



Evaluating the Independent Impact of Renal Function Decline on Coronary Artery Calcification in Patients Undergone Cardiac CT Scan

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Abstract

Background: Cardiovascular events are the leading global cause of death. Calcification of coronary arteries is a common complication of renal failure and the leading cause of death in this population. However, its multifactorial mechanism is not fully understood.

Objectives: The current study aimed to, firstly, investigate the association between renal dysfunction and the calcification of coronary arteries in patients with severe and milder stages of renal failure and, secondly, to determine the role of this variable by eliminating the effect of established confounding factors.

Methods: Following a retrospective design, 261 patients with cardiovascular risk factors or atypical symptoms were investigated. Estimated GFR (glomerular filtration rate) was calculated using both Cockcroft-Gault and MDRD equations. An ECG-gated multidetector CT scan was performed to calculate CACS (coronary artery calcification score) using the Agatston method. The presence of significant CAC (coronary artery calcification) was defined as CACS > 100. Univariate and multivariate analyses were performed using binary logistic regression.

Results: A total of 134 cases were diagnosed with CAC, and the mean CACS was 83.4 ± 18 . According to univariate analysis, older age, male gender, systolic and diastolic blood pressure, and higher TG levels were correlated with the degree of CAC. HbA_{1c} showed a weak correlation with CACS (P-value = 0.04). Renal insufficiency resulted in increased CAC, and lower eGFR (calculated with both Cockcroft-Gault and MDRD equations) was associated with higher calcification (P-value < 0.01). Our analysis shows that serum Ca, P, LDL, and HDL levels do not have a significant influence on calcification changes. After adjusting for confounding factors, male sex, age, triglyceride level, and eGFR were recognized as independent risk factors for CACS ≥ 100 , a marker of coronary artery atherosclerosis. However, HbA_{1c} and systolic and diastolic blood pressure were no longer considered as factors that contribute to the risk of CAC.

Conclusions: We observed a gradual and independent association between lower eGFR and higher CAC scores.

Keywords: Renal Insufficiency, Coronary Artery Disease, Multidetector Computed Tomography

1. Background

Cardiovascular events are the leading global cause of death, accounting for almost half (48.6%) of all deaths alongside cancer each year (1). There is evidence indicating that for patients with coronary artery disease, vascular calcification emerges at the initial course of the disease (before the appearance of symptoms). In this regard, two explanations can be provided: (1) first, calcification in the intima results in calcified atherosclerotic plaques, which can consequently cause ischemic cardiac events; and (2) second, calcification of the media layer of the vessel produces vascular stiffness and eventually leads to left ventricular

hypertrophy and heart failure by increasing the afterload (2). At this early stage, evaluation of calcification of the coronary arteries is only possible by imaging techniques (3); for which matter, the Agatston score is the gold standard that not only is highly sensitive and specific but also is applicable for various age groups (4).

Calcification of coronary arteries is a common complication of renal failure (5) and the leading cause of death in this population. However, its multifactorial mechanism is not fully understood. It can be hypothesized that chondrocyte- or osteoblastic-like changes are induced in smooth muscle cells of the vessel wall, and this modification is due to toxic levels of serum calcium and phos-

phorus, secondary to abnormal bone metabolism and decreased renal excretion (6). In addition, it can be argued that increased calcification observed in this group is due to the complications related to renal failure, including anemia, hypertension, dyslipidemia, oxidative stress, and uremia, or common risk factors such as diabetes and old age, both of which are risk factors for coronary artery calcification (CAC) (7).

Studies intended to evaluate the independent impact of renal failure on CAC have failed to contribute the high prevalence of calcification to the effect of established risk factors, such as hypertension, hyperlipidemia, old age, diabetes, and smoking (8-11). In this sense, renal failure can be considered an independent risk factor for vascular calcification. Although most studies did not consider confounding factors sufficiently; hence, deduction of an independent role for declined renal function in cases that suffer from CAC is not yet possible. Under such an assumption, early diagnosis and early intervention for renal insufficiency may reduce mortality caused by subsequent cardiac events.

Contrary to end-stage renal disease, few studies have investigated the effect of mild kidney dysfunction on vascular calcification. Although most patients suffer from earlier stages of chronic kidney disease, gathering information about this group is of most importance yet (12-16).

