

Carotid intima–media thickness assessment in obese patients with chronic renal failure

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Background/Aim

Measurement of carotid artery intima–media thickness (CIMT) is reliable for early detection of atherosclerosis, one of obesity's complications, which is a leading cause of mortality among patients with end-stage renal disease. The study aimed to evaluate CIMT in relation to obesity, chronic renal failure (CRF) and both, for the early prevention of cardiovascular problems.

Patients and methods

This cross-sectional study included 118 adult individuals of both sexes, aged 30–60 years. Patients with CRF were gathered from the renal dialysis unit of King Fahd Hospital-Kasr El Einy Hospital, and the obese without CRF from the 'Management of Visceral obesity Unit', in 'Medical Excellence Research Center (MERC)', National Research Centre, during the period spanning from June 2015 to April 2016. They were grouped into three groups: a case group, which included 45 obese individuals with CRF, and two control groups: one comprised 39 nonobese patients with CRF and the other group comprised 34 obese patients without CRF. Anthropometric assessment, lipid profile, and ultrasound measurement of CIMT were performed for each patient.

Results

CIMT was greater in all groups than the normal range (0.06–0.08 cm), particularly in the obese group without renal failure. CIMT had a highly significant correlation with waist circumference and insignificant correlation with BMI and lipid profile in different groups.

Conclusion

The increase in CIMT was related to obesity and renal failure, but it was more prominent with obesity. CIMT had highly significant correlation with central obesity in cases wherein obesity and renal failure were coexisting together and insignificant correlation with lipid profile.

Keywords:

carotid artery intima–media thickness, chronic renal failure, lipid profile, obesity, waist circumference

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Introduction

Chronic kidney disease (CKD) is characterized by abnormalities of kidney functions (glomerular filtrate rate <60 ml/min/1.73 m² for ≥3 months) or structure (damage for ≥3 months confirmed by kidney biopsy or markers of kidney damage) present for more than 3 months with implications on health [1,2]. Among patients with end-stage renal disease (ESRD), cardiovascular disease (CVD) is the leading cause of mortality. Death from cardiac causes accounts for 40–50% of all deaths in these patients and is up to 20 times more than in the general population. The prevalence of coronary atheroma in uremic patients is ~30% [3,4].

Obesity is classified, according to fat distribution, into peripheral (mainly due to subcutaneous fat) and central abdominal obesity (visceral fat). Abdominal obesity is more dangerous and associated with high risk of

comorbidity and mortality [5], either by increasing body fat or by producing multiorgan/system complications leading to the presumed CVD. Visceral adipose tissue, acting as an active endocrine organ, is positively associated with coronary and carotid artery calcification by producing proinflammatory state and metabolic abnormalities. These factors are linked with insulin resistance and atherogenic lipoprotein profile [6]. Abdominal obesity, detected by waist circumference (WC), is a risk factor for atherosclerosis in the general population [7,8]. Both increased visceral fat and increased WC augmented the odds to present calcifications [8].

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The high mortality rate in ESRD patients was related to atherosclerosis. Modification of the risk factors for atherosclerosis may lead to reduction in CVD. Early detection of atherosclerosis can be carried out by measurement of carotid artery intima-media thickness (CIMT); which is an early marker of vascular pathology [7]. Janda *et al.* [9] confirmed that, in CKD patients, CIMT examination can be used as a surrogate measure to assess the incidence and severity of arterial medial calcification and in identifying patients at high risk of CVD, which is associated with poor clinical outcome, thus, allowing early prevention of mortality in these patients.

Hence, this study aimed to evaluate the CIMT in relation to obesity, chronic renal failure (CRF) and both, for early prevention and treatment of cardiovascular problems.

