identification of these radiological findings, either by clinical dental surgeons or radiologists involved in the management of CKD patients undergoing hemodialysis.

REFERENCES

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015 Jan 10;385(9963):117–71.

2. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality: a collaborative meta-analysis of general population cohorts. Lancet. 2014; 375(9731): 2073–81.

3. Tonelli M. Chronic Kidney Disease and Mortality Risk: A Systematic Review. J Am Soc Nephrol. 2006 Jun 21;17(7):2034–47.

4. Ardhanari S, Alpert MA, Aggarwal K. Cardiovascular disease in chronic kidney disease: risk factors, pathogenesis, and prevention. Adv Perit Dial. 2014;30(2): 40–53.

5. Afsar B, Turkmen K, Covic A, Kanbay M. An Update on Coronary Artery Disease and Chronic Kidney Disease. Int J Nephrol. Hindawi Publishing Corporation; 2014;2014:1–9

6. Yerram P, Karuparthi PR, Hesemann L, Horst J, Whaley-Connell A. Chronic kidney disease and cardiovascular risk. J Am Soc Hypertens. 2007;1(3):178–84.

7. Chirakarnjanakorn S, Navaneethan SD, Francis GS, Tang WHW. Cardiovascular impact in patients undergoing maintenance hemodialysis: Clinical management considerations. Int J Cardiol. Elsevier B.V.; 2017 Apr;232:12–23.

8. Collado S, Coll E, Nicolau C, Pons M, Cruzado JM, Pascual J, et al. Carotid Atherosclerotic Disease Predicts Cardiovascular Events in Hemodialysis Patients: A Prospective Study. Yang X-F, editor. PLoS One. 2015 Jun 1;10(6)

9. Tanaka M, Abe Y, Furukado S, Miwa K, Sakaguchi M, Sakoda S, et al. Chronic

Kidney Disease and Carotid Atherosclerosis. J Stroke Cerebrovasc Dis. Elsevier Ltd; 2012 Jan;21(1):47–51

10. Almog DM, Horev T, Illig KA, Green RM, Carter LC. Correlating carotid artery stenosis detected by panoramic radiography with clinically relevant carotid artery stenosis determined by duplex ultrasound. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;94(6):768–73.

11. Almog DM, Tsimidis K, Moss ME, Gottlieb RH, Carter LC. Evaluation of a training program for detection of carotid artery calcifications on panoramic radiographs. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;90(1):111–7.

12. Garay I, Netto HD, Olate S. Soft tissue calcified in mandibular angle area observed by means of panoramic radiography. Int J Clin Exp Med. 2014;7(1):51–6.

13. Kansu O, Ozbek M, Avcu N, Gençtoy G, Kansu H, Turgan C. The prevalence of carotid artery calcification on the panoramic radiographs of patients with renal disease. Dentomaxillofac Radiol. 2005;34(1):16–9.

14. Lee JY, Antoniazzi MCC, Perozini C, Ruivo GF, Pallos D. Prevalence of carotid artery calcification in patients with chronic renal disease identified by panoramic radiography. Oral Surg Oral Med Oral Pathol Oral Radiol. Elsevier Inc.; 2014;118(5):612–8.

15. Burton, A. H., et al. Epi Info, Version 6: A word processing, database, and statistics program for epidemiology on microcomputers. Atlanta: Centers of Disease Control and Prevention; 1994.

16. Carter LC. Discrimination between calcified triticeous cartilage and calcified carotid atheroma on panoramic radiography. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;90(1):108–10.

17. Ahmad M, Madden R, Perez L. Triticeous cartilage: Prevalence on panoramic radiographs and diagnostic criteria. Oral Surgery, Oral Med Oral Pathol Oral Radiol

Endodontology. 2005;99(2):225–30.
18. Friedlander AH, Lande A. Panoramic radiographic identification of carotid arterial plaques. Oral Surg Oral Med Oral Pathol. United States; 1981 Jul;52(1):102–4.

19. Bayer S, Helfgen EH, Bös C, Kraus D, Enkling N, Mues S. Prevalence of findings compatible with carotid artery calcifications on dental panoramic radiographs. Clin Oral Investig. 2011;15(4):563–9.

20. Friedlander AH, Cohen SN. Panoramic radiographic atheromas portend adverse vascular events. Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology. 2007;103(6):830–5.

21. Johansson EP, Ahlqvist J, Garoff M, Karp K, Jäghagen EL, Wester P. Ultrasound screening for asymptomatic carotid stenosis in subjects with calcifications in the area of the carotid arteries on panoramic radiographs: a cross-sectional study. BMC Cardiovasc Disord. BioMed Central Ltd; 2011;11(1):44.

22. Lee JS, Kim OS, Chung HJ, Kim YJ, Kweon SS, Lee YH, et al. The prevalence and correlation of carotid artery calcification on panoramic radiographs and peripheral arterial disease in a population from the Republic of Korea: The Dong-gu study. Dentomaxillofacial Radiol. 2013;42(3):2–7.

