ORIGINAL ARTICLE

Value of carotid intimal–medial thickness as independent predictor of endothelial dysfunction in uremic patients

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Abstract Background and aim of the work: Cardiovascular mortality and morbidity are significantly higher among uremic patients. Although the carotid intimal–medial thickness (C-IMT) as a predictor of endothelial dysfunction (ED) has a prognostic value that has been well demonstrated as an independent predictor of future cardiovascular events, its value in uremic patients need to be re-assisted in our locality. The aim of the work is to investigate a correlation between the brachial artery reactivity test (BART) and the carotid intimal–medial thickening (C-IMT) and their value as independent predictors of endothelial dysfunction in uremic patients.

Subjects and methods: The study involved 70 uremic patients, 40 men and 30 women, 36–56 years old, 40 of them on regular hemodialysis (HD) and 30 on conservative therapy, in addition to 30 healthy persons as a control group. They were selected from the General Medicine and Nephrology Departments, Al-Azhar Assiut University and Assiut University Hospitals over a period of 2 years. All of them were subjected to detailed history, thorough clinical examination, laboratory investigations including complete blood picture, renal function tests (urine analysis, blood urea, and serum creatinine), lipid profile, serum calcium and serum phosphorus, parathyroid hormone (PTH), fasting blood glucose, electrocardiography (ECG), high resolution B-mode ultra-sonography for C-IMT evaluation and brachial artery reactivity test (BART), and abdominal ultra-sonography.

Results: The results of the present study showed: (1) uremic patients are at an increased risk for carotid atherosclerotic lesions, with significant increase in C-IMT than controls with more significant increase in HD patients. (2) Uremic patients are characterized by impaired endothelium...
1. Introduction

Available evidence suggests that an excess risk of cardio-vascular disease (CVD) is present very early in the natural history of chronic renal failure (CRF), which is still the major cause of the morbidity and mortality in patients on conservative treatment and in those on regular hemodialysis (HD).\(^1\) The increased incidence of CVD in those patients is probably the result of a high prevalence of both traditional and uremic risk factors.\(^2\) In recent years, the role of non-traditional risk factors has been highlighted. They include severe prolonged oxidative stress, endothelial dysfunction, malnutrition, and chronic inflammation.\(^3\) Abnormalities of endothelial function, and hence vascular dysfunction, commence at an early age and precede the development of overt atherosclerosis.\(^4\) Celermajer et al.\(^4\) standardized the brachial artery reactivity test (BART), in which the endothelial function is assessed through a simple non-invasive vascular ultrasonographic examination. The vascular intimal–medial thickening (IMT) corresponds to the initial stage of atherosclerosis, preceding plaque formation.\(^5\) The aim of the work is to investigate a correlation between the brachial artery reactivity test (BART) and carotid intimal–medial thickening (C-IMT) and their value as independent predictors of endothelial dysfunction in uremic patients on conservative treatment or on regular hemodialysis.

2. Subjects and methods

2.1. Subjects

This study involved 70 patients with chronic renal failure, 40 men and 30 women, 36–56 years old. They were divided into two groups. Group-A: included 40 uremic patients on regular HD. The duration of HD was 3–84 months. Group-B: included 30 uremic patients on conservative treatment in addition to 30 healthy sex and age matched controls (group-C). Informed consent was obtained from each subject in the study. They were selected from Internal Medicine and Nephrology Departments of Al-Azhar Assuit University and Assuit University Hospitals from November 2007 to 2009.

2.2. Methods

All selected subjects were subjected to the following:

(1) Thorough history and full clinical examination. (2) Resting 12 leads ECG. (3) Lab. investigations including: complete blood picture, renal function tests (urine analysis, blood urea, and serum creatinine), lipid profile, serum calcium and phosphorus, parathyroid hormone (PTH), and fasting blood glucose.

(4) Radiological studies including: abdominal ultra-sonography, measurement of the carotid artery intimal–medial thickening (C-IMT) and brachial artery reactivity test (BART). The radiological studies used high-resolution B-mode ultrasound machine (GE general electric LOGIQ9) and 7.5–10 MHz high resolution linear array transducer. Single highly qualified experienced ultrasonographist physician unaware of the clinical and laboratory data, examined all the subjects of different groups to minimize operator variability. The study was performed according to the technique described in the previous studies of Fathi and Marwick\(^6\) and Moens et al.\(^7\) The carotid arteries were examined bilaterally in the areas of the common carotid artery, the carotid bifurcation and the internal carotid artery on the left and right sides. The wall of the common carotid artery is thicker and produces two distinct echoes. The space between the echoes represents the actual vessel wall intima–media thickness which measures normally 0.05 cm thick in the common carotid artery. Each carotid wall and segment was examined independently from continuous angles to identify the thickest intimal–medial site of the far wall and in the plaques free area. Endothelial independent dilatation was measured by a calculation of the vasodilator response to exogenous nitrate 3 min after administration of 5 mg of sublingual nitroglycerine. The percent diameter changes for FMD and nitrate-mediated dilatation was calculated in relation to its respective rest scan.

Microsoft office excel 2007 was used for the analysis of collected data and they were presented as mean ± standard deviations.

3. Results

– The frequency of the traditional CV risk factors increased in both patients groups (A and B) than controls (C) (Table 1).

– Carotid duplex scanning showed that the carotid IMT is significantly thicker in patients groups (groups A and B, more in HD group) than controls (group C) (Table 2 and Fig. 1).

