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Original Article

Association of coronary artery disease and chronic kidney disease in Lebanese population

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Abstract: Background: More evidence is emerging on the strong association between chronic kidney disease (CKD) and cardiovascular disease. We assessed the relationship between coronary artery disease (CAD) and renal dysfunction level (RDL) in a group of Lebanese patients. Methods: A total of 1268 patients undergoing cardiac catheterization were sequentially enrolled in a multicenter cross sectional study. Angiograms were reviewed and CAD severity scores (CADSS) were determined. Estimated glomerular filtration rate (eGFR) was calculated and clinical and laboratory data were obtained. CKD was defined as eGFR < 60 ml/min. Logistic regression model was performed using multivariate analysis including all traditional risk factors associated with both diseases. ANOVA and the Tukeytestswere used to compare subgroups of patients and to assess the impact of each disease on the severity of the other. Results: Among the 82% patients who exhibited variable degrees of CAD, 20.6% had an eGFR < 60 ml/min. Logistic regression analysis revealed a bidirectional independent association between CAD and CKD with an OR = 2.01 (P < 0.01) and an OR = 1.99 (P < 0.01) for CAD and CKD frequencies, respectively. We observed a steady increase in the CADSS mean as eGFR declined and a progressive reduction in renal function with the worsening of CAD (P < 0.05). This correlation remained highly significant despite considerable inter-patient variability and was at its highest at the most advanced stages of both diseases. Conclusions: Our results show a strong, independent and graded bidirectional relationship between CAD severity and RDL. We propose to add CAD to the list of risk factors for the development and progression of CKD.

Keywords: Chronic kidney disease, coronary artery disease, Lebanese population

Introduction

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiological processes associated with a progressive decline in glomerular filtration rate (GFR). CKD has been classified into stages according to the level of estimated GFR (eGFR) and/or presence of proteinuria, abnormal urine sediment or abnormal imaging studies [1]. The epidemiology of the disease and its progression to the uremic syndrome and death makes it an important worldwide health burden and public health problem [2].

Diabetes mellitus (DM), age, gender, dyslipidemia, smoking, obesity, family history for CKD and hypertension are traditional risk factors for the development of CKD [3]. Consanguinity, a well-known cultural phenomenon in the Middle East and the North African region, has been shown to have strong association with kidney disease. Barbari et al., reported an increased risk for familial kidney disease and an earlier

onset of renal failure and dialysis initiation at a younger age in both cystic and non-cystic diseases in the consanguineous patients when compared with their non-consanguineous counterparts [4]. In addition to these well-established risk factors, inter-individual variability in the rate of progression of CKD has an important inheritable component, and a number of genetic loci that contribute to CKD progression have been recently identified [5-8].

Coronary artery disease (CAD) represents the most common, serious and chronic life threatening illness in developed and non-developed countries [9, 10]. In the USA, studies showed that only 2-7% of the general population is risk-free for cardiovascular disease and more than 70% have multiple risk factors [11]. High fat and energy rich diet, smoking, sedentary lifestyle and family history for CAD (FxCAD), are strongly associated with the development of CAD. Obesity, hypertension, age, gender, insulin resistance and type 2 DM are also well-established powerful risk factors for CAD [3, 10].

Chronic kidney disease has been recently suggested as an independent risk factor for CAD. Several reports support a direct link between a decline in GFR and a predisposition to cardiac events. Annual cardiovascular mortality rates are greater in dialysis patients then in the general population, matched for gender, race and age [12-20]. Although the impact of CAD on CKD is also studied [12, 13] CAD is not listed among traditional risk factor for CKD.

We recently suggested that the link between CKD and CAD should be viewed as a continuum that can precede the diagnosis of CKD [21]. Diabetes mellitus, hypertension, atherosclerosis, inflammation, age, gender, obesity and smoking are considered to be major determinants of this continuum and their progression significantly contributes to its exacerbation, in addition to the adverse impact of genetics, ethnic and other environmental factors [21].

Few studies examined the association between CAD and RDL in the Middle East region. Renal failure had an effect on cardiovascular mortality in a study on Turkish patients with ischemic and non-ischemic dilated cardiomyopathy [22]. Cardiovascular diseases and atherosclerotic risk factors were found to be common in patients with ESRD undergoing renal transplantation [23].

The present study was conducted to investigate retrospectively in a cohort of the Lebanese population the relationship between CAD and RDL, in particular CKD defined by an eGFR < 60 ml/min, and the relative contribution of each entity to the severity of the other.

