Prevalence of Chronic Kidney Disease and Anemia in Patients with Coronary Artery Disease with Normal Serum Creatinine Undergoing Percutaneous Coronary Interventions: Relation to New York Heart Association Class

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ABSTRACT: **Background:** Kidney disease and cardiovascular disease seem to be lethally synergistic and both are approaching the epidemic level. A reduced glomerular filtration rate is associated with increased mortality risk in patients with heart failure. Many patients with congestive heart failure are anemic. Anemia is very often associated with chronic kidney disease.

Objectives: To assess – in relation to New York Heart Association class – the prevalence of anemia and chronic kidney disease in patients with normal serum creatinine in a cohort of 526 consecutive patients with coronary artery disease undergoing percutaneous coronary interventions.

Methods: GFR was estimated using the simplified MDRD formula, the Cockcroft-Gault formula, the Jeliffe and the novel CKD-EPI formula.

Results: According to the WHO definition the prevalence of anemia in our study was 21%. We observed a progressive decline in GFR and hemoglobin concentration together with a rise in NYHA class. Significant correlations were observed between eGFR and systolic blood pressure, diastolic blood pressure, age, NYHA class, complications of PCI, including bleeding, and major adverse cardiac events.

Conclusions: The prevalence of anemia and chronic kidney disease is high in patients undergoing PCI despite normal serum creatinine, particularly in higher NYHA class. Lower eGFR and hemoglobin are associated with more complications, including bleeding after PCI and higher prevalence of major adverse cardiac events. In patients with risk factors for cardiovascular disease, GFR should be estimated since renal dysfunction and subsequent anemia are important risk factors for cardiovascular morbidity and mortality.

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KEY WORDS: coronary artery disease, chronic heart failure, anemia, chronic kidney disease, glomerular filtration rate

Kidney disease and cardiovascular disease seem to be lethally synergistic and both are approaching the level of an epidemic, particularly in the elderly. As the population's life expectancy increases, the incidence of both congestive heart failure and end-stage renal disease is progressively increasing. Both diseases are inexorably linked. Chronic kidney disease is common in patients with CHF, and its presence adversely affects patients' survival [1]. Furthermore, cardiovascular disease is the major cause of mortality in CKD. Clinical guidelines recommend screening patients with cardiovascular risk factors for the presence of CKD. The detection and classification of CKD is based on the estimated glomerular filtration rate, calculated by the MDRD formula [2]. Anemia is frequently seen in CHF, with a prevalence ranging from 4% to 55%, depending on the population studied [1]. In an analysis from the SOLVD trial, 22% of the patients had hematocrit < 39% and 4% had values < 35% [2]. A similar rate of anemia (17%) was noted in a population-based cohort of 12,065 patients with newly diagnosed CHF [3]. The incidence of anemia appears to increase with worsening functional class, from 9% for New York Heart Association class I to 79% for NYHA class IV [4]. Moreover, anemia in CHF patients has been associated with increased mortality, increased number of hospitalizations and a greater severity of CHF, as compared to non-anemic subjects [5]. In our previous study we reported that in a cohort of 1413 patients with normal serum creatinine undergoing percutaneous coronary intervention, as many as 33% had stage 3 CKD, i.e., estimated GFR < 60 ml/min/1.73 m^2 [6]. The aim of the present study was to assess – in relation to

CHF = congestive heart failure
CHD = chronic kidney disease
GFR = glomerular filtration rate
NYHA = New York Heart Association
eGFR = estimated GFR
PCI = percutaneous coronary intervention
MDRD = Modification of Diet in Renal Disease study
SOLVD = Studies Of Left Ventricular Dysfunction

NYHA class – the prevalence of CKD and anemia in a cohort of 526 consecutive patients with coronary artery disease and normal serum creatinine undergoing coronary angiography.

PATIENTS AND METHODS

Our study population comprised 526 patients (mean age 57.89 ± 11.33 years) with coronary artery disease (confirmed angiographically, class II/III CCS) and normal serum creatinine (< 1.2 mg/dl in females and < 1.5 mg/dl in males). The patients were recruited prospectively for PCI from the Invasive Cardiology Department. All patients were informed about the aim of the study and gave their informed consent. We excluded patients with preexisting CKD, namely elevated serum creatinine and/or history of kidney disease, such as proteinuria, erythrocyturia, etc. The study was approved by the Medical University Ethics Committee. Anemia was defined according to the World Health Organization criteria, i.e., hemoglobin below 12 g/dl in females and 13 g/dl in males [7]. CHF was defined according to the NYHA classification. Echocardiography was performed in each patient to assess the ejection fraction and left ventricular end-diastolic dimension. Hemoglobin, albumin, cholesterol and serum creatinine were analyzed by the standard laboratory methods in the central laboratory at the University Hospital. GFR was estimated using the simplified MDRD formula: eGFR = 186.3 x serum creatinine (mg/dl)$^{-1.14}$ x age$^{-0.203}$ x 0.742 if female x 1.21 if Afro-American; the Cockcroft-Gault formula: creatinine clearance = (140-age) x body weight/serum creatinine x 72 if female x 0.85; and the Jeliffe formula: 0.9 x 98 - (0.8 x [age {years} - 20])/serum creatinine (mg/dl). The CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration) is represented as the equation below, in which the values of the constants of *a*, *b*, and *c* vary on the basis of race, gender, and serum creatinine [8].