2. Objectives

The current study aimed to, firstly, investigate the association between renal dysfunction and the calcification of coronary arteries in patients with severe and milder stages of renal failure and, secondly, to determine the role of this variable by eliminating the effect of established confounding factors.

3. Methods

3.1. Patient Selection

A total of 261 individuals were enrolled in this retrospective study (from September 2019 to October 2020). Most of the patients were asymptomatic with cardiovascular risk factors or manifested atypical symptoms. Exclusion criteria included: (1) previous CABG (coronary artery bypass graft surgery) or history of coronary stent placement; (2) cardiac valve replacement; (3) dialysis-dependent renal failure; and (4) incomplete demographic and lab data.

3.2. CT Scan Protocol

Patients with an initial heart rate greater than 65 bpm received an oral dose of B-blocker (50 mg metoprolol) approximately one hour before imaging. An ECG-gated multidetector CT scan was performed using a 128-slice scanner (Siemens Medical Systems, Forchheim, Germany) without IV contrast injection to quantify CAC. Coronary CT scan images were interpreted by a radiologist experienced in cardiac radiology.

3.3. Data Collection

Demographic information, medical history, and health-related behaviors were recorded by a self-administered questionnaire with the help of a trained employee. Demographic and blood pressure data were recorded by a trained nurse. Laboratory results were collected from the medical records of patients.

Estimated GFR was calculated using the Cockcroft-Gault and MDRD equations based on the lowest serum creatinine level recorded three months before imaging.

3.4. Measurement of CAC

The CAC score was calculated using the method described by Agatston et al., which is based on the area of a calcified plaque and density factor (4). CACS is divided into 5 stages as follow: no calcification (0), minimal calcification (1 - 10), mild calcification (11 - 99), moderate calcification (101 - 400), and extensive calcification (> 400). According to the previous studies, the presence of significant CAC was defined as CACS > 100 (17-19).

3.5. Statistical Analyzes

Independent t-test, Mann-Whitney U test, Pearson correlation, and multivariate logistic regression analysis were used to analyze the data. Continuous variables are described as mean \pm standard deviation (SD). The association between dichotomous data was analyzed by the chi-square test. An independent sample t-test was used to compare means of quantitative variables in subgroups of CACS. The significance of the association between demographic and clinical variables with the mean CAC scores was evaluated using the Mann-Whitney U test. Pearson correlation was used to evaluate the correlation between continuous variables and CACS as well as to calculate the correlation coefficients. Univariate analysis in binary logistic regression was also employed to define the association between predictors and outcome using odds ratio and confidence interval. Eventually, logistic regression was used for multivariate analysis. We administered SPSS version 16 for data analysis.

4. Results

A total of 261 patients were recruited for this study [121 females (44%) and 140 males (56%)], with a mean age of 54.6 ± 11.1 years. Of all participants, 134 cases were diagnosed with CAC, with a mean CAC score of 83.4 ± 18 . The association between CAC score and different demographic and laboratory factors was evaluated using Pearson correlation (Table 1). In addition, a comparison of each characteristic separated by the sub-group ($CACS \leq 100$ and $CACS > 100$) is provided in Table 2.

According to the findings, the older the case, the higher was the degree of CAC. Accordingly, participants in the $CACS \leq 100$ subgroup were younger than those in the $CACS > 100$ subgroups by 10.1 years (51.5 ± 11 vs. 61.6 ± 7.9 , respectively; $P < 0.01$). Men had higher CAC scores than females (113.08 vs 49.05, respectively; P -value = 0.003), and only 18 patients in $CACS > 100$ subgroup were women (33.3%).

Systolic and diastolic blood pressures were both positively correlated with CAC scores (P -value = 0.02 and P -value = 0.03, respectively). Hypertension was reported in 40 and 62% of patients with $CACS \leq 100$ and $CACS > 100$, respectively (P -value < 0.01). HbA_{1c} showed a weak correlation with the CAC score (P -value = 0.04). This correlation remained significant only in $CACS > 100$, suggesting no considerable impact on lower grade calcification. In addition, a history of diabetes did not have a significant effect on the degree of coronary calcification (P -value = 0.55). Higher triglyceride levels demonstrated a direct association with the formation of atherosclerotic plaques; however, similar to HbA_{1c}, this effect was non-significant in CAC scores < 100 . Not surprisingly, renal insufficiency was associated with increased CAC; while lower eGFR (calculated using both Cockcroft-Gault and MDRD equations) was associated with more calcification (P -value < 0.01). Only 18.5% of patients with moderate and severe CAC had normal kidney function (eGFR ≥ 90) in comparison to 52.7% among those with mild calcification.