Methods

Study population and description

A total of 1268 Lebanese patients undergoing cardiac catheterization were sequentially enrolled for the FGENTCARD study (Functional Genomic diagnostic Tools for Coronary Artery Disease (http://www.well.ox.ac.uk/fgentcard/) as part of a multi-center cross-sectional study conducted between May 2007 and June 2010. Patients were presenting for cardiac catheterization at the Rafik Hariri University Hospital (RHUH), the Saint Georges Hospital, and the "Centre Hospitalier du Nord" (CHN) in Lebanon.

The study was performed in compliance with the declaration of Helsinki. The Institutional Review Board at the Lebanese American University approved the study protocol and all subjects participating in the study gave informed consent before their enrollment. Catheterization by Judkins' technique was performed in case of myocardial infarction, unstable angina, or other reasons such as failure of exercise treadmill testing in reversible ischemia. Coronary lesions were assessed visually by comparing the reduction in the diameter of the narrowed vessel to a proximal normal arterial segment. The angiograms were reviewed by two experienced interventional cardiologists in each site.

A questionnaire was specifically developed to measure the impact of CAD risk factors and family history was duly filled and signed by each participant. Diabetes, hypertension and dyslipidemia were diagnosed when an ascertained physician reported the condition. A family history of CAD was annotated positive when CAD was present in a parent, sibling, or second degree relative. Body mass index (BMI) was calculated according to standard measurements and subjects were classified as obese when their BMI was superior to 30. Smokers were

Table 1. Descriptive demographics of patients' population

	eGFR ≥ 60 (% by row)	eGFR < 60 (% by row)	Total (% by column)
N/(%)	1022 (80.6%)	246 (19.4%)	1268 (100%)
Age			
Mean ± SD	63.2 ± 10.0	72.6 ± 9.3	64.9 ± 10.5
Male	62.3 ± 9.9	72.5 ± 9.5	64.1 ± 10.6
Female	64.8 ± 9.9	72.7± 8.9	66.5 ± 10.2
Gender			
Male	659 (81.8%)	146 (18.2%)	805 (63.5%)
Female	363 (78.4%)	100 (21.6%)	463 (36.5%)
Smoking	699 (82.3%)	150 (17.6%)	849 (66.9%)
CAD	826 (79.4%)	214 (20.6%)	1040 (82.0%)
Diabetes mellitus	322 (80.9%)	76 (19.1%)	398 (31.4%)
Obesity	374 (88.2%)	50 (11.8%)	424 (33.4%)
Hypertension	652 (77.7%)	187(22.3%)	839 (66.2%)
Dyslipidemia	513 (82.3%)	110 (17.6%)	623 (49.1%)
FxCAD	552 (83.5%)	109 (16.5%)	661 (52.1%)
Consanguinity	253 (80.8%)	60 (19.2%)	313 (24.7%)

CAD: Coronary Artery Disease, FxCAD: Family History of Coronary Artery Disease.

defined as subjects who smoked cigarettes before or at the time of enrollment for the study. Annotations were coded from medical charts for additional data such as laboratory tests, prescribed medications, and presence of other diseases and conditions. Serum creatinine was measured before catheterization and eGFR was calculated using both the Cockroft-Gault and MDRD equations.

Subjects were stratified according to their RDL, defined by an eGFR range, into 5 levels: level 0 (normal-control) with eGFR > 90 ml/min, level 1 with 60 < eGFR < 89 ml/min; level 2 with 30 < eGFR < 59 ml/min; level 3 with 15 < eGFR < 29 ml/min and level 4 with eGFR < 15 ml/min.

As for CAD, we created a severity scoring (CADSS) system influenced by both Gensini and Syntax scores [24, 25] in order to classify patients according to disease severity. Patients were stratified according to their CADSS into 5 CAD stages: CADSS 0: normal-control (score = 0), CADSS 1: mild (score = 1-40), CADSS 2: moderate (score = 41-80), CADSS 3: severe (score = 81-120) and CADSS 4: thrombosis (score > 120). The CADSS takes into account the degree of stenosis, the type of artery and the number of vessels involved. CADSS was calculated as follows: the degree of stenosis was allocated a number that was multiplied by another number allocated for each specific vessel and the number of vessels involved multiplied the result. The numbers allocated for the degree of stenosis were: 3 for a < 50% stenosis, 12 for a 50-90% stenosis, 42 for a > 90% stenosis with occlusion. For the vessels involved multipliers were 5 for the left main coronary artery, 2.5 for the proximal segment of the left anterior descending coronary artery (LAD) and circumflex artery, 1.5 for the mid-segment of the LAD, 1 for the right coronary artery, the distal segment of the LAD, the posterolateral artery, and the obtuse marginal artery and finally 0.5 for other segments.

