Gender-Related Determinants of Advanced Subclinical Atherosclerosis in Patients Undergoing Kidney Transplantation

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Key Words
Atherosclerosis, subclinical • End-stage renal disease • Kidney transplantation • Cardiovascular risk • Lipid disorders • Atherogenic index of plasma • Soluble receptor for advanced glycation end products • Asymmetric dimethyl L-arginine

Abstract
Background: Cardiovascular disease caused by atherosclerosis remains a major cause of morbidity and mortality in patients with end-stage renal disease (ESRD). We evaluated the potential association of cardiovascular risk factors including asymmetric dimethyl L-arginine (ADMA) and the soluble receptor for advanced glycation end products (sRAGE) with preclinical atherosclerosis in patients undergoing kidney transplantation. Patients and Methods: In 92 males and 47 females undergoing the first cadaveric renal transplantation, ADMA, sRAGE and common risk factors including lipid parameters were evaluated as potential predictors of preclinical atherosclerosis defined as the Belcaro score (focused on advanced atherosclerotic changes) measured by ultrasound. Results: The prevalence of atherosclerotic changes was approximately 70% in men and women. In logistic regression, age, history of smoking, presence of diabetes mellitus, and plasma triglycerides were the strongest independent predictors for advanced atherosclerosis in the whole group. In unadjusted analyses advanced atherosclerosis was also associated with sRAGE in men and with the atherogenic index of plasma in women. Conclusion: Apart from traditional cardiovascular risk factors, plasma triglycerides were found to be strong and independent predictors of advanced atherosclerosis in patients with ESRD. In addition, sRAGE was associated with atherosclerosis in men and the atherogenic index of plasma in women.

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Introduction
Cardiovascular disease caused by atherosclerosis remains a major cause of morbidity and mortality in patients with end-stage renal disease (ESRD). The high risk of patients with ESRD including those after kidney transplantation is undoubtedly caused by the increased prevalence of traditional cardiovascular risk factors already detected in the general population: higher age, smoking, hypertension, diabetes mellitus, obesity and dyslipid-
emias. Nevertheless, several other factors associated with renal disease could have unique effects on the initiation and acceleration of atherosclerosis. Among those most frequently discussed is the duration of hemodialysis, elevated plasma creatinine, infections and others [1, 2]. One of recently discussed newer biomarkers indicating increased cardiovascular risk is asymmetric dimethyl L-arginine (ADMA) [3–7]. In contrast, the soluble receptor for advanced glycation end products (sRAGE) has been recognized as a potential protective factor [8–14]. These factors could be at least partly responsible for the failure of preventive strategies aimed at the prevention of cardiovascular disease, mainly hypolipemic treatment focused on LDL-cholesterol [15–17].

Studying the association of risk factors with subclinical atherosclerosis detected by ultrasound is a valuable tool for assessment of newer risk factors of atherosclerosis. This approach has already been used to evaluate the impact of various cardiovascular risk factors on carotid arteries in patients with chronic kidney diseases [18–23] including women with renal impairment [24].

Another promising approach to better individualize preventive strategies is studying gender differences. Recent recommendations for women almost do not differ from those for men [25] and thus do not fully appreciate gender differences in cardiovascular disease development and management [26]. A recent study in patients treated by hemodialysis observed greater impact of C-reactive protein and troponin T on cardiovascular and non-cardiovascular mortality in women [27].

In this study we analyzed potential associations of preclinical atherosclerosis in carotid and femoral arteries with traditional and newly discussed risk factors (circuitating ADMA and sRAGE) in patients with ESRD undergoing kidney transplantation including potential gender differences.

**Patients and Methods**

The study was approved by the Human Ethical Review Committee, Institute for Clinical and Experimental Medicine, Prague, Czech Republic, and complies with the Declaration of Helsinki including current revisions and the Good Clinical Practice Guidelines. The procedures followed were in accordance with institutional guidelines. All subjects gave written informed consent before being enrolled in the study.

One hundred and thirty-nine patients (92 males and 47 females) were included in the study. These patients underwent first cadaveric renal transplantation at the Transplant Centre, Institute for Clinical and Experimental Medicine, Prague, Czech Republic, between January 1, 2007 and July 12, 2008. The only exclusion criterion was the patient’s refusal to be involved in the study (none). Biochemical measurements and collection of patient data were completed by September 31, 2009.