$$GFR = a \times (\text{serum creatinine}/b)^{c} \times (0.993)^{\text{age}}$$

The variable *a* takes on the following values on the basis of race and gender:

- Black
  - Women = 166
  - Men = 163
- White/other
  - Women = 144
  - Men = 141

The variable *b* takes on the following values on the basis of gender:

- Women = 0.7
- Men = 0.9

The variable *c* takes on the following values on the basis of gender and creatinine measurement:

- Women
  - Serum creatinine ≤ 0.7 mg/dl = -0.329
  - Serum creatinine > 0.7 mg/dl = -1.209
- Men
  - Serum creatinine ≤ 0.9 mg/dl = -0.411
  - Serum creatinine > 0.9 mg/dl = -1.209

We also estimated GFR using this new formula. Comparisons between groups were made by ANOVA (Statistica 6.0, StatSoft, Poland). Correlations between hemoglobin and other variables were evaluated by Pearson's or Spearman's test, as appropriate.

CCS = Canadian Cardiovascular Society

Table 1. Basal clinical and biochemical characteristics of the studied groups

	NYHA class I (n=237)	NYHA class II (n=261)	NYHA class III (n=20)	NYHA class IV (n=12)
Age (yrs)	55.94 ± 10.91	57.75 ± 11.42	61.07 ± 11.11	60.58 ± 11.77
Systolic BP (mmHg)	136 ± 25	127 ± 31	123 ± 45	121 ± 32
Diastolic BP (mmHg)	84 ± 19	80 ± 22	79 ± 25	78 ± 21
Ejection fraction (%)	58.76 ± 19.54	52.76 ± 17.43	48.54 ± 14.85*	44.32 ± 14.43**
LVIDd (mm)	4.29 ± 0.72	4.35 ± 1.14	5.49 ± 1.02*	5.67 ± 1.01**
Hb (g/dl)	14.35 ± 1.56	13.46 ± 0.69	12.69 ± 0.89 *	11.74 ± 1.12***
Urea (mg/dl)	37.97 ± 12.07	41.46 ± 2.94*	43.79 ± 12.65*	48.76 ± 13.54
eGFR (ml/min) (MDRD)	90.77 ± 21.32	82.54 ± 29.71*	74.00 ± 30.95***	59.23 ± 24.36***
eGFR (ml/min) (CKD-EPI)	86.52 ± 17.93	78.43 ± 18.60*	69.69 ± 23.35***	49.53 ± 19.30***
Creatinine clearance (ml/min) (Cockcroft-Gault formula)	73.88 ± 23.28	68.07 ± 23.56	65.92 ± 22.48*	58.15 ± 19.77***
Creatinine clearance (ml/min) (Cockcroft-Gault formula, weight adjusted)	79.42 ± 25.17	72.33 ± 28.65*	68.94 ± 21.55	62.95 ± 25.08***
eGFR (ml/min) (Jeliffe formula)	76.65 ± 25.17	72.33 ± 28.65	70.42 ± 24.92	63.52 ± 25.81***
Creatinine (mg/dl)	1.06 ± 0.26	1.09 ± 0.46	1.12 ± 0.38*	1.22 ± 0.25***
Cholesterol (mg/dl)	183.78 ± 58.54	180.45 ± 47.89	172.89 ± 52.76	169.76 ± 41.09

Values are mean ± SD

*$P < 0.05$, ** $P < 0.01$, ***$P < 0.001$ vs. NYHA class I

RESULTS

We observed a progressive decline in eGFR, creatinine clearance and hemoglobin concentrations, together with a rise in NYHA class [Table 1].

