Serum catalytic Iron: A novel biomarker for coronary artery disease in patients on maintenance hemodialysis

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ABSTRACT

Cardiovascular disease is the leading cause of morbidity and mortality in maintenance hemodialysis (MHD) patients. We evaluated the role of serum catalytic iron (SCI) as a biomarker for coronary artery disease (CAD) in patients on MHD. SCI was measured in 59 stable MHD patients. All patients underwent coronary angiography. Significant CAD was defined as a > 70% narrowing in at least one epicardial coronary artery. Levels of SCI were compared with a group of healthy controls. Significant CAD was detected in 22 (37.3%) patients, with one vessel disease in 14 (63.63%) and multi-vessel disease in eight (36.36%) patients. The MHD patients had elevated levels of SCI (4.70 ± 1.79 μmol/L) compared with normal health survey participants (0.11 ± 0.01 μmol/L) (P < 0.0001). MHD patients who had no CAD had SCI levels of 1.36 ± 0.34 μmol/L compared with those having significant CAD (8.92 ± 4.12 μmol/L) (P < 0.0001). Patients on MHD and diabetes had stronger correlation between SCI and prevalence of CAD compared with non-diabetics. Patients having one vessel disease had SCI of 8.85 ± 4.67 μmol/L versus multi-vessel disease with SCI of 9.05 ± 8.34 μmol/L, P = 0.48. In multivariate analysis, SCI and diabetes mellitus were independently associated with significant CAD. We confirm the high prevalence of significant CAD in MHD patients. Elevated SCI levels are associated with presence of significant coronary disease in such patients. The association of SCI is higher in diabetic versus the non-diabetic subgroup. This is an important potentially modifiable biomarker of CAD in MHD patients.

Key words: Coronary artery disease, maintenance hemodialysis, oxidative stress, serum catalytic iron

Introduction

Atherosclerotic cardiovascular disease (CVD) has a great impact on morbidity and mortality in patients with chronic kidney disease (CKD) undergoing renal replacement therapy, and accounts for approximately half of the deaths in patients with end-stage renal disease.[1] The incidence of acute myocardial infarction and cerebrovascular accidents in patients with end-stage renal disease on dialysis is 5- to 15-fold higher[2] and mortality 10- to 30-fold higher[3] than that seen in the general population.[4-6]

Systemic inflammation[7] and oxidative stress[8] have been implicated both in atherosclerotic CVD and in CKD. Renal dysfunction has emerged as a potent independent risk factor for mortality in patients with acute coronary syndrome. A common vascular link between CVD and renal disease, aptly called the cardio–renal syndrome, has been the subject of intense research interest.

Serum catalytic iron (SCI) or "free" iron is the circulating iron that is not bound to transferrin or ferritin and is available to generate reactive oxygen species that may have deleterious vascular effects. We have recently reported the role of SCI as a vascular biomarker in patients with acute coronary syndrome both in assisting early diagnosis and in predicting adverse outcomes.[9,10] High levels of circulating catalytic iron may accelerate atherosclerosis by a variety of mechanisms, including generation of oxidized low-density lipoprotein (LDL),[11] endothelial dysfunction, arterial smooth proliferation

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and ischemic reperfusion injury.[12,13] In this study, we evaluated the role of SCI for the presence of obstructive coronary disease in patients with CKD on maintenance hemodialysis (MHD).

Materials and Methods

Study population

This was a single-center cross-sectional study done between October 2008 and June 2009 including 59 stable patients with end-stage kidney disease who were on MHD for at least 6 months prior to enrolment at the Muljibhai Patel Urological Hospital, Nadiad, India. The study was approved by the Institution's Ethics Committee and a written informed consent was obtained from all participants. A detailed clinical history, physical examination, and electrocardiogram were recorded in all cases. Known risk factors for coronary artery disease (CAD), including diabetes, gender, hypertension, tobacco abuser (smoking or chewing) and family history of CVD, were carefully recorded. An extended lipid profile was also obtained in all patients. All patients were assessed by echocardiogram and Dobutamine stress echocardiogram. Carotid intimal thickness was also measured. At the time of enrolment, none of the patients had evidence of active infection and had not received intravenous iron for at least 48 h prior to blood sample collection. All patients were dialyzed using the F8 Fresenius Polysulphone UF 7.5 (Fresinius Medical Care AG and Co. KGaA-D-61346 Bad Homburg) dialyzer. Vascular access was native arterio-venous fistula for all except two patients who had tunneled cuffed catheters. We also measured catalytic iron in a contemporary cohort of 250 healthy volunteers who took part in a health survey of government employees in the Nadiad region of India during the same time frame.