Regression models and statistical analysis

A first logistic regression model was used to calculate the odds of having CAD in patients with eGFR < 90 ml/min corrected for the traditional CAD risk factors such as age, male gender, hypertension, smoking, obesity, DM, dyslipidemia, consanguinity and FxCAD *versus* normal control cases.

A second binomial logistic regression model was used to calculate the odds of having eGFR level less than 90 ml/min in patients with CAD corrected for the traditional CKD risk factors (age, male gender, hypertension, smoking, obesity, DM, dyslipidemia and consanguinity) *versus*normal control cases.

In addition, patients were divided into several groups according to their RDL defined by eGFR ranges. The corresponding CADSS mean among these different groups was analyzed using an ANOVA test and the Tukey Honest Significant Differences (TukeyHSD) test was performed for multiple comparisons. Similarly, patients were divided into several groups according to their CADSS. The corresponding means of the eGFR values among these different groups were analyzed using an ANOVA test and the TukeyHSD test was performed for multiple comparisons.

Table 2. Patients' distribution by CAD stages and by levels of renal dysfunction defined by ranges of eGFR expressed in ml/min

			CAD staging		
			Normal	Mild to Moderate	Severe to Thrombosis
	eGFR ml/min	N	228	745	295
Renal dysfunction levels expressed by ranges of eGFR (ml/min)	Normal				
	90-120 (N/% by row)	495	107 (21.6%)	293 (59.2%)	95 (19.2%)
	Level 1				
	60-89 (N/% by row)	527	89 (16.9%)	316 (60.0%)	122 (23.1%)
	Level 2				
	30-59 (N/% by row)	215	30 (13.9%)	121 (56.3%)	64 (29.8%)
	Level 3				
	15-29 (N/% by row)	18	1 (5.5%)	10 (55.6%)	7 (38.9%)
	Level 4				
	< 15 (N/% by row)	13	1 (7.7%)	5 (38.5%)	7 (53.8%)

Table 3. Adjusted odds ratios predicting CAD as outcome variable

	OR	CI 95%	*P* value
RDL (eGFR < 90 ml/min)	1.74	1.27-2.40	< 0.001
Obesity	1.20	0.85-1.70	0.31
Smoking	1.46	1.05-2.02	0.02
Diabetes	1.80	1.24-2.63	< 0.01
Hypertension	1.40	1.01-1.95	0.05
Hyperlipidemia	1.09	0.79-1.49	0.62
FxCAD	1.60	1.17-2.19	< 0.01
Consanguinity level 1	0.66	0.44-0.98	0.04
Consanguinity level 2	0.87	0.52-1.45	0.59

CI 95%: confidence interval 95%, FxCAD: Family history of CAD, consanguinity level 1: parents first degree cousins, consanguinity level 2: parents second or more degree cousins.

Table 4. Adjusted odds ratios predicting RDL (eGFR < 90 ml/min) as outcome variable

	OR	IC 95%	*P* value
CAD	1.75	1.27-2.41	< 0.001
Obesity	0.41	0.32-0.53	< 0.001
Smoking	0.60	0.46-0.78	< 0.001
Diabetes	1.01	0.78-1.31	0.94
Hypertension	1.91	1.47-2.47	< 0.001
Hyperlipidemia	0.95	0.75-1.22	0.71
FxCAD	0.77	0.60-0.97	0.03
Consanguinity level 1	0.94	0.67-1.31	0.71
Consanguinity level 2	0.79	0.53-1.17	0.24

CI 95%: confidence interval 95%, FxCAD: Family history of CKD, consanguinity level 1: parents first degree cousins, consanguinity level 2: parents second or more degree cousins.

The average area under the curve (AUC) was computed for all logistic regression models. The R statistical software (version 2.14) was used for the analysis and the glomerular function from the "stats" package was used for building the logistic regression models. *P* value of 0.05 indicated statistical significance.

Results

The study population (n = 1268), mean age 65 years, consisted of 805 males (63.5%) and 463 females (36.5%). Two hundred twenty eight (18%) of the total studied population had normal angiogram with no or minor lesions in all coronary arteries, and the remaining 1040 were labeled as CAD patients (82% of the total studied population; 66% males and 34% females) presenting with variable degrees of coronary lesions. A total of 246 patients (19.4% of the total studied population) were identified as CKD patientshaving eGFR < 60 ml/min calculated by Cockroft-Gault formula. Among these patients, 214 (86.7%) had CAD. All patients' characteristics are summarized in **Table 1**. All results reported in this section concerning eGFR determination were based on the Cockcroft-Gault equation. Comparable results were found when eGFR was calculated using MDRD equation (data now shown).

