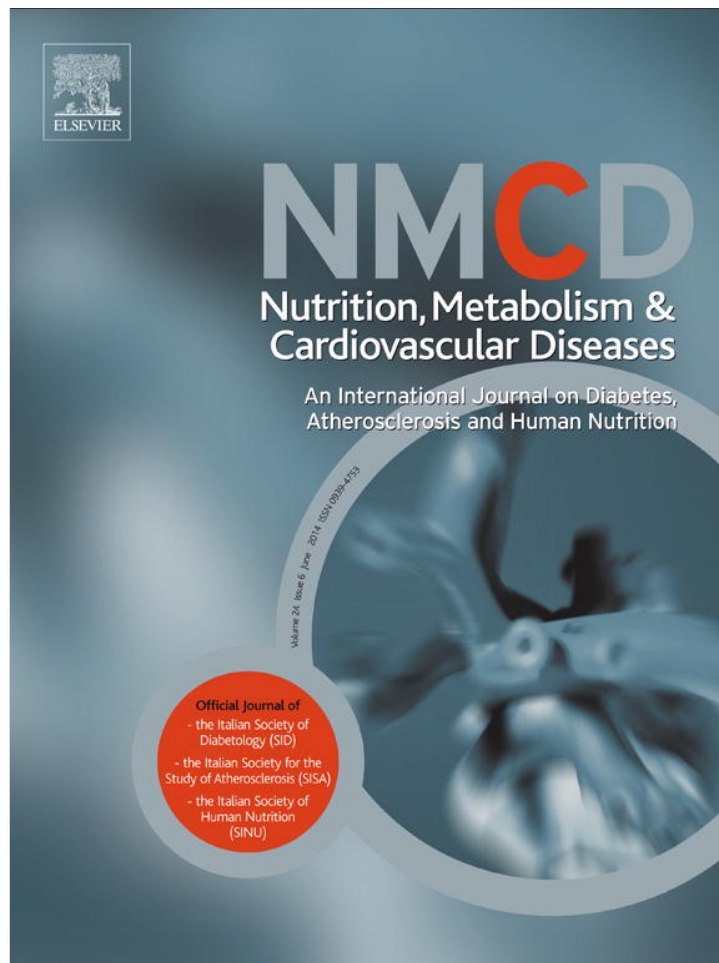


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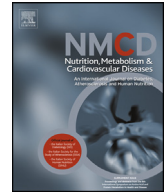


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SHORT COMMUNICATION

Plasma creatinine levels, estimated glomerular filtration rate and carotid intima media thickness in middle-aged women: A population based cohort study



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Abstract *Background and aim:* The relationships between high Creatinine (Cr) levels or low estimated Glomerular Filtration Rate (eGFR) and common carotid Intima Media thickness (IMT) have been evaluated in a population-based cohort study in women, aged 30–69 (Progetto ATENA).

Methods and results: Serum Cr and eGFR were measured in 310 women, as a part of 5.062. In this group carotid ultrasound examination (B-Mode imaging) was performed and mean max IMT was calculated. Women were classified by Cr levels >1 mg/dL or eGFR < 56 ml/min.

Women with Cr > 1 mg/dL (90th percentile of creatinine distribution) or eGFR less than 56 ml/min (5th percentile of eGFR distribution) had relatively more carotid plaques as compared to the rest of the cohort.

Multivariate logistic analysis, after adjustment for age, demonstrated a significant association between Cr (>1 mg/dL) and IMT (≥ 1.2 mm): OR 4.12 (C.I. 1.22–13.86), $p = 0.022$; or eGFR (<56 ml/min) and IMT (≥ 1.2 mm): OR 4.31 (C.I. 1.27–14.66), $p = 0.019$.

Conclusions: These findings on an independent relationship between Cr and common carotid plaques in this population of middle aged women, independently of age, suggest the value of screening for early carotid disease in asymptomatic middle aged-women with mild renal insufficiency, in order to predict those at relatively higher risk for future cardiovascular events.

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Introduction

The presence of kidney disease, as detected by low glomerular filtration rates (GFR) is independently associated with increased rates of cardiovascular disease [1–3].

GFR is currently estimated on the basis of some formula including plasma creatinine concentration and age [4].

Over the last decade, high-resolution B-mode ultrasound has been used for the non-invasive assessment of carotid intima-media thickness (IMT), a marker of early atherosclerosis [5]. Cardiovascular risk factors relate positively to IMT in the carotid arteries, in parallel with their relation to clinical events [5–7].

In the present analysis, we evaluated whether creatinine concentrations and/or estimated GFR (eGFR) were associated with subclinical carotid atherosclerosis in a

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sample of women participating in a large, ongoing, prospective study ("Progetto ATENA") on chronic disease in women [8].

Methods

Study population

We studied a cohort of 310 middle-aged women (20% menopausal) as a part of 5.062, who were clinically healthy and were living in the area of Naples (Southern Italy) and participating in the "Progetto ATENA" study [8]. Criteria of selection of women and data on the representativeness of the sample have been published [6].