– The frequency of both types of vascular plaques is significantly increased in both patient groups than controls (Table 3 and Fig. 2).
Regarding BART: brachial artery FMD is significantly reduced in patient groups (more in HD patients) than in controls (Table 3 and Fig. 3). While the nitroglycerin mediated dilatation (NMD%), no significant difference among all groups was observed (Table 3 and Fig. 4).

The study revealed:
(A) Significant positive correlation between carotid artery intimal–medial thickening (C-IMT) and age (Fig. 5).
(B) Significant positive correlation between C-IMT and creatinine (Fig. 6).
(C) Significant positive correlation between C-IMT and FMD% reduction (Fig. 7).
(D) Significant positive correlation between C-IMT and triglyceride (Fig. 8).

4. Discussion

Endothelial dysfunction (an important phenomenon in atherogenesis) contributes to the progression of atherosclerosis in patients with renal failure, which is not corrected by HD. Carotid artery IMT is an independent predictor of CV mortality in HD patients, so it is useful for risk stratification in the dialysis population. High-resolution echo color Doppler ultrasonography is a non-invasive, reliable, and reproducible method for detecting and monitoring the progression of preclinical atherosclerosis. The association of endothelial dysfunction with renal failure has previously been demonstrated in the brachial artery of pre-dialysis children and in the forearm microcirculation of uremic adults.

In the current study, we found a significant difference in C-IMT and plaques, as markers of atherosclerosis among HD patients and controls, which is in agreement with many studies. They found extensive remodeling of a “vascular tree”

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<th>Table 2: Comparative measures of IMT, FMD, and NMD.</th>
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NS, non-significant.
* Significant.
** Highly significant.
*** Very highly significant.
in this population of patients which results in a high risk of CVD complications reported in ESRD. Also, we found a significant increase in C-IMT in HD patients more than in uremic patients on conservative treatment and this may be attributed to the effect of HD per se as independent risk factor for accelerated atherosclerosis. This is in agreement with the study of Benedetto et al.13

In our study, we found that carotid plaques were significantly prevalent in HD patients (60%) and in patients on conservative treatment (56.66%) more than in healthy controls (20%). Also, calcified plaques were more prevalent in uremic patient whether on HD (37.5%) or on conservative treatment (30%) in comparison with controls (3.3%). This is in agreement with many related studies14.

Our results confirmed the presence of impaired endothelium-dependent vasodilatation in the brachial artery of uremic adults. Serum creatinine showed significant negative correlation with FMD in uremic patients, suggesting that endothelial dysfunction is probably associated with the development of renal insufficiency. HD patients showed further FMD impairment, while the response to nitroglycerin has no difference compared either to uremic patients or to healthy controls, this indicates a more pronounced endothelial dysfunction in the brachial artery on HD patients. This is in accordance with many related studies.15,16 They revealed that the brachial
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artery FMD in uremic patients (on HD or on conservative treatment) was reduced compared to controls. While endothelium-independent response to glyceryl tri-nitrate was similar in the two patient groups compared with healthy controls. Also, Karakitsos et al.17 study resulted in a significant increase in C-IMT and plaque prevalence and reduced brachial artery FMD and NMD in ESRD patients on HD. The increased incidence of CVD in ESRD patients is probably the result of high prevalence of both traditional and non-traditional risk factors. HD patients have some uremia-related CV risk factors.

Age is a risk factor for atherosclerosis in general population. Our study showed a significant correlation between age and C-IMT values and the presence of plaque. This result showed that age is also an independent risk factor for atherosclerosis in uremic patient whether on conservative treatment or on HD. This is in agreement with the studies of Magyar et al.18 and Brzosko et al.19 However, this contradicts with Burdick et al.19, who found no correlation between carotid IMT and the age of the uremic patients and the control subjects and this may be because of the fact that the mean age of the patients in our study was higher than that in their study. In our study, a significant negative correlation was seen between age and brachial artery FMD of both patients on conservative treatment and those on HD which is in accordance with Ghiadoni et al.20

In our study, the serum creatinine of uremic patients was significantly positively correlated with carotid IMT and inversely correlated with FMD%. It is very likely that the greater and presumably the longer renal function derangement could lead to a more severe abnormality of the endothelium-dependent vasodilatation in HD patients.16

In the current study, the C-IMT and the prevalence of the carotid plaques were significantly correlated with the duration of HD (patients on HD). This is in agreement with Grekas et al.21 and Delucchi et al.22

The Nakashima’s23 study found no significant correlation between the IMT and the duration of HD. In this context, some previous studies have suggested that carotid atherosclerosis might be accelerated by the uremic state present rather than by hemodialysis (Kawagishi et al.).24

5. Conclusions and recommendations

1. The study confirmed that high-resolution B-mode ultrasound is a useful and non-invasive technique which allows the uremic patient to be checked repeatedly during the treatment for protection from CVD events.
2. There was negative correlation between brachial artery FMD and carotid IMT in the uremic patients.
3. Carotid IMT and brachial artery FMD and NMD as valid surrogate end points can also be used in intervention studies in which cardiovascular risk factors are modified in the uremic population.
4. Interventional strategies leading to reversal of endothelial dysfunction in humans are highly recommended in uremic patients such as: (A) general interventions (physical activity, smoking cessation, lipid-lowering therapy, and glycemic control of diabetes). (B) Pharmaceuticals (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins, peroxisome proliferator-activated receptor-γ activators, and estrogens), (C) Dietary supplements (n-3 fatty acids, folate, tetrahydrobiopterin, l-arginine, vitamin C, vitamine E, and dietary flavonoids).

References