Patients and methods

Patients

This is a cross-sectional case control study, which included 118 adult individuals of both sexes. Their ages ranged between 30 and 60 years. They were categorized into three groups: (i) the case group, which included 45 obese patients with CRF of both sexes (CRF determined by their abnormal renal function and obesity determined by anthropometric measurements, that is $\text{BMI} \geq 25 \text{ kg/m}^2$), (ii) another two groups, serving as control groups: (a) one group comprised 39 nonobese patients with CRF (CRF determined by their abnormal renal function with no obesity determined by anthropometric measurements; $\text{BMI} < 25 \text{ kg/m}^2$), and (b) the second control group comprised 34 obese patients with no CRF (no CRF determined by normal renal function and obesity determined by anthropometric measurements; i.e. $\text{BMI} \geq 25 \text{ kg/m}^2$). Patients with CRF were gathered from the renal dialysis unit of King Fahd Hospital-Kasr El Einy Hospital, and the obese without CRF from the 'Management of Visceral obesity Unit', in 'Medical Excellence Research Center (MERC)', National Research Centre, during the period spanning from June 2015 to April 2016.

Ethical approval

Participants were informed about the purpose of the study, and their permission in the form of written consent was obtained. The protocol was approved by the 'Ethical Committee' of the 'National Research Centre'. The agreement reference number is 13/152.

Methods

All the participants underwent complete clinical examination, anthropometric, laboratory, and ultrasonographic assessment.

Complete clinical examination

Complete clinical examination included cardiac, chest, and abdominal examinations to exclude organic and genetic disorders that might interfere with the anthropometric measurements of the subjects under study, with special emphasis on endocrinal diseases, that would interfere with the type of obesity.

Anthropometric assessment

For all the participants, body weight, height, and waist and hip circumferences were measured. Body weight was measured using a Seca scale (Seca Balance Beam Scale, Model 700, SecaDeutschland Medical Scales and Measuring Systems; seca GmbH & Co. Kg, Hamburg, Germany) approximated to the nearest 0.01 kg, and with minimal clothes on, for which no correction was made, and body height without shoes, using a Holtainstadiometer (Portable Harpenden Stadiometer; Holtain, Wales, UK); the measurement was approximated to the nearest 0.1 cm. WC was measured at a level midway between the lower rib margin and iliac crest, and hip circumference at the level of the widest circumference over the buttocks with the patient standing, using a simple measuring tape all around the body in a horizontal position; the measurement was approximated to the nearest 0.1 cm. Three consecutive measurements were taken, and, when the difference between the readings was acceptable, the mean was recorded. The landmarks, instruments and techniques used were those recommended by the International Biological Program [10]. Thereafter, BMI [$\text{BMI} = \text{weight (kg)} / \text{height (m)}^2$] and waist/hip ratio (WHR) (cm/cm) were calculated. The participants were classified according to their BMI: those with BMI more than 17 to less than 25 kg/m^2 were considered as having normal weight, while BMI of at least 25 kg/m^2 was considered overweight/obese.

Laboratory investigations

Early morning forearm venous blood samples (5 ml) were obtained from each patient, before breakfast, for biochemical screening tests of plasma lipid profile, after 12-h overnight fasting. Professional staff performed venipuncture. The blood samples were left to clot; sera were separated by centrifugation for 10 min at 5000 rpm, then stored at -80°C until assays. Serum concentrations of total cholesterol and triglycerides (TG) were estimated in serum using calorimetric assay kit produced by P.Z. company (Lublin, Poland). High-density lipoprotein-cholesterol (HDL-C) was determined in sera, using calorimetric assay kits produced by Stanbio Laboratory (Boerne,

Texas, USA). Low-density lipoprotein-cholesterol (LDL-C) was calculated according to the equation developed by Friedewald *et al.* [11] as follows: $LDL = \text{total cholesterol} - TG/5 + HDL$.

