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THE ASSOCIATION OF CORONARY ARTERY CALCIUM SCORE WITH GLOMERULAR FILTRATION RATE AND THE INFLUENCE OF SEX, AGE, BLOOD PRESSURE, AND CHOLESTEROL

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Abstract. The association of coronary artery calcium score with glomerular filtration rate and the influence of sex, age, blood pressure, and cholesterol

Key words: coronary artery calcium score, glomerular filtration rate, sex, age, blood pressure, cholesterol

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Chronic kidney disease (CKD) puts an individual at a higher risk of all-cause and cardiovascular death, starting from the decline of the glomerular filtration rate (GFR) below 90 ml/min [4]. Coronary artery calcium score (CACS) reflects the accumulation of calcium in the walls of the coronary arteries and a higher CACS is associated with lower survival rates [11]. The progression of atherosclerosis and the accumulation of coronary calcium in CKD is more rapid, than in the general population, due to the presence of additional CKD-related risk factors [1].

An increased risk of death may be a reason to attempt to prevent further decline of renal function and to achieve stricter target values for blood pressure and blood lipids [10, 18]. However, there is some discussion about the target blood pressure values [17, 18] and the rationale of treatment with statins for patients with CKD [10]. It is unclear if control of conventional risk factors is enough to reduce cardiovascular risk in patients with CKD.

Both reduction of renal function and changes in presentation of conventional cardiovascular risk factors (i.e. age, blood pressure and total cholesterol (TC)) may influence the accumulation of coronary artery calcium [7, 14]. However, in the Ukrainian population, cardiovascular disease and CKD develop earlier than in other European regions [12, 16]. This, in turn, may influence the association between GFR and CACS with conventional cardiovascular risk factors. The aim of this study was to investigate if the association between glomerular filtration rate and coronary artery calcium score in the Ukrainian population differs by sex, age, blood pressure, and total cholesterol.

MATERIALS AND METHODS OF RESEARCH

Study population. This cross-sectional study was conducted on a sample of patients who underwent measurement of CACS at Dnipropetrovsk Mchnikov Regional Hospital, Dnipro, Ukraine. Inclusion criteria: age >40 years old, available data about CACS and eGFR. Exclusion criteria: presence of known cardiovascular disease, diagnosis of diabetes mellitus, eGFR <30 ml/min and extreme coronary artery calcification (CACS <1500 Agatston units (AU)).

CACS was estimated after cardiac computed tomography using Optima CT660, GE Healthcare, Wisconsin, USA (2017), and reported in AU. CACS was classified into three groups according to ESC/EAS 2019 guidelines: 0 AU, 1-100 AU and >100 AU [19]. eGFR was calculated using the CKD-EPI equation, which requires data about patient’s sex, age and serum creatinine [9]. Patients were classified into groups by eGFR according to KDIGO stages of chronic kidney disease [9]. Blood pressure was measured using automated methods. Stratification of patients by the level of systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) ≥90 mmHg was performed according to recommended blood pressure targets in treatment of arterial hypertension [18]. Measurements of total cholesterol (TC) and serum creatinine were performed using standard procedures. Stratification of patients by the level of...
TC ≥5.0 mmol/l was performed according to European Guidelines on cardiovascular disease prevention in clinical practice [5].

Data were analyzed using LibreOffice and R (version 3.6.3) [6, 15]. The type of data distribution was assessed using Shapiro-Wilk tests. As all the variables in the study had a non-normal distribution, non-parametric statistical methods were applied. Continuous data were reported as median with the first and the third quartiles (Me [Q1;Q3]). Assessment of the difference of medians of continuous variables between two groups was performed using a Mann-Whitney test. Assessment of difference of medians of continuous variables between three groups was performed using a Kruskal-Wallis test. The significance of the trend in medians was assessed with a Jonckheere-Terpstra test. Categorical data were reported as n (%), and were compared using a Chi-square test. The critical value of p-values in testing statistical hypotheses was defined as p<0.05 [13].

RESULTS AND DISCUSSION

Percentage of females in the study was slightly higher than men, but the sex difference of patients with eGFR ≥90 ml/min, eGFR 60-89 ml/min, and eGFR 30-59 ml/min was the same (Table). In the patients with lower eGFR there was a significantly higher age (p=0.01) and non-significantly higher CACS (p=0.07). All the patients in the study had a BP close to the upper recommended target value of 140/90 or exceeded it. TC values of all patients were close to or higher than the upper normal limit of 5.0 mmol/l regardless of eGFR category. Among the patients with lower eGFR there was a lower proportion of patients with CACS =0 AU and a higher proportion of patients with CACS >100 AU. However, this difference was not statistically significant. The proportion of patients with CACS 1-100 AU was equal regardless of eGFR. The proportion of patients with CACS >100 AU and median CACS increased abruptly in the patients with eGFR 30-59 ml/min, when compared to the patients with eGFR 60-89 and ≥90 ml/min.

In males with eGFR ≥90 ml/min, eGFR 60-89 ml/min, and eGFR 30-59 ml/min CACS didn’t differ significantly, while in females lower eGFR was associated with higher CACS (Fig.). Moreover, the median CACS in males (50 [5;200] AU) was higher than in females (10 [0;103] AU, p=0.02). A higher CACS was associated with a lower eGFR in patients aged above 55 years old (p=0.01), but not in patients younger than 55 years old. In older patients, the median CACS was higher (52 [4;156] AU), than in younger patients (0 [0;29] AU, p<0.01). A lower eGFR was significantly associated with a higher CACS in the patients with SBP ≥140 mmHg (p=0.04), but not in patients with DBP ≥90 mmHg. In the patients with SBP <140 mmHg and DBP <90 mmHg, CACS was roughly the same regardless of eGFR. In the patients with TC <5.0 mmol/l and ≥5.0 mmol/l CACS tended to be higher in the patients with lower eGFR.