The study population was then divided into three groups according to the CADSS: patients with normal angiogram (controls), patients with mild to moderate CAD and patients with occlu-

Table 5. Mean CAD severity scores (CADSS) for different levels of renal dysfunction

RDL level	CADSS (Mean (95% CI))	Tukey HSD test *P* value
Normal renal function (eGFR 90-120 ml/min)	41.9 (38.5-45.4)	
RDL 1 (eGFR 60-89 ml/min)	47.1 (43.4-50.7)	0.298
RDL 2 (eGFR 30-59 ml/min)	58.3 (51.9-64.8)	< 0.001
RDL 3 (eGFR 15-29 ml/min)	65.5 (41.9-88.9)	0.14
RDL 4 (eGFR < 15 ml/min)	79.5 (51.0-107.9)	< 0.05

Tukey HSD test *P* values presented are only related to comparison with the normal renal function group.

sive CAD (severe to thrombosis) and compared according to RDL defined by the value of eGFR in ml/min (**Table 2**). We observed a significant relationship between RDL and the CAD severity staging (X^2 test, P = 0.001). The proportion of patients in the most advanced CAD stage (severe to thrombosis) increased with the decline in the eGFR from 23.1% in level 1 reaching 53.8% of the cases in level 4 as opposed to the proportion of patients with normal coronary angiogram that decreased with the deterioration in renal function from 21.6% to 7.7%. All results reported concerning RDL evaluation were done according to Cockcroft-Gault equation. Comparable results were found when eGFR was calculated using MDRD equation (data now shown).

Logistic regression analysis

The first logistic regression model of CAD occurrence according to RDL corrected for all other confounding factors (age, gender, obesity, dyslipidemia, DM, smoking, consanguinity and FxCAD) demonstrated a strong effect of RDL (eGFR < 90 ml/min) (OR = 1.74, CI: 1.27-2.40, P = 0.0006) (**Table 3**) and more importantly in patients with CKD with an eGFR less than 60 ml/min (OR = 2.01, CI: 1.27-3.18, P = 0.0029) (Supplementary Table 1).

The second logistic regression model was built to assess the impact of CAD on RDL and in particular on the occurrence of CKD. This model showed that CAD is strongly associated with RDL (eGFR < 90 ml/min) (OR: 1.75, CI: 1.27-2.41, P = 0.0005) (**Table 4**) and specifically with an increased risk of CKD (eGFR < 60 ml/min) (OR = 1.99, CI: 1.26-3.14, P = 0.0032) (Supplementary Table 2). These OR were obtained after correction for all other CKD risk factors (age, gender, obesity, dyslipidemia, DM, smoking and consanguinity).

Impact of RDL on CAD severity

When we examined the effect of RDL on CAD severity by correlating patients mean eGFR within each RDL level with their corresponding CADSS means; we observed a steady increase in the CADSS mean as renal function declined. Patients' with normal renal function (eGFR 90-120 ml/min) had a mean score of 41.9 (38.5-45.4). Mean CADSS increased progressively as renal function declined in CKD patients with RDL 1, RDL 2 and RDL 3 (eGFR 15-29 ml/min). The most striking augmentation was noted in the group of patients with the most advanced CKD (RDL 4). ANOVA and Tukey test both showed significant differences between the groups and among each other when compared two by two. Results are shown in **Table 5** and **Figure 1A**.

As expected, we have also observed noticeable inter-patient variability in the CAD staging within each level of renal dysfunction (**Figure 1B**). Despite this variability, the ANOVA and Tukey test both showed significant positive correlation between the increase in the CADSS and the reduction in eGFR (P < 0.05).

Impact of CAD severity on RDL

Our study showed a steady decline in mean eGFR as CADSS increased. In the subgroup of patients with normal coronary angiogram, mean eGFR was 86.1 ml/min (83.1-89.1). We observed a further decline in the mean eGFR in patients with mild CAD (CADSS: 1-40), moderate CAD (CADSS: 41-80) and severe CAD (CADSS: 81-120). Sharp fall in the mean eGFR was noted in patients with CADSS above 120 (thrombotic CAD). ANOVA and Tukey test both showed significant differences between the groups and among each other when compared two by two. Results are detailed in **Table 6** and **Figure 2A**.

Moreover, there was a clear inter-patient variability in relation to the means of eGFR within each CAD stage (**Figure 2B**). Despite this variability, the ANOVA and Tukey test both showed a significant correlation between the reduction in the mean eGFR and the severity of CAD (P < 0.05).