Ultrasound assessment

B-mode Doppler ultrasound measurement of the CIMT was carried out following these steps:

- (1) The patient lay in the supine position comfortably with his neck well exposed with no clothes covering his neck.
- (2) His neck was slightly hyperextended and rotated 45° away from the side being examined. The patient was comfortable and excessive extension of the neck was avoided.
- (3) Some patients may not be able to lie supine. They were examined adequately in a sitting position. The examiner sat beside the patient's thorax and scanned the neck from this position, or sat at the patient's head and scanned the neck from that location.
- (4) A high frequency linear superficial transducer (7–12 MHz) is ideal for intima-media CIMT measurements and plaque morphology assessment.
- (5) The examination starts with a transverse scan of the carotid artery from as low in the neck as possible (common carotid artery) to as high in the neck as possible behind the angle of the mandible. This approach allows a better orientation and demonstration of the relationship between common carotid artery, internal jugular vein, thyroid, and trachea, and sternomastoid muscle. It helps in taking a general idea of the depth and course of the vessels, together with the level of the bifurcation and the orientation of its branches. In addition, areas of major disease could be identified and noted for further assessment.
- (6) Longitudinal scan was then performed. Longitudinal views of the layers of the normal carotid wall demonstrate two nearly parallel echogenic lines separated by a hypoechoic to anechoic region; the distance between these lines represents the combined thickness of the intima and media (I-M complex).
- (7) Thickening of the I-M complex greater than 0.08 mm was considered abnormal and represents earliest changes of atherosclerotic disease.

Statistical analysis

Statistical analysis was performed using the computer program SPSS statistical package software for Windows, version 16 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics (mean±SD) were

calculated for the anthropometric and laboratory assessment of the total lipid profile and the ultrasound findings. Analysis of variance was used to compare between three groups. BMI cutoff point of 25 kg/m² was used to classify all the obese patients under study (obese and control). Pearson's correlation was used to assess the association between the CIMT and the anthropometric measurements and laboratory assessment of total lipid profile. Standards of probability were set to *P* less than 0.01, which was considered to be highly significant, and *P* less than 0.05 was considered to be statistically significant in all analyses.

Results

The CIMT was higher in the three groups under study than the normal range (0.6–0.8 mm); the highest thickness was observed in the obese group without renal failure (1.72±2.8 mm), followed by the obese group with renal failure (1.1±0.3 mm), and the least thickness in the nonobese group with renal failure (0.9±0.2 mm) (Table 1). There were also highly significant differences between the three groups in the anthropometric measurements and lipid profile. The obese group without renal failure had the highest significant values of weight, BMI, hip circumferences, total cholesterol, and LDL. While the obese group with renal failure had the highest significant values of WCs and WHR, the nonobese with renal failure group had the lowest significant values of HDL. In spite of the increase in the TG values in the three groups above the normal range, insignificant differences were recorded. The highest values of anthropometric measurements, total cholesterol and LDL were recorded in the obese group without renal failure, followed by the obese group with renal failure.

Correlations between CIMT and the anthropometric measurements and lipid profile for the total sample and subgroups are presented in Table 2. The CIMT had highly significant correlations with weight in obese and nonobese subjects with CRF and in the total sample, with height in nonobese patients with CRF, as well as with waist and hip circumferences in obese subjects with CRF and in the total sample. Insignificant correlation was detected between CIMT and lipid profile.

Discussion

Endothelial dysfunction is an early phenomenon in increased CIMT and atherosclerosis that precedes

Table 1 Anthropometric and biochemical characteristics of obese and nonobese patients with or without renal failure under study

Variables	Obese with renal failure (N=45) (mean±SD)	Nonobese with renal failure (N=39) (mean±SD)	Obese without renal failure (N=34) (mean±SD)	F	P
Age					
Weight (kg)	80.18±15.17	56.23±10.92	93.29±15.97	65.296	0.000**
Height (cm)	160.87±16.57	159.92±11.61	160.26±8.88	0.056	0.946
BMI (kg/m ²)	31.10±5.12	21.83±2.50	36.31±5.63	94.044	0.000**
Waist C (cm)	107.09±16.07	87.67±13.82	106.29±13.21	22.454	0.000**
Hip C (cm)	114.76±16.80	95.82±12.35	124.32±12.47	38.547	0.000**
WHR	0.93±0.05	0.91±0.07	0.86±0.08	12.226	0.000**
Lipid profile					
Total cholesterol (mg/dl)	162.73±66.62	149.10±48.46	207.47±45.48	10.919	0.000**
Triglycerides (mg/dl)	147.67±76.52	127.77±81.95	125.29±50.31	1.200	0.305
HDL (mg/dl)	43.16±13.52	41.67±18.44	58.79±19.44	11.178	0.000**
LDL (mg/dl)	174.13±55.14	165.21±54.27	241.21±52.21	18.174	0.000**
IMT	0.11±0.03	0.09±0.02	0.172±0.28	2.948	0.056

C, circumference; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; WHR, waist/hip ratio.