PREVALENCE OF CKD

The mean estimated GFR using the MDRD equation was 82 ml/min/1.73 m^2; with the new CKD-EPI formula it was 77 ml/min, while the mean creatinine clearance according to the Cockcroft-Gault formula was 68 ml/min. A higher degree of NYHA class was observed in more advanced stages of kidney disease [Table 1]. In 163 patients with stage 1 CKD (eGFR > 90 ml/min/1.73 m^2) the mean NYHA class was 1.41 ± 0.63. In 272 patients with stage 2 CKD (eGFR 60–89 ml/

min/1.73 m^2) the mean NYHA class was 1.59 ± 0.73 (P < 0.01 vs. stage 1 CKD). The mean NYHA class in 86 patients with stage 3 CKD (eGFR 30–59 ml/min/1.73 m^2) was 1.8 ± 0.83 (P < 0.001 vs. stage 1 CKD), and in 5 patients with stage 4 CKD (eGFR 15–29 ml/min/1.73 m^2) it was 2.03 ± 0.93 (P < 0.001 vs. stage 1 CKD). The prevalence of stages 3 and 4 CKD (eGFR below 60 ml/min/1.73 m^2) in the study population was dependent on the formula used for assessing kidney function: 17% using the MDRD formula, 22% with the CKD-EPI formula, 48% with the Jeliffe formula, 49% according to the Cockcroft-Gault formula (weight adjusted), and 55% with the Cockcroft-Gault formula. The estimated GFR (MDRD) correlated significantly with systolic blood pressure (r = 0.18, P < 0.001), diastolic blood pressure (r = 0.19, P < 0.001), age (r = -0.63, P < 0.001), NYHA class (r = -0.16, P < 0.001), complications after PCI (r = -0.12, P < 0.01), especially bleeding from the insertion site (r = -0.19, P < 0.001), and major adverse cardiac events (r = -0.16, P < 0.01). The prevalence of diabetes mellitus in the study population was 23% and the prevalence of hypertension 79%. With regard to medications, 72% of the patients were treated with angiotensin-converting inhibitors, 90% with beta-blockers and 70% with statins.

PREVALENCE OF ANEMIA

According to the WHO definition, the prevalence of anemia in the studied cohort was 21%. The hemoglobin concentrations declined concomitantly with a rise in NYHA class [Table 1]. The mean hemoglobin concentration in patients with NYHA class I was 14.35 ± 1.56 g/dl. Hemoglobin concentration declined to 13.46 ± 0.69 g/dl in patients with NYHA class II, to 12.69 ± 0.89 g/dl in patients with NYHA class III (P < 0.05 vs. NYHA class I) and to 11.74 ± 1.12 g/dl in patients with NYHA class IV (P < 0.001 vs. NYHA class I). Hemoglobin correlated significantly with NYHA class (r = -0.21, P < 0.01), presence of diabetes (r = -0.17, P < 0.01), presence of hypertension (r = -0.18, P < 0.01), ejection fraction (r = 0.25, P < 0.001), LVEDd (r = 0.16, P < 0.01), serum creatinine (r = -0.43, P < 0.001) and estimated GFR (r = 0.18, P < 0.01).

COMPLICATIONS AFTER PCI

The most frequent complication was bleeding from the insertion site. This complication was observed in 8.3% of the patients undergoing PCI in the study. Three percent of patients developed cardiac arrhythmias and 1% developed a major cardiac adverse event. Hematuria was detected in 0.8% of patients after the PCI. Stroke was present in 0.6% of patients, 0.4% developed hemophthisis and 0.3% experienced acute coronary syndrome. All of the above-mentioned complications occurred in patients with eGFR below 60 ml/min.

LVEDd = left ventricular end-diastolic dimension

DISCUSSION

Congestive heart failure and CKD share a number of risk factors and pathophysiologic pathways. CKD is common in patients with CHF, reaching up to 34.3% in the report by Gotsman et al. [9]. In the present study we found that many patients with stable coronary artery disease and normal serum creatinine levels have impaired kidney function. Zamora and co-authors [10] recently reported that even a mild degree of renal function impairment is associated with higher mortality rates. In the study of Freimark et al. [11] renal failure was more commonly the cause of death in patients with CHF than stroke and acute myocardial infarction. CHF and CKD appear to act together in a vicious cycle in which each condition causes or exacerbates the other. Both CHF and CKD are often underdiagnosed and undertreated in patients with normal or slightly elevated serum creatinine. In the present study, higher NYHA class was associated with more advanced stages of CKD and with a progressive decline in eGFR and creatinine clearance. In current practice, serum creatinine is an imperfect measurement to assess the GFR, because the production of creatinine differs among and within people over time. Serum creatinine depends on various variables, such as age, gender, muscle mass and metabolism, medications and the hydration status. Efforts have been made to estimate the GFR from a single measurement of creatinine, using various formulas, to account for dependent variables, such as in the MDRD study. In our study, clinically significant CKD (as defined by estimated GFR below 60 ml/min/1.73 m^2) was found in 17–55% of the study population, depending on the formula used to estimate GFR. It should be mentioned that age over 65 years is usually, but not always, associated with lowered GFR [12,13]. As reported by Antonelli and colleagues [14], patients over 70 years old had more cardiovascular pathologies and require significantly more drugs, including those known to affect GFR, than their younger counterparts.