Patients were examined in the Clearance Laboratory, Division of Metabolism, Department of Nephrology, 1 month after renal transplantation, including blood sampling for biochemical measures. Patients were treated by a long-term triple-drug immunosuppression protocol including cyclosporin A (Neoral; Novartis) or FK506 tacrolimus (Prograf; Astellas) based regimes. The other drugs used in the management of patients were mycophenolate mofetil (Cell Cept; Roche) 1–2 g/day and steroids up to 10 mg/day (prednisone; Zentiva, Czech Republic). In addition, all patients were treated by ACE inhibitors, angiotensin receptor blockers and statins to achieve recommended values of blood pressure and plasma lipids.

Body height, weight, and blood pressure were measured according to a standardized protocol. Body mass index was calculated as weight in kilograms divided by height in square meters. Patients with a history of current and past regular smoking were defined as ever smokers. A history of diabetes mellitus was obtained from patients’ documents. Systolic and diastolic blood pressure was measured on the right arm or the arm without an arteriovenous fistula with the subject in the sitting position after at least 5 min at rest.

Blood samples were obtained within 2 days after renal transplantation. All patients fasted for at least 10 h before sampling and none of the patients suffered from acute infection at the time of the examination. Blood samples were collected into evacuated tubes with EDTA and the blood was immediately centrifuged at 3,600 g for 5 min at 20°C.

Plasma total cholesterol and triglycerides were measured using a fully automated (Hitachi 911 autoanalyzer; Japan) enzymatic method (reagents from Hoffmann-La Roche, Basel, Switzerland). HDL-cholesterol was determined by the same method after precipitation of serum lipoproteins with sodium phosphotungstate and magnesium chloride kits. Serum LDL-cholesterol was measured by an automated method with direct determination using kit LDL-C plus from Hoffmann-La Roche. Non-HDL-cholesterol was calculated by subtracting HDL-cholesterol from total cholesterol. In addition, the atherogenic index of plasma (AIP) related to the particle size of lipoproteins was calculated as log (triglycerides/HDL-cholesterol) [28].

For ADMA quantification, the ELISA method (kit ADMA, ELISA; DLD Diagnostika GmbH, Hamburg, Germany) and Auto-ELIA II microplate reader (Labsystems Oy, Espoo, Finland) were used. The concentration of sRAGE in randomly selected males (n = 43) and females (n = 27) was measured by a sandwich ELISA using standard kits (Quantikine, R&D Systems) according to the manufacturer’s protocol as described previously [8]. Albumin was measured by standard methods in the central laboratory of the institute.

**Ultrasound Studies**

Ultrasound studies were performed within 7 days after renal transplantation in 103 patients, within 2 months in 7 patients and in 3–6 months in 19 patients. The reasons for postponed examinations were postoperative complications and non-availability of ultrasound at the time of hospitalization. All subjects were examined in the supine position. Bilateral ultrasound assessment of the carotid and femoral arteries by Toshiba APLIO 50 XV (Tochigi,
Japan) ultrasound system with a 7.5- to 10-MHz linear array transducer was performed. The carotid arteries were examined with the patient in the supine position with the neck rotated 45° in the direction opposite the site being examined. The images of the common carotid arteries, bifurcation, internal and external carotid arteries were obtained. Subsequently, the femoral arteries were examined with the patient supine and images of the common femoral artery and bifurcation were obtained. All arteries were scanned by transverse and longitudinal projection. The images were digitalized and read offline (using vPACS DS software, version 6.9.25, Czech Republic) by an operator blinded to the clinical status of the patients (J.P.).