**P<0.01=highly significant differences.

Table 2 Correlation between intima-media thickness and the anthropometric measurements and lipid profile for the total sample and subgroups

Variables	IMT							
	Obese with renal failure (N=45)		Nonobese with renal failure (N=39)		Obese without renal failure (N=34)		Total sample	
	r	P	r	P	r	P	r	P
Weight (kg)	0.428	0.003**	0.342	0.033*	0.094	0.598	0.208	0.024
Height (cm)	0.258	0.087	0.318	0.048*	0.114	0.520	0.072	0.441
BMI (kg/m ²)	0.136	0.372	0.191	0.245	0.026	0.882	0.174	0.059
Waist C (cm)	0.502	0.000**	0.119	0.472	0.246	0.162	0.207	0.024
Hip C (cm)	0.481	0.001**	0.247	0.129	0.204	0.247	0.229	0.012
WHR	0.112	0.465	-0.165	0.315	0.089	0.616	-0.031	0.740
Lipid profile								
Total cholesterol (mg/dl)	0.161	0.291	-0.041	0.804	-0.015	0.935	0.140	0.130
Triglycerides (mg/dl)	0.106	0.490	0.052	0.752	-0.060	0.735	0.093	0.317
HDL (mg/dl)	-0.122	0.423	-0.114	0.488	-0.297	0.143	-0.023	0.805
LDL (mg/dl)	0.119	0.435	-0.091	0.580	-0.097	0.586	-0.061	0.511

HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; WHR, waist/hip ratio. *P<0.05=significant differences. **P<0.01=highly significant differences.

structural changes and clinical manifestations. Decreased endothelial function is thought, primarily, to reflect a decreased bioavailability of nitric oxide, a critical endothelium-derived vasoactive factor with vasodilator and antiatherosclerotic properties. Presence of endothelial dysfunction in CKD occurs because of many factors such as oxidative stress, l-arginine deficiency, and arterial stiffness and calcification [12,13].

The occurrence of an endothelial lesion would be initially recognized by monocytes, which together with plasma lipids would enter into the vessel wall, followed by subsequent platelet adhesion and aggregation. The damaged endothelial cells,

monocytes, and aggregated platelets at the site of more severe damage and through the release of mitogenic factors, such as platelet-derived growth factor, may potentiate the migration and proliferation of vascular smooth muscle cells. These together with the increased receptor-mediated lipid accumulation and connective tissue synthesis would configure the typical atherosclerotic plaque. Occasionally, disruption of an atherosclerotic plaque occurs with subsequent superimposed thrombus formation, which may be responsible for the onset of acute symptoms [14].

In the current study, the CIMT was higher in all groups than the normal range (0.6–0.8 mm).

Although the increase in the CIMT was related to obesity and renal failure, it was more prominent with obesity. This agrees with the finding of Cullen *et al.* [15], who reported that the coexistence of one or more risk factors contribute to the occurrence of some form of endothelial injury manifested in many forms such as interference with the permeability barrier role of the endothelium, alterations in the nonthrombogenic properties of the endothelium, increased release of vasoconstrictor molecules leading to a sequence of cellular interactions and finally to atherosclerosis. Tołwińska *et al.* [16] found that CIMT is high in obese groups, especially if associated with hypertension. Stabouli *et al.* [17] reported that obese CRF patients had thicker mean CIMT of internal carotid arteries ($P<0.005$) than nonobese patients. Omran *et al.* [18] and Nitta *et al.* [19] also stated that patients with renal disease have greater oxidative power, which results in higher levels of oxidized glutathione, advanced glycation end products, and increased oxidation of lipoproteins. The initial and requisite step in the development of atherosclerosis is the oxidative change in LDL. Paul *et al.* [20] and Dayem *et al.* [21] reported that the increase of CIMT up to 0.74 ± 0.14 mm is associated with atherosclerosis and significantly increased CVD risk in any age group.