Blood sampling and biochemical analysis

On enrolment, 10 mL of blood was collected in a plain non-barrier tube and centrifuged at 1400-2000 Relative centrifugal force (RCF) for 10 min at 4°C. The serum component was frozen and stored at –70°C. The blood sample was processed at the Department of Biochemistry of Muljibhai Patel Society for Research in Nephro-Urology, Nadiad. All the samples were thawed at the time of analysis and all samples were analyzed for catalytic iron levels in the same batch. The catalytic iron levels were measured by a modified Bleomycin detectable catalytic iron assay.[14] The assay is based on the observation that the anti-tumor antibiotic, Bleomycin, in the presence of free iron and a suitable reducing agent, binds to and degrades DNA with the formation of a product that reacts with thiobarbituric acid to form a chromogen. The assay detects non-transferrin-bound free iron capable of catalyzing free-radical reactions in biological samples. The reactions were carried out in one-half the recommended volume and performed in disposable polypropylene tubes to avoid iron contamination from external sources. All of the reagent solutions except the Bleomycin were treated overnight with chelex (Bio-Rad Laboratories Inc., California, USA) (300 mg for 10 mL solution) to remove any iron in the chemical reagents. Serum iron level was measured using a biochemical kit (Teco Diagnostics, California, USA).

Coronary angiography

None of the patients have symptomatic angina. They were explained that asymptomatic CAD is not uncommon in patients on MHD. It was explained that the gold standard test to confirm the presence of CAD is to undergo coronary angiography irrespective of the results of non-invasive tests. In the study published from our institute, we have demonstrated that non-invasive tests are not sufficient to diagnose CAD in patients of diabetes being evaluated for kidney transplantation.[15]

The angiography was performed in all the patients through the left femoral route. Quantification of the extent and severity of obstructive coronary disease was performed by Quantification of Coronary Angiogram using a software program supplied by Philips Medical Systems, Netherlands. Significant obstructive coronary disease was defined as luminal narrowing ≥70% in epicardial coronary vessels.

Statistical analysis

It was planned to enroll 56 patients so as to have a power of study as 90% and the level of significance as 95%. The total number of patients enrolled was 59; hence, the power of the study became 91% at the same level of significance (Power and Sample Size Calculation version 3.0.7). Patients were studied in two groups distributed as per the presence or absence of CAD. Comparisons were also made based on the extent of the obstructive coronary disease. The sample size was limited to 59 patients because of the number of stable patients on MHD who gave informed consent to take part in this study. The multiple regression analysis using backward elimination method was performed using the software IBM Statistical Package for Social Sciences Version 15 (SPSS) version 15.0. Comparison of catalytic iron in various groups was performed by Student's *t*-test for independent samples. Chi-square test was used to test the significant difference in 2 × 2 arrays using Yates correction.

Results

The baseline characteristics of the 59 patients enrolled in the study are shown in Table 1. The mean age of the study group was 54.8 ± 9.4 years, the range being 40-82 years. Forty-one (69.5%) were male and 18 (30.5%) were female. The mean duration of hemodialysis of the study population was 32.57 ± 32.1 months (mean + standard deviation) (range was 6-130 months).

The native kidney disease was diabetic nephropathy in 19 (32.2%), hypertensive nephrosclerosis in 4 (6.7%), chronic glomerulonephritis in 7 (11.84%), chronic tubulo-interstitial disease in 6 (10.16%), autosomal-dominant polycystic kidney disease in 3 (5.08%), chronic allograft nephropathy in 6 (10.16%), ischemic nephropathy in 4 (6.7%) and undetermined etiology in 10 (16.94%) patients.

Table 1: Baseline clinical characteristics of the two groups studied

Characteristics	No of cases	CAD absent *n* (%)	CAD present *n* (%)
Number of patients	59	37 (62.7)	22 (37.3)
Age (years) (mean±SEM)		53.03±1.50	57.27±2.18
Duration of MHD (months) (mean±SEM)		31.22±5.56	34.86±6.31
Gender			
Females	18	13 (72.2)	5 (27.8)
Males	41	24 (58.5)	17 (41.5)
Diabetes mellitus			
Yes	22	8 (36.36)	14 (63.63)
No	37	29 (78.4)	8 (21.6)
Hypertension			
Yes	53	32 (60.4)	21 (39.6)
No	6	5 (83.3)	1 (16.7)
Tobacco abuse			
Yes	27	13 (48.2)	14 (51.8)
No	32	24 (75)	8 (25)
Family history of CVD			
Yes	10	4 (40)	6 (60)
No	49	33 (68.3)	16 (32.7)

CAD: Coronary artery disease, MHD: Maintenance hemodialysis, CVD: Cardiovascular disease

Serum total iron levels as well as SCI levels were measured in all the MHD patients. A correlation coefficient (R) of 0.008 and significance of $P = 0.95$ was found between SCI and serum total iron level.