23. Brito ACR De, Nascimento HAR, Argento R, Beline T, Ambrosano GMB, Freitas DQ. Prevalence of suggestive images of carotid artery calcifications on panoramic radiographs and its relationship with predisposing factors. Cien Saude Colet. 2016 Jul;21(7):2201–8.

24. Pecoits-filho R, Stevinkel P, Lindholm B, Bergström J. Revisão : Desnutrição, inflamação e aterosclerose (síndrome MIA) em pacientes portadores de insuficiência renal crônica. J Bras Nefrol. 2002;24(3):136–46.

25. Dummer CD, Thomé FS, Veronese FV. Doença renal crônica, inflamação e aterosclerose: novos conceitos de um velho problema. Rev Assoc Med Bras. 2007;53(5):446–50.

26. Stenvinkel P, Alvestrand A. Review Articles: Inflammation in End- stage Renal Disease: Sources, Consequences, and Therapy. Semin Dial. Wiley Online Library; 2002;15(5):329–37.

27. Vaziri ND. Oxidative stress in uremia: Nature, mechanisms, and potential consequences. Semin Nephrol. 2004 Sep;24(5):469–73.

28. Nguyen-Khoa T, Massy Z a, De Bandt JP, Kebede M, Salama L, Lambrey G, et al. Oxidative stress and haemodialysis: role of inflammation and duration of dialysis treatment. Nephrol Dial Transplant. 2001;16(2):335–40.

29. Covic A, Kanbay M, Voroneanu L, Turgut F, Serban DN, Serban IL, et al. Vascular calcification in chronic kidney disease: Figure 1. Clin Sci. 2010 Aug 1;119(3):111–21.

30. Tejwani V, Qian Q. Calcium regulation and bone mineral metabolism in elderly patients with chronic kidney disease. Nutrients. 2013;5(6):1913–36.

31. Patil S, Maheshwari S, Khandelwal S, Malhotra R, Desmukh A. Prevalence of calcified carotid artery atheromas on panoramic radiographs of renal stone patients. Saudi J Kidney Dis Transpl. 2016;27(1):62–6.

32. Friedlander AH, Maeder LA. The prevalence of calcified carotid artery atheromas on the panoramic radiographs of patients with type 2 diabetes mellitus. Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology. 2000 Apr;89(4):420–4.

33. Constantin CRC, Lbulescu DANAAA, Lbu VAAA, Anciu ANRAD. Correlations between etiological factors and lesion severity in carotid artery atheromatosis. 2016;57(3):1011–6.

34. Amarante RDM, Castro R, Lage AV, Cisternas JR. Diabetes Mellitus como fator de risco na aterogênese: Diabetes Mellitus as a risk factor in vascular diseases. Arq Med Hosp Fac Med St Casa São Paulo. 2007;52(3):87–93.

35. Göksan B, Erkol G, Bozluolcay M, Ince B. Diabetes as a determinant of high-grade carotid artery stenosis: Evaluation of 1, 058 cases by Doppler sonography. J Stroke Cerebrovasc Dis. 2001;10(6):252–6.

36. Herrington W, Haynes R, Staplin N, Emberson J, Baigent C, Landray M. Evidence for the Prevention and Treatment of Stroke in Dialysis Patients. Semin Dial. 2015;28(1):35–47.

LEGEND FOR ILLUSTRATION

Figure 1. Radiopacities such as these, observed on the panoramic radiograph at the level of the C3 and C4 vertebrae below the angle of the jaw (arrow), were considered suggestive of CAC.

Table I- Characteristics of the sample population.

Variables	**n**	**Mean ± Standard deviation**	**Reference values**
Age	309	43.75 ± 14.15	------
Variables	**n**	**Median**	**Q25 – Q75**
Time spent in hemodialysis (in months)	275	17.0	5.0 – 53.0
Variables	**n**	**Mean ± Standard deviation**	**Reference values**
Creatinine	199	9.48 ± 3.70	0.3 to 1.6 mg/dL
Urea	199	134.64 ± 45.87	10 to 45 mg/dL
Glycemia	172	102.97 ± 38.70	75 to 99 mg/dL
Potassium	195	5.55 ± 1.08	3.5 to 5.0 mEq/L
Total Cholesterol	132	165.36 ± 1.08	<200 mg/dL
LDL	96	87.35 ± 36.19	<129 mg/dL
HDL	100	45.13 ± 21.46	>60 mg/dL
Triglycerides	122	168.35 ± 85.37	<150 mg/dL
Calcium	187	9.26 ± 1.24	8 to 10 mg/dL
Phosphorus	182	5.26 ± 1.72	2.5 to 4.5 mg/dL
Gender		**n**	**%**
Female		129	41.7
Male		180	58.3
Systemic disease*		**n**	**%**
Arterial hypertension		208	75.4
Diabetes Mellitus		65	23.6
Other Diseases**		17	6.1

* Patients may have more than one comorbidity. The total number of patients for whom data on the presence of systemic diseases was collected was 276.

** Gout (1); uterine cancer (1); hyperparathyroidism (1); anemia (2); systemic lupus erythematosus (12)

Table II – Distribution of age, gender, time spent in hemodialysis, arterial hypertension, diabetes mellitus, and biochemical parameters in patients with CKD with and without CAC, p value, prevalence ratio and 95% confidence intervals.