Since current equations have limited precision and systematically underestimate measured GFR at higher values, a new estimating equation for GFR was needed. Developed by Levey et al. [8], the Chronic Kidney Disease Epidemiology Collaboration equation was derived from research studies and clinical populations ("studies") with measured GFR (using iothalamate) and NHANES (National Health and Nutrition Examination Survey) during the period 1999–2006 on 8254 subjects and validated in 3896 participants (with GFR assessed by iothalamate and other markers).

The new formula was proven to be more accurate and more precise than MDRD, but it does have limitations. The sample did not comprise enough elderly people, racial and ethnic minorities with measured GFR. In our study we found that the estimated GFR was slightly lower when using the CKD-EPI formula compared to the MDRD formula.

On the basis of our results, it should be emphasized that the prevalence of CKD in patients with coronary artery disease undergoing PCI is probably underestimated. Moreover, it should be stressed that the prevalence of CKD is high among patients with apparently normal serum creatinine undergoing PCI. We must also keep in mind that the risk of contrast-induced nephropathy is enhanced in patients with CKD, as reported by Shema et al. [15]. Therefore, CKD has to be diagnosed before any procedure using contrast agents, particularly in the elderly with comorbidities as we discussed recently [16].

Anemia is more prevalent in advanced CHF. Previous studies in CHF patients showed that anemia may be incidental or directly related to CHF itself. Increased circulating cytokines, hemodilution, iron deficiency, the use of ACE inhibitors, renal dysfunction, poor nutrition and decreased bone marrow perfusion may all contribute to the development of anemia in this population [17]. In the present study the prevalence of anemia in the studied cohort was 21%. We found a progressive decline in hemoglobin concentration which correlated to a rise in NYHA class. In our population, ACE inhibitors were administered to 72% of the patients. However, the expected relative decrease in hemoglobin concentration with those drugs might only be 0.2–0.3 g/dl [1]. In our study, patients treated with ACE inhibitors had significantly lower eGFR and lower hemoglobin levels. The adverse effect of ACE inhibitors may be mediated by Ac-SDKP (goralatide), a tetrapeptide that inhibits erythropoiesis [18]. In the last century, anemia in CHF was under-recognized and not even discussed in the U.S. guidelines committee report [19]. However, after several trials, including the SOLVD, ELITE II, COPERNICUS, CHARM, VAL-HEFT and others, anemia was recognized as an important risk factor for morbidity and mortality in CHF patients [20,21]. The odds ratio of mortality and hospitalization in patients with anemia are similar to those of four other common cardiovascular risk factors, namely smoking, diabetes mellitus, hypertension and hypercholesterolemia. It is for this reason that we have termed anemia "the fifth cardiovascular risk factor" [22].

In the present study hemoglobin levels were correlated to renal function, to the presence of diabetes and hypertension, and to NYHA class. However, we studied only patients with normal serum creatinine. The anemia in fact exacerbates the CHF [23]. Several controlled and uncontrolled trials showed that successfully treating the anemia leads to a significant amelioration of the CHF, especially in patients with CKD [4]. However, in the recent TREAT trial, it was reported that patients with type 2 diabetes, CKD (GFR between 20 and 60 ml/min calculated with the MDRD formula) and moderate anemia did not benefit from darbepoetin alfa. Active treatment did not reduce the risk of either of the two composite outcomes (death or a cardiovascular event, or death or a renal event) and was associated with an increased risk of stroke [24]. In the TREAT trial the prevalence of CHF was over 30% in the placebo and active treatment groups; it was even significantly higher in the placebo group at baseline (35.2% vs. 31.5%, $P = 0.01$). However, the ongoing RED-HF trial, designed to evaluate the effect of the long-acting erythropoietin-stimulating agent darbepoetin alfa on mortality and morbidity (and quality of life) in patients with heart failure and anemia, will probably answer the question of potential benefit of the correction of anemia in CHF [25].

In conclusion, since the prevalence of CKD is significantly increased in patients with advanced CHF and higher degree of NYHA class, and is also significantly related to a higher rate of complications after PCI, all patients with cardiovascular risk factors should be screened for the presence of CKD before undergoing invasive cardiac interventions. The currently used estimated GFR (MDRD) formula and the new CKD-EPI equation seem to be more sensitive than serum creatinine in detecting CKD and should be used for this purpose.

Cooperation between cardiologists and nephrologists in the treatment of patients with cardiovascular disease (particularly CHF) undergoing interventions may improve the quality of care and the subsequent prognosis and reduce the complications rate in this vulnerable population.

ACE = angiotensin-converting enzyme

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