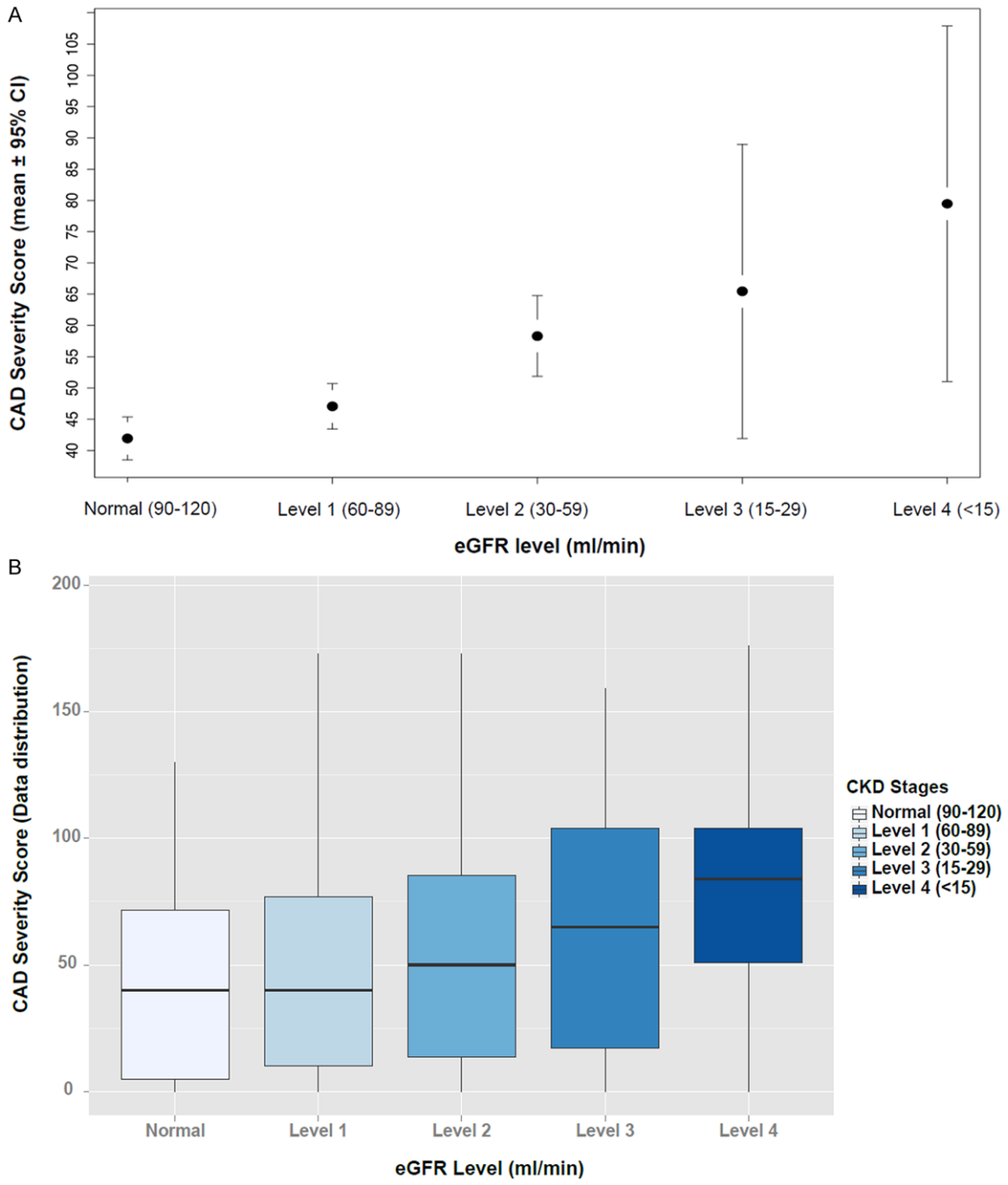

Figure 1. A: Variation of the mean CAD severity score (CADSS, ± 95% CI) of patients according to renal dysfunction levels defined by the corresponding means of eGFR expressed in ml/min. B: Data distribution of patient's CAD severity score (CADSS) of patients according to renal dysfunction level (RDL) defined by ranges of eGFR expressed in ml/min.

Discussion

Our study aimed to investigate the association between CAD and RDL and to assess the impact of each of the two diseases, CAD and CKD, on the risk of occurrence of the other, as well as on its staging and degree of severity. Similarly, other well-established traditional risk factors common for both CKD and CAD were also analyzed and odds ratios predicting CKD or CAD as outcome variables were corrected for all of them.