Variables	With CAC n (%)	Without CAC n (%)	p value	PR (CI 95%)
Age				
< 35 years	5 (5.4)	87 (94.6)	< **0.001**	1
36 to 50 years	18 (15.0)	102 (85.0)		2.760(1.064 – 7.157)
> 50 years	26 (26.8)	71 (73.2)		4.932(1.978 – 12.297)
Time spent in hemodialysis				
< 1 year	13 (11.4)	101 (88.6)	0.056	1
1 to 3 years	9 (12.9)	61 (87.1)		1.127(0.509 – 2.499)
> 3 years	21(23.1)	70 (79.6)		2.024(1.073 – 3.817)
Creatinine				
< 8.0 mg/dL	8 (10.1)	71 (89.9)	0.450	1
8.0 to 11mg/dL	7 (12.3)	50 (87.7)		1.213(0.466 – 3.153)
>11.0 mg/dL	11 (17.2)	53 (82.8)		1.697(0.726 – 3.967)
Urea				
< 115 mg/dL	6 (8.7)	63 (91.3)	0.484	1
115 to 155 mg/dL	10 (14.9)	57 (85.1)		1.716(0.661 – 4.459)
>155 mg/dL	9 (14.3)	54 (85.7)		1.643(0.620 – 4.355)
Glycemia				
≤99 mg/dL	11 (9.7)	102 (90.3)	0.097	1.915 (0.883 – 4.154)
>99 mg/dL	11 (18.6)	48 (81.4)		
Potassium				
≤5.0 mg/ dL	8 (11.9)	59 (88.1)	0.790	1.112 (0.507 – 2.443)
>5.0 mg/dL	17 (13.3)	111 (86.7)		
Total cholesterol				
≤ 200 mg/dL	10 (9.8)	92 (90.2)	0.198*	2.040 (0.808 – 5.153)
>200 mg/dL	6 (20.0)	24 (80.0)		

LDL cholesterol				
≤129 mg/dL	7 (8.3)	77 (91.7)	0.109*	3.000 (0.895 – 10.058)
>129 mg/dL	3 (25.0)	9 (75.0)		
HDL cholesterol				
≤60 mg/dL	8 (9.5)	76 (90.5)	0.098*	0.381 (0.130 – 1.116)
>60 mg/dL	4 (25.0)	12 (75.0)		
Triglycerides				
≤150 mg/ dL	4 (7.4)	50 (92.6)	0.143	2.184 (0.736 – 6.477)
>150 mg/dL	11 (16.2)	57 (83.8)		
Calcium				
≤10.0 mg/dL	17 (12.1)	123 (87.9)	0.626	1.227 (0.542 – 2.773)
>10.0 mg/dL	7 (14.9)	40 (85.1)		
Phosphorus				
≤4.5 mg/dL	9 (14.1)	55 (85.9)	0.797	0.904 (0.419 – 1.949)
> 4.5mg/dL	15 (12.7)	103 (87.3)		
Gender				
Female	27 (20.9)	102 (79.1)	**0.039**	1.712 (1.023 – 2.868)
Male	22 (12.2)	158 (87.8)		
Arterial hypertension				
Yes	34 (16.3)	174 (83.7)	0.539	1.235 (0.625 – 2.442
No	9 (13.2)	59 (86.8)		
Diabetes Mellitus				
Yes	16 (24.6)	49 (75.4)	**0.022**	1.924(1.107 – 3.342)
No	27 (12.7)	184 (87.3)		

* Fisher's Exact Test.

Table III – Results of multivariate analysis. Model includes variables of age and gender.

Variables	**With CAC n(%)**	**PR CI (95%)**	**p value**	**$PR_{adjusted}$ (CI 95%)**
Age				
≤35 years	5 (5.4)	1	**0.001**	1
36 to 50 years	18 (15.0)	2.760 (1.064 – 7.157)	**<0.001**	1.842 (1.073 – 3.161)
>50 years	26 (26.8)	4.932 (1.978 – 12.297)	**0.027**	1.612 (1.063 – 2.443)
Gender				
Female	27 (20.9)	1.712 (1.023 – 2.868)	**0.025**	2.004 (1.012 – 3.966)
Male	22 (12.2)			

Hosmer test = 0.583

Table IV – Results of multivariate analysis. Model includes variables of time spent in hemodialysis and diabetes mellitus.

Variables	**With CAC n(%)**	**PR CI (95%)**	**p value**	**$PR_{adjusted}$ (CI 95%)**
Time spent in hemodialysis				
<1 year	13 (11.4)	1	**0.008**	1
1 to 3 years	9 (12.9)	1.127 (0.509 – 2.499)	**0.005**	2.439 (1.164 – 5.111)
>3 years	21 (23.1)	2.024 (1.073 – 3.817)	**0.018**	1.612 (1.063 – 2.443)
Diabetes mellitus				
Yes	16 (24.6)	1.924 (1.107 – 3.342)	**0.002**	2.585 (1.418 – 4.712)
No	27 (12.7)			

Hosmer test = 0.855

Fig 1 ok.tif