The study was approved by the ethical committees of the institutions involved, and the subjects recruited gave their informed consent.

Clinical and biochemical assessment

Anthropometric and blood pressure measurements, biochemical analyses were performed as previously published [6]. In addition serum creatinine levels were measured with automated methods (Cobas-Mira; Roche, Milan, Italy). Glomerular filtration rate (eGFR), was calculated using MDRD formula [9]: $186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203}$. The obtained value has been multiplied for 0.742 (all participants were women).

High resolution carotid ultrasound

Carotid B-mode ultrasound examinations [6] were accomplished using the Biosound 2000 II SA equipped with an 8 MHz annular array mechanical transducer. This system provides high resolution ultrasonic images with 0.3 mm axial resolution. Scans were performed according to a standardized protocol developed by the Division of Vascular Ultrasound Research at the Wake Forest University School of Medicine. The key features of the protocol were the identification of two anatomical landmarks, i.e. the dilation of the bulb and flow divider, and the use of different scanning angles, i.e. anterior, lateral and posterior, in order to measure IMT in 2 carotid segments – the distal 1 cm of the common carotid artery and the carotid bifurcation. Statistical analyses were based on mean of maximum IMT values of the near and far wall for 2 carotid segments for both sides (means of 8 sites), called mean max IMT. In order to detect clinically significant, although asymptomatic arterial disease, we defined as outcome values a mean max IMT value ≥ 1.20 mm, which corresponds to the 90th percentile of mean max IMT distribution. This value is generally associated with loss of parallelism among ultrasound interfaces and considered [10] as evidence of clinically significant arterial disease.

In our vascular laboratory, which has participated in interventional clinical trials using ultrasound, the within-subject coefficient of variation previously reported for IMT is $< 6\%$.

Statistical analyses

Statistical analyses were performed on 310 women using SPSS version 11.0 (SPSS, Inc., Chicago, Illinois). Continuous variables were described as mean and standard deviation.

Logistic regression analysis at univariate and multivariate level was used to test the independent relation between the Common carotid IMT (≥ 1.20 mm, dependent discrete variable, \geq to the 90th percentile of mean max IMT distribution) and age, Creatinine (above 1 mg/dL, corresponding to the 90th percentile of creatinine distribution) or eGFR (less than 56 ml/min, corresponding to the 5th percentile of eGFR distribution) as independent variables. Odds ratio (OR) for the presence of Common carotid IMT were calculated by unconditional logistic regression and 95% confidence intervals (CI) of the odds ratio were computed. Comparisons between women with creatinine > 1 mg/dL or eGFR less than 56 ml/min and the rest of the cohort were performed using chi square statistics or Fisher exact test, when appropriate.

Results

Physical and biochemical characteristics of the study participants are shown in Table 1.

Moderate reduction in eGFR (eGFR ≤ 60 ml/min) was detected in 12% of our middle-aged women. None of them had severe reduction in eGFR (eGFR < 30 ml/min).

Women with creatinine > 1 mg/dL or eGFR less than 56 ml/min did not differ from the rest of the cohort with regard to age, prevalence of diabetes, smoking, obesity or overweight, high blood pressure (Systolic Blood pressure ≥ 130 mm Hg, or Diastolic Blood pressure ≥ 85 mm Hg), high LDL cholesterol (≥ 130 mg/dL), low HDL cholesterol (≤ 40 mg/dL), high Triglycerides (≥ 150 mg/dL) (Tables 2,3).

Table 1 Clinical and biochemical characteristics of study population.

Variable	n = 310
Age (yrs)	55.6 \pm 7.8
Total cholesterol (mg/dL)	246.5 \pm 53.4
Triglycerides (mg/dL)	122.8 \pm 66.2
High-density lipoprotein cholesterol (mg/dL)	64.0 \pm 15.8
Low-density lipoprotein cholesterol (mg/dL)	158.0 \pm 47.4
Fasting glucose (mg/dL)	100.5 \pm 19.6
Insulin (mU/L)	5.2 \pm 4.6
Body mass index (kg/m ²)	27.7 \pm 4.5
Creatinine (mg/dL)	0.9 \pm 0.1
eGFR (ml/min)	73.2 \pm 11.7
Waist Circumference (cm)	86.1 \pm 10.9
Homeostatic assessment model index (HOMA)	1.3 \pm 1.2
Systolic blood pressure (mm Hg)	140.1 \pm 22.1
Diastolic blood pressure (mm Hg)	83.2 \pm 10.5

Values are expressed as mean \pm SD. International System conversion factors: to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert high-density lipoprotein cholesterol to millimoles per liter, multiply by 0.02586; to convert glucose to millimoles per liter, multiply by 0.05551; to convert total and low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.02586.

Table 2 Clinical and biochemical characteristics of women categorized by the eGFR levels.