The current study found that BMI was significantly lower in the obese with renal failure than among the obese without renal failure, which means that, in spite of obesity, renal failure was associated with a decrease in BMI. Concurrent with the current finding, Bossola *et al.* [22] reported that obesity is associated with improved survival in hemodialysis patients. A recent cohort study among US veterans with CKD observed a consistent U-shaped association between BMI and the outcomes of kidney disease progression and mortality, with the best outcomes observed in overweight and obese groups I and II (BMI: $25\text{--}39.9$ kg/m²) but not in obese groups III and IV (BMI >40 kg/m²) [6]. They concluded that increased BMI is a predictor of better clinical outcome in dialysis patients with decreased risk of kidney disease progression in stage 3–4 CKD [6,22].

In the current study, the obese group without renal failure had the highest significant values of weight, BMI, and hip circumference. However, the obese group with renal failure had the highest significant values of WC and WHR. This came in agreement with Postorino *et al.* [23], who demonstrated increased WC in predialysis CKD patients and ESRD patients. Lean *et al.* [24] also reported that guidelines tend to focus on WC to estimate disease risk.

In the current study, the significant increase in total cholesterol and LDL were related mainly to obesity, while the significant decrease in HDL was related mainly to renal failure. These findings coincided with those of Schreier *et al.* [25], who found that patients with ESRD had lower levels of HDL-C, but higher triglyceride levels and LDL-C than controls. Stabouli *et al.* [17] reported that obese CRF patients had higher triglycerides ($P<0.001$) and lower HDL cholesterol ($P<0.01$) than nonobese patients. Omran *et al.* [18] and Nitta *et al.* [19] reported that lipid profiles in ESRD patients are different from those in individuals without kidney disease. In patients with renal failure, total cholesterol, and LDL-C levels were often within the normal range, while HDL-C levels were decreased. Thompson *et al.* [26] also reported that dyslipidemia is a highly prevalent risk factor for CKD. It is characterized by decreased HDL-C and increased TG concentrations; however, LDL and total cholesterol may be normal or moderately raised. They stated that kidney impairment itself is sufficient to induce disorders in lipoprotein metabolism and dyslipidemia, thus contributing to excess burden of CVD in CKD.

Kato *et al.* [27] and Thompson *et al.* [26] found that albumin decreased with increasing kidney impairment ($P=0.006$). Albumin has an important role in transforming cholesterol to HDL. Hypoalbuminemia contributes to deregulation of lipoprotein metabolism, particularly HDL, contributing to the high prevalence of low HDL observed in patients with CKD.

HDL plays an anti-inflammatory role in healthy individuals in the absence of systemic oxidative stress and inflammation. On the contrary, in chronic illnesses such as renal failure, HDL may become dysfunctional and actually promote inflammation (reduced levels and protective capacity of HDL). It is not capable of preventing LDL oxidation, and it induces monocyte migration in artery wall model systems [28].

Concurrent with the present results, Tołwińska *et al.* [16] found that the level of triglycerides was high in isolated obesity. While Tsimihodimos *et al.* [29] concluded that the most common lipid abnormalities in CKD patients is the increased triglycerides' level, they found that triglyceride levels were significantly higher in obese and overweight patients than in those with normal weight.