Because of the expected high prevalence of advanced atherosclerotic changes in this group of patients, the presence of preclinical atherosclerosis was defined by a semiquantitative classification – the Belcaro score. The classification by Belcaro et al. [29] has been described elsewhere. In short, this classification evaluates the degree of preclinical atherosclerosis according to the following ultrasonic findings: class I = normal, three ultrasonic layers (intima-media, adventitia, and periadventitia) were clearly separated, no disruption of the lumen-intima interface for at least 3.0 cm, and/or initial alterations (lumen-intima interface disruption at intervals of <0.5 cm); class II = intima-media granulation, granular echogenicity of the deep, normally unechoic intimal-medial layer and/or increased intima-media thickness (>1 mm); class III = plaque without hemodynamic disturbance, localized wall thickening and increased density involving all ultrasonic layers, intima-media thickness ≥2 mm; class IV = stenotic plaque, as in class III but with hemodynamic stenosis on duplex scanning (sample volume in the center of the lumen), indicating stenosis >50%. The highest value of the Belcaro score found in the arterial system (either in carotid or femoral arteries) in each subject was used for subsequent analyses. Advanced atherosclerosis was defined as a Belcaro score of >II.

Intra-observer variability was assessed by repeat measurements in 10 randomly chosen patients (5 men and 5 women) at a 1-week interval (J.P.). The intraclass correlation coefficient of measurements was 0.96.

Statistical Analysis

Data are presented as the absolute and relative frequencies for categorical variables and means with standard deviations for continuous ones. Between groups comparison of continuous variables was calculated using Mann-Whitney U test. For discrete variables Pearson χ² test was applied, or Yates χ² test in the case of low numbers in the subgroups analyzed. Paired t test was used to analyze ADMA blood levels obtained 2 days and 3 months after transplantation. Linear regression was used to evaluate the independent predictors of preclinical atherosclerosis – the Belcaro score. All results are considered to be statistically significant at p < 0.05.

Results

Patient characteristics are shown separately for men and women in table 1. The duration of hemodialysis, total, and HDL-cholesterol in plasma were significantly higher in women, while the prevalence of ischemic heart disease and smoking was significantly higher in men. No other significant differences between men and women were found, including the prevalence of advanced preclinical atherosclerosis in the carotid and femoral arteries, defined as a Belcaro score of >II, which was highly prevalent in both groups (fig. 1). As shown in table 1, delayed graft function after transplantation was detected in 32% of men and in 23% of women, rejection was observed in 29% of men and 20% of women. However, because all these complications occurred after blood samples were taken, and all but 5 occurred also after ultrasound studies, they were not included in the statistical analyses.

Compared to patients without advanced atherosclerosis (Belcaro ≤II) patients with advanced atherosclerosis (Belcaro >II) were older (56.8 ± 8.8 vs. 41.0 ± 10.4 years; p < 0.0001), had a higher prevalence of smoking (59.2 vs. 41.5%; p = 0.017), a higher prevalence of diabetes mellitus (25.5 vs. 2.4%; p = 0.006) and a higher prevalence of ischemic heart disease (0.0 vs. 21.4%; p = 0.005), higher body mass index (27.0 ± 4.3 vs. 24.8 ± 3.9; p = 0.007), higher plasma triglycerides (2.81 ± 1.76 vs. 2.09 ± 0.97 mmol/l; p = 0.015), lower plasma albumin (39.27 ± 4.21 vs. 41.57 ± 4.87 g/l; p = 0.006), and lower sRAGE (2,784.3 ± 1,505.3 vs. 4,131.9 ± 1,052.1 pg/ml; p = 0.003). No differences between patients with and without atherosclerosis were observed regarding gender, duration of hemodialysis, subsequent prevalence of delayed graft function, rejection rate, prevalence of medication and other risk factors under study.

Subsequently, we analyzed differences between patients with and without advanced atherosclerosis, separately for men and women (table 2). Men with advanced preclinical atherosclerosis were significantly older (p < 0.0001), had a higher prevalence of smoking (p = 0.003) and diabetes mellitus (p = 0.016), had a higher body mass index (p = 0.014), lower serum albumin (p = 0.003), were treated more frequently by hypolipemic drugs (p = 0.005), and had a lower level of sRAGE (p = 0.001) than men without signs of advanced atherosclerosis. Women with advanced preclinical atherosclerosis were significantly older (p = 0.0001), had a longer duration of hemodialysis (p = 0.05), had higher triglycerides (p = 0.019) and had a higher AIP (p = 0.009). No other risk factors under study, including ADMA were found to be significantly different between patients with and without advanced atherosclerosis in either men or women. Because ADMA could change immediately after transplantation [30] we checked the levels of ADMA obtained from 76 patients 2 days and 3 months after transplantation. No significant change...
was observed \((0.96 \pm 0.20 \text{ vs. } 0.98 \pm 0.54 \mu\text{mol/l; } p = 0.67)\).