Catalytic iron level in the study population was 4.18 ± 1.61 μmol/L. The control population without any co-morbidity had a catalytic iron level of 0.1 ± 0.06 μmol/L ($P < 0.0001$) (mean + SEM) [Figure 1].

Prevalence of significant CAD was associated with presence of diabetes mellitus (OR = 6.34, $P = 0.003$), male gender (OR = 1.84, $P = 0.48$), hypertension (OR = 3.28, $P = 0.51$), tobacco abusers (OR = 3.23, $P = 0.06$), family history of CVD (OR = 3.09, $P = 0.2$) and patients with elevated levels of catalytic iron ($P < 0.0001$) [Table 1].

On coronary angiography, no significant obstructive coronary disease was detected in 37 patients (62.7%). In this group, the mean catalytic iron was 1.35 ± 0.34 μmol/L. Significant obstructive coronary disease was detected in 22 patients (37.3%). In this group, catalytic iron was 8.92 ± 4.12 μmol/L ($P < 0.0001$) [Figure 2].

Out of the 59 patients 22 had diabetes (37.3%) and, as a group, their catalytic iron level was 5.34 ± 3.06 μmol/L. Of these 22 diabetic patients, 14 (63.6%) had significant obstructive coronary disease and their catalytic

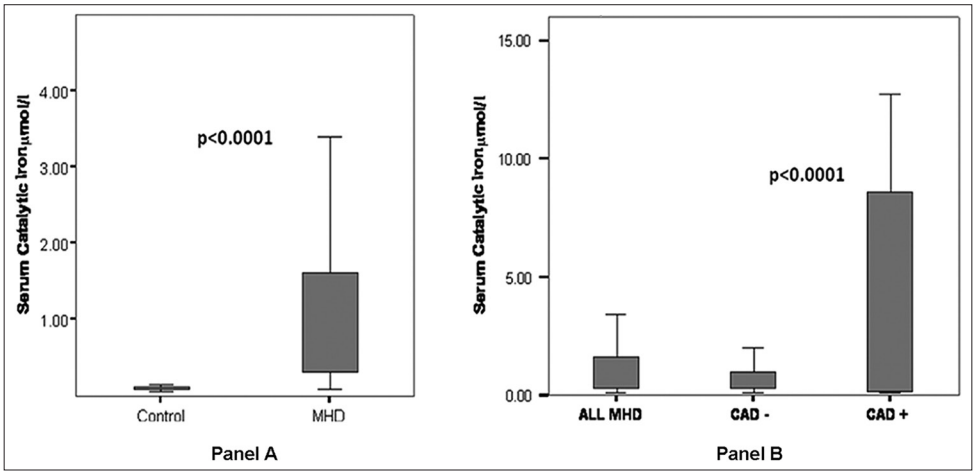

Figure 1: Panel A: Box plots showing catalytic iron (Mean ± SEM) levels in normal control population, *n* = 250 (catalytic iron - 0.1 ± 0.06 μmol/L) as compared to hemodialysis (maintenance hemodialysis) patients, *n* = 59. (Catalytic iron - 4.18 ± 1.61 μmol/L). Panel B: Box plots showing catalytic iron (Mean ± SEM) levels in all hemodialysispatients (4.18 ± 1.61 μmol/L), without coronary artery disease (CAD−) (1.35 ± 0.338 μmol/L) and with CAD+ (8.92 ± 4.12 μmol/L). Boxes show interquartile ranges and the bar represents highest and lowest values

iron levels were 8.06 ± 4.71 μmol/L, and the remaining eight without obstructive coronary disease had catalytic iron levels of 0.59 ± 0.08 μmol/L (P = 0.0004) (mean + SEM).

In the 37 non-diabetic patients, 8 (21.6%) had significant obstructive coronary disease and catalytic iron levels of 10.43 ± 8.24 μmol/L compared with 29 (78.4%) without obstructive coronary disease, who had catalytic iron levels of 1.57 ± 0.43 μmol/L (P = 0.0004) (mean + SEM).