The current study revealed that CIMT had highly significant correlation with central obesity (WC) in

cases wherein obesity and renal failure were coexisting together. This was documented previously by Asicioglu *et al.* [7], who reported, in univariate and multivariate analysis that WC was positively correlated with CIMT. They recommended use of WC as a simple and reliable method of evaluating risk of atherosclerosis. Moreover, the association of WC with CVDs was well recognized by them. Postorino *et al.* [23] also considered WC as an independent predictor for cardiovascular mortality in predialysis CKD patients and ESRD patients. This could be attributed to the strong relation between WC and abdominal obesity, as proved in previous studies. A study performed by Bazanelli *et al.* [30] showed strong correlation of WC with abdominal obesity ($r=0.81$; $P<0.001$). In the logistic regression analysis, changes in WC were independently associated with changes in trunk fat in patients under dialysis, concluding that the simple anthropometric method for measuring WC is a reliable marker of abdominal adiposity. Bossola *et al.* [22] and Davis *et al.* [6] suggested that central obesity may be better prognostic indicators in CKD patients.

In crude analysis, Cordeiro *et al.* [8] reported that every SD increase in visceral fat increases the odds to present increase in CIMT and calcification by 60%. However, Maddaloni *et al.* [31], stated that CIMT, but not body circumference, was associated with advanced atherosclerosis. Hence, anthropometric measurements can be used as practical tools for assessment of metabolic risk in overweight obese subjects but not as markers of advanced atherosclerosis.

In the current study, there was insignificant correlation between BMI and CIMT in the different groups. This coincided with the finding of Elsayed *et al.* [32] and Asicioglu *et al.* [7]. Elsayed *et al.* [32] stated that depending on BMI alone underestimates the importance of obesity as a CVD risk factor, particularly in CKD patients. Asicioglu *et al.* [7] explained this by the fact that BMI does not differentiate between muscle and fat mass. Furthermore, dialysis patients usually have lower muscle mass with increased fluid mass, which could not be detected by using BMI. In support of this view, the concept of 'obese sarcopenia' has recently emerged, which means high body mass and low muscle mass with protein energy malnutrition, and is associated with high mortality rates in patients with ESRD [7].

The current study revealed insignificant correlation between lipid profile and CIMT in the different groups. This coincides with the finding of Asicioglu *et al.* [7] and Tarantino *et al.* [33], who reported that

serum lipoprotein concentration was not associated with CIMT or with early atherosclerosis. This may be attributable to the fact that, in their studies, the majority of their cases were on statin therapy; thus, the effects of these parameters on CIMT measurements cannot be ruled out.

The study of Tsimihodimos *et al.* [29] indicated the limited effect of the use of lipid-lowering medications in CKD patients; however, a minority of those receiving these drugs achieved significant improvement in cardiovascular morbidity and mortality independently of the baseline lipid values. All patients with renal failure included in the current study were receiving lipid-lowering medications from the time they had been diagnosed. This may be the cause for insignificant differences in lipid profile among the obese and nonobese patients with renal failure (as all of them were taking the medications) and the significant differences among the obese with and without renal failure (as the obese without renal failure did not take these medications).

Meta-analysis of 26 studies (about 25 000 participants) concluded that statin use in predialysis CKD patients is followed by significant improvement in lipid profile and cardiovascular mortality by 20%. They concluded that statin use in early CKD patients with dyslipidaemia is safe for the prevention of ischemic events [34]. Similarly, a Scandinavian study reported a significant decrease of cardiovascular complications after statin administration in predialysis CKD patients, but with no effect in patients who were on maintenance hemodialysis HD [35]. The results of the AURORA study (a study to evaluate the use of rosuvastatin in patients on regular hemodialysis: an assessment of survival and cardiovascular events) led to the conception of 'a point of no return', that is a point in renal function impairment beyond which the beneficial effect of statins is offset in the reduction of cardiovascular morbidity and mortality [29,36].

Conclusion

CIMT increase is related to obesity and renal failure, but it was more prominent with obesity. The significant increase in total cholesterol and LDL were related mainly to obesity, while the significant decrease in HDL was related mainly to renal failure. CIMT had highly significant correlation with central obesity (WC) in cases where obesity and renal failure were coexisting together. However, it has insignificant correlation with lipid profile in the current study.

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Conflicts of interest

There are no conflicts of interest.

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