**Presentation of conventional cardiovascular risk factors in patients with normal, mildly reduced and moderately reduced eGFR**

| Variable                          | Total (n=137) | eGFR≥90 ml/min | eGFR 60-89 ml/min | eGFR 30-59 ml/min | P for difference | P for trend |
|-----------------------------------|---------------|----------------|-------------------|------------------|------------------|-------------|
| Females, n (%)                    | 83 (60.5)     | 23 (62.1)      | 47 (60.2)         | 13 (59.0)        | 0.96             | -           |
| Age, years                        | 59.0 [54.0;67.0] | 56.0 [54.0;63.0] | 58.5 [54.0;66.8] | 66.0 [57.5;76.0] | 0.02             | 0.01        |
| SBP, mmHg                         | 140.0 [125.0;150.0] | 140.0 [130.0;150.0] | 135.0 [120.0;143.8] | 140.0 [122.5;150.0] | 0.13             | 0.23        |
| DBP, mmHg                         | 80.0 [80.0;90.0] | 90.0 [80.0;93.0] | 80.0 [80.0;90.0] | 80.0 [80.0;90.0] | 0.24             | 0.11        |
| Total cholesterol, mmol/l         | 5.3 [4.5;6.0] | 5.2 [4.4;6.0]  | 5.5 [4.8;6.1]    | 5.1 [4.5;5.5]    | 0.65             | 0.86        |
| Total CACS, AU                    | 23.0 [0.0;116.0] | 14.0 [0.0;60.0] | 12.0 [0.0;113.5] | 87.0 [15.0;204.0] | 0.04             | 0.07        |
| CACS = 0 AU, n (%)                | 42 (30.7)     | 11 (29.7)      | 28 (35.9)         | 3 (13.6)         |                  |             |
| CACS 1-100 AU, n (%)              | 55 (40.1)     | 18 (48.6)      | 29 (37.2)         | 8 (36.4)         | 0.10             | -           |
| CACS >100 AU, n (%)               | 40 (29.2)     | 8 (21.6)       | 21 (26.9)         | 11 (50.0)        |                  |             |
The association of eGFR category with total CACS stratified by conventional cardiovascular risk factors

Among the variables in the study only age and coronary artery calcium score were higher in the patients with lower estimated glomerular filtration rate. CACS was significantly higher in the patients with lower eGFR who were either female, older than 55 years or had a SBP >140 mmHg, but remained roughly the same in other subgroups of patients.

The increase of CACS with the decrease of eGFR category (≥90 ml/min, 60-89 ml/min, and 30-59 ml/min) in our study is not surprising and was well studied in the previous works [7]. A decline of renal function leads to the development of conditions specific to CKD, such as volume overload, mineral-bone disorder, inflammation etc., which in turn may cause damage to the cardiovascular system [1]. Progression of atherosclerosis with calcification of the atherosclerotic plaques happens faster in CKD, than in the general population [1], which may be due to the development of mediosclerosis [3]. As aging is usually accompanied by physiological loss of the renal function, the association of age with decline of eGFR in our study was expected [2].

However, similar SBP, DBP and TC in patients with different eGFR (≥90 ml/min, 60-89 ml/min, and 30-59 ml/min) was surprising. A decline of renal function is often accompanied by an elevation of the blood pressure and an increase of the prevalence of arterial hypertension (HTN) [8]. This finding may be explained by the treatment of the patients in the study according to the severity of arterial hypertension. The progression of CKD is often followed by the elevation of TC levels [10]. But in some cases of dyslipidemia in CKD there may be normal TC with elevated triglycerides and low-density lipoproteins and decreased high-density lipoproteins [10]. Thus, even a normal TC in the CKD lipid profile may be highly atherogenic [10], and the investigation of cholesterol fractions in patients with CKD is essential.

The poor association of CACS with eGFR category together with the higher median CACS in males in our study may indicate a more severe course of atherosclerosis and worse cardiovascular prognosis. Lower median CACS in females with eGFR ≥90 ml/min and 60-89 ml/min may reflect the advanced stages of CKD, HTN is more difficult to control, and proportion of the patients with resistant HTN is higher [8]. This finding may be explained by the later onset of cardiovascular disease in females than in males [12]. More females were enrolled in the study, due to the higher chance of being asymptomatic in the middle age.
The possibility of prevention of atherosclerosis progression for females in early CKD. The presence of the association of CACS with eGFR category in young patients (≤55 years old) could be expected, as the association of the decline of eGFR with poor cardiovascular prognosis is believed to be stronger in younger individuals [2]. The paradoxical association of CACS with eGFR category after stratification by SBP and DBP, where individuals with higher blood pressure tended to have lower CACS, will require further investigation. In our study a higher TC did not result in a higher CACS. It may be implied that the patients with elevated blood pressure or TC were prescribed antihypertensive treatment, which could slow down the evolution of atherosclerosis and the accumulation of coronary calcium. Control of blood pressure and TC in our study was not strictly related to lower CACS, therefore it may be assumed that a decline of eGFR was the main factor driving the increase of CACS.

Closer attention to the early diagnosis of CKD and wider implementation of preventive measures for the reduction of eGFR may be beneficial for improving patients' outcomes.

**CONCLUSIONS**

A lower estimated glomerular filtration rate in our study was associated with a higher coronary artery calcium score in females, patients aged ≥55 years old and in patients with systolic blood pressure≥140 mmHg.

Conflict of interests. The authors declare no conflict of interest.

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