Table 6. Mean eGFR values for different levels of CAD severity

CAD severity level	eGFR (in ml/min) (Mean (95% CI))	Tukey HSD test *P* value
Normal angiogram	86.1 (83.1-89.1)	
Mild CAD (CADSS: 1-40)	82.3 (80.1-84.5)	0.28
Moderate CAD (CADSS: 41-80)	80.3 (77.7-82.9)	< 0.05
Severe CAD (CADSS: 81-120)	77.5 (74.2-80.7)	< 0.001
Thrombotic CAD (CADSS > 120)	65.9 (59.0-72.7)	< 0.001

Tukey HSD test *P* values presented are only related to comparison with the Normal angiogram group.

Impact of RDL on CAD

The majority of our patients in the RDL 1-4 with an eGFR < 90 ml/min and in particular in the CKD subpopulation (eGFR < 60 ml/min) had various degrees of CAD. We have demonstrated an independent and strong graded association between RDL (measured by both the Cockroft-Gault and MDRD equations) and CAD severity. These results are in agreement with the findings from several epidemiological and observational studies on the high prevalence and strong association of CAD with adverse outcomes in patients with impaired renal function. Recent observations show an independent increase in the risk of cardiovascular events and mortality in individuals with impaired as compared to those with preserved kidney function [12-20]. Our study demonstrated a graded impact of RDL on CAD severity, with the highest CADSS being observed in the sub-group of patients with the most advanced level of renal dysfunction (level 4). Similarly, a study involving a Chinese cohort of patients suggested that screening and prevention of cardiovascular disease should begin, not only in people with advanced renal failure, but at an earlier stage of renal function impairment [26]. In contrast to these observations, some studies have found little or no significant increase in all-cause mortality in the setting of mild to moderate CKD [27, 28]. This variability could be explained by the fact that the most prominent increase in CADSS, which is expected to be associated with the highest rates of cardio-vascular mortality, is observed among the sub-group of patients with the most advanced level of renal failure, as reflected in our results.

Impact of CAD severity on renal function

While several studies investigated the impact of renal dysfunction on CAD onset and severity; very few examined the effect of CAD on renal function. To our knowledge, this is the first study in the Middle East region to evaluate the association between CAD and RDL using disease burden angiographic quantification. We have demonstrated that CAD represents a strong and independent risk factor for loss of renal function. This risk was also suggested by a considerable decrease in eGFR as CAD severity worsens. When patients were stratified according to their mean CADSS scores and their corresponding means of eGFR, renal function was shown to decrease significantly with worsening CAD severity. The lowest mean of eGFR was observed in the sub-group of patients with the lowest CADSS mean. These findings are supported by the results from other studies that reported lower GFR values in patients with multi-vessels CAD compared to patients without significant coronary artery stenosis [12, 29]. In a recent meta-analysis including 18634 patients with CAD, Damman K et al. reported that renal failure occurred in 25% of cases and was associated with higher hospitalization and mortality rates [30]. In another study including patients with both atherosclerotic disease and renal dysfunction, it was shown that cerebral infarction and peripheral vascular diseasewere predictors for renal artery stenosis and 44% of patients with CAD had increased risk of renal dysfunction and renal artery stenosis [31]. Similarly, Ford ML et al. demonstrated that an increase in aortic stiffness, marked by an exaggeration in aortic pulse wave velocity (PWV), a marker of atherosclerosis, would lead to more rapid decline in renal function independent of the impact of known risk factors for CKD progression including hypertension [32].

Atherosclerosis and CKD: Multi-pathogenic association

Several pathogenic mechanisms might be suggested to explain this strong interaction between atherosclerosis, CAD and level of renal dysfunction. Nakamura et al. suggested that coronary artery calcifications to be the causal link connecting CKD and cardiovascular disease and concluded that calcification is present in the intimal plaque of both non-renal