Variable	eGFR < 56 (n = 15) (%)	eGFR ≥ 56 (n = 293) (%)	OR	p
Age > 50 yrs	77	80	0.100	0.997
Diabetes (yes/not)	6	5	0.343	0.332
Smoking (yes/not)	20	30	0.410	0.174
Waist circumference >88 cm	53	40	0.628	0.381
Systolic blood pressure >130 (mm Hg)	80	63	0.422	0.189
Diastolic blood pressure >85 (mm Hg)	60	64	0.629	0.383
HDL-Cholesterol <50 (mg/dL)	20	20	0.306	0.258
LDL-Cholesterol >130 (mg/dL)	71	70	0.914	0.881
Triglycerides >150 (mg/dL)	25	26	0.929	0.902
Overweight (BMI >25) (yes/not)	80	70	0.573	0.397

Table 3 Clinical and biochemical characteristics of women categorized by the Creatinine serum levels.

Variable	Creatinine >1 (n = 17) %	Creatinine ≤1 (n = 291) %	OR	p
Age > 50 yrs	90	80	2.072	0.342
Diabetes (yes/not)	6	5	2.536	0.397
Smoking (yes/not)	23	35	1.970	0.244
Waist circumference >88 cm	55	40	2.024	0.164
Systolic blood pressure >130 (mm Hg)	80	63	2.795	0.113
Diastolic blood pressure >85 (mm Hg)	58	64	2.085	0.143
HDL-Cholesterol <50 (mg/dL)	15	20	1.723	0.478
LDL-Cholesterol >130 (mg/dL)	75	70	1.327	0.633
Triglycerides >150 (mg/dL)	24	26	1.108	0.861
Overweight (BMI >25) (yes/not)	80	70	2.056	0.267

Women with creatinine >1 mg/dL or eGFR less than 56 ml/min had relatively more carotid plaques as compared to the rest of the cohort (Fig. 1).

Multivariate logistic analysis, after adjustment for age, demonstrated a significant association between Creatinine (>1 mg/dL) and IMT (≥1.2 mm): OR 4.12 (C.I 1.22–13.86), p = 0.022; or EGFR (<56 ml/min) and IMT (≥1.2 mm): OR 4.31 (C.I 1.27–14.66), p = 0.019.

This association remained statistically significant after adjustment for main cardiovascular risk factors (i.e. hypertension, hyperglycemia, hypertriglyceridemia, overweight/obesity, smoking, and menopausal state).

Discussion

The main finding of the present study is that in this group of middle-age women mildly elevated creatinine levels >1 mg/dL (corresponding to the 90th percentile of

creatinine distribution) or eGFR less than 56 ml/min (corresponding to the 5th percentile of eGFR distribution) have higher prevalence of significant carotid plaque. This association persisted after adjustment for age and hyperglycemia, high waist circumference, hypertension, high Triglycerides, smoke and metabolic syndrome.

Women with creatinine >1 mg/dL or eGFR less than 56 ml/min had mild chronic renal insufficiency, without disease symptoms. Their condition was associated with significant carotid disease (atherosclerotic plaque), in a pre-symptomatic stage. Population based selection of the sample allows generalization of the finding for middle-aged women.

The present results are in agreement with previous papers [11–13]. We think that our study provides more clinically relevant information because:

- 1) Our measurement are based on both far and near wall of Common Carotid artery, while other studies are based only on measurements at the level of the far wall of the artery.
- 2) We use a marker of severe and diffuse arterial disease (mean max ≥1.20 mm) of definite clinical relevance.

Our finding complement the data demonstrating an association between nephrosclerosis and increased IMT, in healthy renal transplantation donors [14]. Their individuals were relatively few, of young age and of both genders. The relationship was detected between pathology markers of nephrosclerosis and increased IMT, not plaques (very few because of young age and extremely good cardiovascular risk profile). It is likely that with age

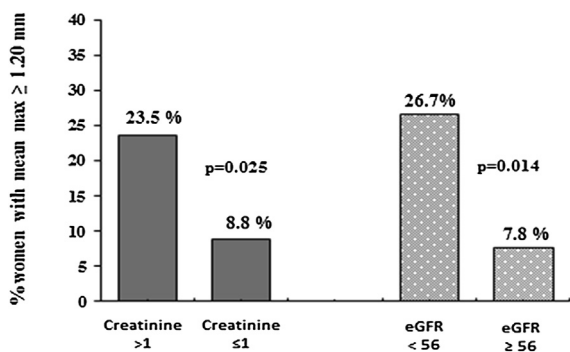


Figure 1 Relationships between common carotid IMT (≥1.20 mm), Creatinine and eGFR.

progression, atherosclerosis prone areas of increase IMT develop into atherosclerotic plaques, as suggested by the finding of more severe atherosclerotic disease in our women, who were older and with a less favorable cardiovascular risk profile.

Our data suggest the value of screening for early carotid disease in asymptomatic middle aged-women with mild renal insufficiency, in order to predict those at relatively higher risk for future cardiovascular events.

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