Among patients who had significant obstructive coronary disease, 14 (63.63%) had single vessel disease and 8 (36.36%) had multi-vessel disease. The catalytic iron levels were 8.85 ± 4.67 μmol/L in patients having single vessel disease and 9.04 ± 8.34 μmol/L in patients having multi-vessel disease (P = 0.48).

Multiple regression analysis using backward elimination method was performed using SPSS version 15.0. The dependent variable of the prevalence of obstructive CAD was assessed against the following factors: gender, age, diabetes mellitus, hypertension, tobacco abuse, family history of CVD, and catalytic iron levels. Diabetes mellitus (P = 0.001) and catalytic iron levels (P = 0.024) were the two independently significantly associated variables for obstructive coronary disease in this cohort of patients with end-stage renal disease on MHD [Table 2].

Discussion

Cardio–renal syndrome is a term often used to describe the intricate relationship between obstructive coronary disease and end-stage renal disease. Renal dysfunction has been noted to be an important predictor of adverse cardiac events like stent thrombosis[16] and mortality in patients with acute coronary syndrome.[17] Conversely, in patients with end-stage renal disease, the prevalence of obstructive coronary disease is extremely high and cardiovascular events account for over half the mortality that is seen in patients with end-stage renal disease. We have recently shown[9] that a rise in catalytic iron levels in serum detects the onset of acute coronary syndrome in patients with chest pain, and a progressive elevation over the next 24 h predicts adverse cardiac events including stent thrombosis and death.

In the present study, we showed a distinct relationship between elevated catalytic iron levels in serum and prevalence of obstructive coronary disease in patients with end-stage renal disease on MHD. This relationship appears even more striking in patients with diabetes compared with those without diabetes.

Various previous studies have documented a very high prevalence of obstructive coronary disease in patients with end-stage renal disease on MHD. Independent predictors of coronary disease in patients with end-stage renal disease includes older age,[5,18] male gender,[18,19] smoking,[19,20] diabetes,[18] a high systolic or diastolic blood pressure,[5,19-22] hypercholesterolemia,[18,22] low High density lipoprotein (HDL) cholesterol,[20] increased lipoprotein (a),[23] increased fibrinogen,[20] decreased alkaline phosphatase,[20] abnormal left ventricular motion[18] and the presence of symptomatic ischemic heart disease before initiation of renal replacement therapy (RRT).[18]

Among these factors, those that were reported as independent risk factors for Coronary angiography (CAG-proven) significant CAD are smoking and diabetes in pre-dialysis CKD patients and dialysis patients by Hase *et al.*,[19] smoking, high systolic blood pressure, low HDL cholesterol and increased fibrinogen in pre-dialysis CKD patients by Jungers *et al.*,[20] and low molecular weight Apo (a) phenotype in dialysis patients by Kronenberg *et al.*,[22] Independent risk factors for significant CAD in

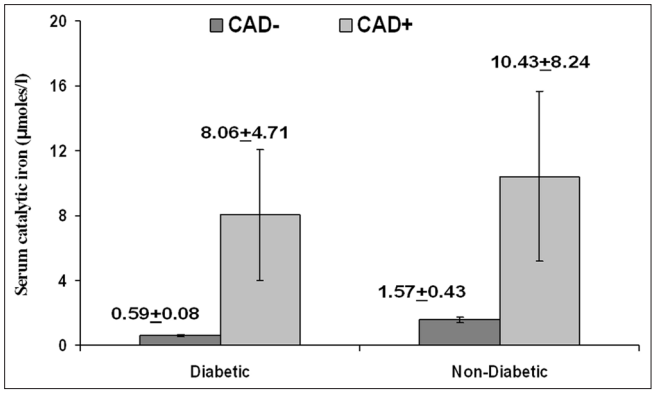

Figure 2: Histogram showing catalytic iron levels in μmol/L (Mean ± SEM) in patients with diabetes and non-diabetic patients, with respect to those having coronary artery disease (CAD+) and those without CAD−

Table 2: Multiple regression analysis

Variable	β-coefficient	t value	P value	95% confidence interval	
				Lower	Upper
Age	0.189	1.625	0.110	−0.002	0.022
Family history of CVD	0.215	1.805	0.077	−0.031	0.585
Tobacco abuse	0.168	1.475	0.146	−0.059	0.385
Male gender	−0.058	−0.407	0.685	−0.359	0.238
Hypertension	0.027	0.230	0.819	−0.328	0.413
Diabetes mellitus	0.400	3.447	0.001*	0.168	0.633
Catalytic iron	0.270	2.324	0.024	0.001	0.020