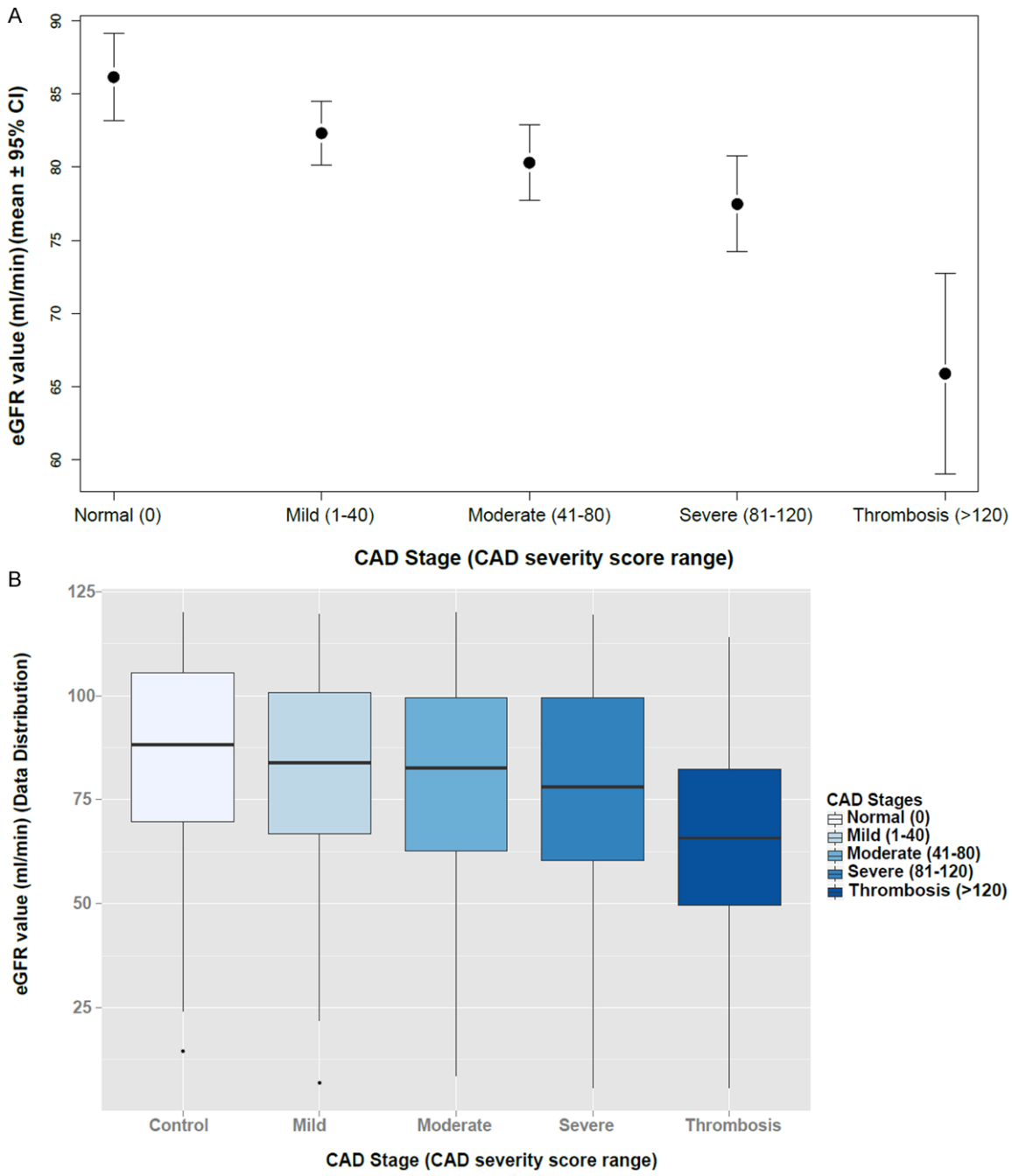

Figure 2. A: Variation of the mean eGFR (ml/min ± 95% CI) of patients according to different CAD severity stages defined by the corresponding means of coronary artery disease severity scores (CADSS). B: Data distribution of the eGFR level (ml/min) of patients according to different CAD severity stages defined by ranges of coronary artery disease severity score (CADSS).

and renal patients, but medial calcification occurred only in CKD patients mainly in those with advanced stages 4-5 [33]. This was confirmed later by Nakano et al. who have demonstrated a strong and inverse association between RDL and degree of coronary atherosclerosis and arteriosclerosis in autopsy samples from Japanese elders in the Hisayama study [34].

Some studies suggested that atherosclerosis is not the only mechanism of cardiovascular disease in CKD patients. In fact, cardiovascular abnormalities in the uremic setting involve arte-

riosclerosis, left ventricular diastolic dysfunction and left ventricular hypertrophy, which are often accompanied by atherosclerosis [35]. Inflammation may represent another culprit in the association between atherosclerosis and CKD. Many inflammatory markers such as pentraxin and C-reactive protein as well as iron are associated with an increase in the risk and in the severity of CAD in patients with mild to moderate CKD, even after adjustment for traditional risk factors [36-38]. Prominent novel factors for cardiovascular disease, not related to lipids, include high levels of homocysteine, and elevated plasma fibrinogen levels [39, 40] both of which are present in CKD patients,in addition to an increased rates of abnormal mutations in several thrombophilia genes such as PAI-1, Factor V Leiden, MTHFR1, MTHFR2 and Angiotensin Converting Enzyme (personal unpublished data), where 75% of ESRD dialysis patients were found to have between 4 and 7 mutations. Moreover, the progression of the kidney disease leads to the gradual appearance of additional aggravating factors specific to uremia that are deleterious on the innate immune system which facilitates accelerated atherogenesis [41-44].