Our analysis shows that serum Ca, P, LDL, and HDL levels did not have a significant influence on calcification changes.

The results of multivariate logistic regression analysis are provided in Table 3. After adjusting for confounding factors, male sex, age, triglyceride level, and eGFR were recognized as independent risk factors of $CACS \geq 100$, a marker of coronary artery atherosclerosis. However, HbA_{1c} and systolic and diastolic blood pressure were no longer considered effective in adding to the risk of CAC. Even after considering hypertension a categorical variable, similar results were obtained, and still, there was no significant association between CACS and hypertension.

5. Discussion

The primary objective of this research was to evaluate the association between renal function decline and CAC. The findings of the present study are consistent with previous studies, which demonstrate a positive correlation between lower eGFR and higher calcification (20-22). Our observation indicates a higher frequency of CAC among older patients and men, which is in accordance with the findings of other studies. For instance, Shemesh reported that CAC is three times more frequent in men, and among those older than 50 years, the frequency increases for both sexes, but the increase is greater for women (23).

According to the findings of the univariate analysis, systolic and diastolic blood pressure were both predictors of a greater degree of calcification of the coronary arteries. However, after applying multivariate logistic regression, the level of their significance was declined. Some studies reported similar results (24), while some proposed an independent role for hypertension. It seems studies that considered hypertension as a strong predictor have either limited their findings to univariate analysis or have not considered eGFR as a confounding factor (25, 26). In this survey, we proposed an important role for impaired kidney function as a confounding factor that determines the outcome. Hence, probably hypertension is an intermediate variable. By increasing the sample size, more strong results can be obtained.

According to our analysis, HbA_{1c} is positively correlated with calcification, although this correlation was confined to higher degrees of calcification. On the other hand, a history of diabetes alone was not considered a major risk factor for the prediction of coronary calcification, which emphasizes the importance of blood sugar control in the long term for the prevention of cardiac events. Although some authors reported a role for diabetes, regardless of the glycemic control (27-29), the Multi-Ethnic Study of Atherosclerosis (MESA) did not confirm this association (30). Other researchers such as Carson et al. considered a greater weight for HbA_{1c} and believed that advanced CAC progression is correlated with higher HbA_{1c} levels, even among non-diabetic patients (31). Similar to previous studies (32, 33), our findings indicate that higher triglyceride levels are associated with an increased probability of CAC. This correlation is stronger in higher CACS and remains positive after adjusting for confounding factors.

Concerning the evaluation of the association between CAC and glomerular filtration rate, we observed a gradual and independent association between lower eGFRs and higher CAC scores. In the present study, patients were classified based on their eGFR (≥ 90 , $90 - 60$, < 60) in order to evaluate the effect of mild renal insufficiency on clinically

Table 1. Pearson's Correlation Coefficient for the Relationship between Predictors and the Severity of Coronary Artery Calcification

Predictors	CACS		
	Mean \pm SD	r	P Value
Age	53.6 \pm 11.2	0.31	< 0.01
Systolic blood pressure	129 \pm 17.4	0.17	0.02
Diastolic blood pressure	82.5 \pm 6.8	0.17	0.03
Cr	1.01 \pm 0.17	0.35	< 0.01
BUN	14.7 \pm 3.7	0.26	< 0.01
HbA1c	6.7 \pm 1.7	0.16	0.04
Ca	8.7 \pm 0.9	-0.03	0.64
Ph	3.8 \pm 0.6	0.01	0.89
TG	168.2 \pm 69.5	0.23	< 0.01
LDL	91.6 \pm 24.1	0.06	0.43
HDL	46.2 \pm 12.9	0.03	0.69
eGFR (MDRD)	73.5 \pm 13.4	-0.28	< 0.01
eGFR (Cockcroft-Gault)	88.7 \pm 21.6	-0.34	< 0.01