Diabetes mellitus (P=0.001) and catalytic iron levels (P=0.024) were the two independent predictors for obstructive coronary disease in this cohort of patients with end stage renal disease on maintenance hemodialysis, CVD: Cardiovascular disease

CKD patients at the initiation of RRT were diabetes and fibrinogen in a study by Ohtake *et al*.[23]

Sullivan in 1981 had suggested the possible role of iron in CVDs.[24] However, the relationship between serum total iron and obstructive coronary disease[25] or acute coronary syndrome is extremely weak.[26] Catalytic iron is a subfraction of the total iron that is non-transferrin bound, in the ferric state, is unstable and is highly reactive. Two deleterious effects of this catalytic iron are now clearly understood. Free iron acts as a catalyst in the Haber Weiss reaction and promotes the generation of reactive oxygen species, like the highly reactive hydroxyl ion (-OH). The hydroxyl ion causes oxidative damage to the tissue by acting on substrates like LDL, amino acids and DNA. The second and potentially more relevant effect of catalytic iron is its ability to cause endothelial cell damage by promoting endothelial cell apoptosis.[27] This breach in the integrity of the endothelial cell lining is an important nidus leading to accelerated atherosclerosis.

Uremia itself also plays a role in increasing oxidant injury and subsequent atherogenesis by increased cytokines, complement activation, retained solutes, neutrophil priming, malnutrition, hemodialysis characteristics (biocompatibility, purity of water for dialysis catheter use), infection, raised β2-microglobulin levels and abnormal lipids increased LDL, Poly unsaturated fatty acids (PUFA).

Our findings in the current study suggest that high catalytic iron is significantly associated with and may play a role in accelerated atherosclerosis in patients with end-stage renal disease on MHD. Comparing multiple known risk factors for accelerated atherosclerosis, diabetes and a high SCI level stand out as important independent associations in such patients. In fact, the relationship between an elevated SCI and obstructive coronary disease is even more marked in patients with diabetes.

Although there is a strong correlation between elevated SCI and obstructive coronary disease, we found no correlation between the extent of coronary disease and the elevation of catalytic iron. This could indeed be a function of smaller numbers or a reflection of the generic effect of the elevation of catalytic iron on vascular damage.

Although speculative, the relationship between elevated SCI levels and obstructive coronary disease and acute coronary syndromes opens novel alternative ways to modify and regress the atherosclerotic process and minimize adverse cardiac events. One such therapeutic approach could be the use of iron chelating agent in the subset of patients who are at a high risk for accelerated atherosclerosis and have documented high SCI levels in the serum.

Limitations of the study

This was single-center study and, therefore, the sample size was limited. The power of the study was 91% and the level of significance was 95% (Power and Sample Size Calculation version 3.0.7). Further studies are needed with large population numbers to establish the positive predictive value and reliability of SCI as a marker of atherosclerosis in patients with end-stage renal disease.

There were few outliers with very high SCI levels that influenced the results of our study. These patients had significant obstructive coronary disease on angiography.

This was a cross-sectional study. Longitudinal studies are needed to determine whether the patients with elevated SCI levels and obstructive coronary disease on coronary angiography develop acute cardiac events.

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Commentary

Atherosclerosis in chronic kidney disease: Striking while the Iron is labile

Cardiovascular disease (CVD) due to atherosclerosis is a leading cause of morbidity and mortality in both developing and developed world. This holds true for patients with all stages of the chronic kidney disease (CKD) so much hence that it has been remarked that "only the lucky reach dialysis" since the majority of the pre-dialysis subjects experience cardiovascular events before progressing to end stage renal disease. It is well-known that even on dialysis cardiovascular disease is the most important cause for mortality. In fact, a recent study endorsed the long prevailing perception that CKD, like diabetes, should be considered as a coronary artery disease (CAD) equivalent.[1]

The understanding of pathogenesis of atherosclerosis has grown immensely and it is now known that inflammation in all its hues is plays a significant role in addition to conventional risk factors. Oxidative stress is ubiquitous in all cellular activities and its role has been implicated in a host of the disease conditions including atherovascular disease. However, unfortunately, exogenous anti-oxidant therapy has so far delivered very limited therapeutic success in most conditions.

This issue of the journal carries an article about serum catalytic iron as a biomarker for coronary artery disease in