The observed variability in the degree of CAD severity within different RDL may be explained by genetic predisposition to atherosclerosis of some but not all patients, as well as by evidence of consanguinity and family history of coronary artery disease that strongly predict early stenosis [45]. Many studies support this hypothesis on this complex genetic-environmental interaction with the well-established genetic contribution to CAD development and progression, and the beneficial response to the modifications of risk factors and lifestyle choices [46]. Similarly, CKD has also an inherited component of susceptibility [47, 48]. Genetic factors however, may have less direct influence on renal disease development and become manifest only in the presence of 'permissive conditions' that have a cumulative impact on the development and progression of CKD. Conversely, not all patients suffering from these conditions develop renal disease or progress to ESRD, and it is likely that the additive interaction between these genetic variables and the superimposed environmental risk factors determine the time of onset and the rate of progression of kidney disease (21). This may explain the observed inter-patients variability in the level of renal dysfunction within each CAD disease severity stage. The emerging evidence on the probable role of shared genetic anomalies on the development and progression of both CAD and CKD will impact our understanding of how genetic variation influences susceptibility to these diseases, and will help us understand the bidirectional link between CKD and CAD.

Limitations

Our study presents certain limitations: first, it is a retrospective study using data collected from a group of patients with suspected CAD who underwent cardiac catheterization. Second, in our analysis, we used the eGFR as the only defining criteria for impaired renal function; however, new definition includes renal imaging and proteinuria. Unfortunately, routine urianalysis, microalbuminuria, urinary protein/creatinine and imaging evaluation were not part of the routine screening process and hence were not available in patient's medical record for analysis. The use of both proteinuria and eGFR would have given a more accurate estimation of CKD [49]. However, we adopted an eGFR < 60 ml/min (measured by both the Cockroft-Gault and MDRD equations) as a cut point for CKD. Moreover, we demonstrated a linear and gradual relationship between CAD severity and all RDL. These findings make the observed association between CAD and CKD very robust.

Conclusion

In a group of Lebanese patients with CAD, we have shown a strong, independent and graded bidirectional relationship between CAD severity and RDL. CAD represents an independent predictor of CKD. Similarly, CKD is strongly associated with an increased risk for CAD. This association was at its highest at the most advanced stages of both diseases. The impact of this bidirectional link is further amplified by the greater prevalence of most of the common traditional risk factors, mainly in those patients with combined CAD-CKD. We propose to add CAD particularly in its advanced stages to the list of criteria defining people at highest risk for the development and progression of CKD. Based on this added important and clinically relevant findings by our study, we are currently investigating the genetic basis of both diseases in the Lebanese population.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Adjusted odds ratios predicting CAD as outcome variable

	OR	CI 95%	*P* value
CKD	2.01	1.27-3.18	< 0.01
Obesity	1.16	0.83-1.62	0.38
Smoking	1.46	1.07-2.00	0.02
Diabetes	1.83	1.27-2.62	< 0.001
Hypertension	1.44	1.06-1.97	0.02
Hyperlipidemia	1.09	0.80-1.48	0.59
FxCAD	1.56	1.16-2.10	< 0.01
Consaguinity level 1	0.62	0.42-0.90	0.01
Consaguinity level 2	0.91	0.55-1.50	0.71

CI 95%: confidence interval 95%, FxCAD: Family history of CAD, consanguinity level 1: parents first degree cousins, consanguinity level 2: parents second or more degree cousins.

Supplementary Table 2. Adjusted odds ratios predicting CKD (eGFR < 60 ml/min) as outcome variable

	OR	CI 95%	*P* value
CAD	1.99	1.26-3.14	< 0.01
Obesity	0.41	0.29-0.58	< 0.001
Smoking	0.68	0.51-0.92	0.01
Diabetes	0.84	0.62-1.15	0.29
Hypertension	2.21	1.58-3.07	< 0.001
Hyperlipidemia	0.84	0.63-1.12	0.23
FxCAD	0.68	0.51-0.90	0.01
Consaguinity level 1	0.88	0.58-1.33	0.55
Consaguinity level 2	1.03	0.65-1.64	0.90

CI 95%: confidence interval 95%, FxCAD: Family history of CKD, consanguinity level 1: parents first degree cousins, consanguinity level 2: parents second or more degree cousins.