Table 2. Basic Demographic and Medical Information in Relation to CACS, Univariate Analysis^a

Characteristics	Total	CACS \leq 100	CACS > 100	P Value
Age (y)	53.6 \pm 11.2	51.5 \pm 11	61.6 \pm 7.9	< 0.01
Male sex	140 (53.6)	104 (50.2)	36 (66.6)	0.03
Creatinine (mg/dL)	1.01 \pm 0.17	0.99 \pm 0.16	1.12 \pm 0.18	< 0.01
BUN (mg/dL)	14.7 \pm 3.7	14.3 \pm 3.4	16.1 \pm 4.5	< 0.01
HbA1c (mmol/mol)	6.8 \pm 1.7	6.7 \pm 1.7	6.9 \pm 1.7	0.54
Calcium (mg/dL)	8.8 \pm 0.9	8.8 \pm 0.9	8.7 \pm 0.8	0.43
Phosphorus (mg/dL)	3.8 \pm 0.6	3.8 \pm 0.5	3.8 \pm 0.9	0.87
Triglyceride (mg/dL)	168.3 \pm 69.5	163 \pm 65.4	184.7 \pm 79.6	0.11
LDL cholesterol (mg/dL)	91.7 \pm 24.1	91.8 \pm 24.4	91.5 \pm 23.3	0.94
HDL cholesterol (mg/dL)	46.2 \pm 12.9	45.7 \pm 12.8	48 \pm 13.5	0.3
Hypertension	118 (45)	84 (40)	34 (62)	< 0.01
Diabetes	37 (14)	28 (13)	9 (16)	0.55
eGFR (MDRD) (mL/min)	73.5 \pm 13.4	75.4 \pm 13.1	66 \pm 11.8	< 0.01
eGFR (Cockcroft-Gault) (mL/min)	88.7 \pm 21.6	92.5 \pm 21.1	74 \pm 16.9	< 0.01

^a Values are expressed as No. (%) or mean \pm SD unless otherwise indicated.

significant vascular calcification (CACS > 100). Mild kidney dysfunction was not associated with a significant increase in calcification. In the same vein, Kramer et al. reported (34) that calcification was increased in coronary arteries of patients with eGFR < 60. They also suggested that concurrent diabetes mellitus caused a 9-fold increase in the risk of CAC development. Also, in a cross-sectional study, Hyun et al. (2019) evaluated the independent effect of eGFR on CAC

score and demonstrated a positive and independent association between eGFR and CAC (21). On the contrary, some studies reported no significant association between eGFR and vascular calcification (26, 32).

Some researchers mentioned serum phosphorus levels as important predictors of CAC (35, 36). Nevertheless, others questioned this conclusion, which is in line with this study (no significant correlation). Tuttle and Short pro-

Table 3. Predictors of Increased CACS in Multivariate Analysis by Logistic Regression

Predictor	Odds Ratio (95% Confidence Interval)	P-Value in Multivariate Analysis
Gender	0.28 (0.11 - 0.77)	0.01
Age	1.07 (1.02 - 1.13)	< 0.01
Triglyceride	1.01 (1 - 1.01)	0.03
eGFR (MDRD)	0.94 (0.89 - 0.98)	0.01
Systolic blood pressure	0.99 (0.96 - 1.02)	0.45
Diastolic blood pressure	1.03 (0.94 - 1.14)	0.52
HbA1C	0.91 (0.67 - 1.18)	0.47

posed that baseline CAC score was not related to serum phosphorus level; however, after five years of follow-up, higher phosphorus levels proved to be associated with CAC score progression or development of new calcification (26).

5.1. Conclusion

The present study intended to evaluate the impact of renal failure on CAC. After adjusting for confounding factors, male sex, older age, triglyceride level, and eGFR were recognized as independent risk factors of increased CAC.

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Footnotes

Authors' Contribution: Study concept and design, M. A., and R. J.; Acquisition of data, M. A.; Analysis and interpretation of data, MA. KA. and S. R.; Drafting of the manuscript, M. A. and MA. KA.; Critical revision of the manuscript for important intellectual content, M. A. and R. J.; Statistical analysis, S. R.; Administrative, technical, and material support, R. J.; Study supervision, R. J.

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