In men, sRAGE was negatively and significantly correlated only with age (correlation coefficient \(-0.48\); linear regression coefficient \(-54.5\); 95% CI \(-87.4\), \(-21.6\)). No significant association was found between sRAGE and other risk factors (body mass index, plasma lipids, plasma albumin, blood pressure, smoking and hypolipemic treatment).

In women, AIP was positively correlated with the duration of hemodialysis (correlation coefficient \(0.012\); 95% CI \(0.002\), \(0.021\)). No significant association was found between AIP and other risk factors under study including age, smoking and hypolipemic treatment.

To assess independent predictors for the Belcaro score, we used logistic regression model comprising variables associated with the Belcaro score in previous analyses.

### Table 1. Patient characteristics of men and women after kidney transplantation

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 92)</th>
<th>Women (n = 47)</th>
<th>p (t or (\chi^2) test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>52.0 ± 12.1</td>
<td>52.4 ± 11.2</td>
<td>0.960</td>
</tr>
<tr>
<td>Duration of hemodialysis, months</td>
<td>27.7 ± 19.9</td>
<td>36.3 ± 23.1</td>
<td>0.042</td>
</tr>
<tr>
<td>Delayed graft function, n</td>
<td>29 (31.5%)</td>
<td>11 (23.4%)</td>
<td>0.429</td>
</tr>
<tr>
<td>Rejection during the first year, n</td>
<td>25 (29.1%)</td>
<td>8 (19.5%)</td>
<td>0.286</td>
</tr>
<tr>
<td>Ever smokers, n</td>
<td>54 (58.7%)</td>
<td>19 (40.4%)</td>
<td>0.041</td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>19 (20.7%)</td>
<td>7 (14.9%)</td>
<td>0.772</td>
</tr>
<tr>
<td>Ischemic heart disease, n</td>
<td>19 (20.7%)</td>
<td>2 (4.3%)</td>
<td>0.034</td>
</tr>
<tr>
<td>Strokes, n</td>
<td>2 (2.2%)</td>
<td>1 (2.1%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Peripheral artery disease, n</td>
<td>6 (6.5%)</td>
<td>2 (4.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetic nephropathy, n</td>
<td>14 (15.2%)</td>
<td>2 (4.3%)</td>
<td>0.060</td>
</tr>
<tr>
<td>Use of hypolipemic drugs, n</td>
<td>33 (35.9%)</td>
<td>22 (43.8%)</td>
<td>0.212</td>
</tr>
<tr>
<td>Use of antihypertensive drugs, n</td>
<td>78 (84.8%)</td>
<td>41 (87.2%)</td>
<td>0.700</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.4 ± 4.1</td>
<td>26.1 ± 4.7</td>
<td>0.448</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>148.5 ± 22.6</td>
<td>146.3 ± 25.1</td>
<td>0.848</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>88.3 ± 12.5</td>
<td>88.2 ± 13.1</td>
<td>0.886</td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>4.66 ± 1.11</td>
<td>5.30 ± 1.62</td>
<td>0.009</td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>2.66 ± 1.7</td>
<td>2.50 ± 1.4</td>
<td>0.950</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/l</td>
<td>1.10 ± 0.3</td>
<td>1.34 ± 0.5</td>
<td>0.0002</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/l</td>
<td>2.40 ± 0.8</td>
<td>2.76 ± 1.1</td>
<td>0.110</td>
</tr>
<tr>
<td>Atherogenic index of plasma</td>
<td>0.32 ± 0.32</td>
<td>0.23 ± 0.27</td>
<td>0.110</td>
</tr>
<tr>
<td>Non-HDL-cholesterol, mmol/l</td>
<td>3.56 ± 1.13</td>
<td>3.96 ± 1.62</td>
<td>0.150</td>
</tr>
<tr>
<td>Albumin, g/l</td>
<td>40.1 ± 4.9</td>
<td>39.7 ± 3.7</td>
<td>0.670</td>
</tr>
<tr>
<td>ADMA, (\mu\text{mol/l})</td>
<td>0.97 ± 0.17</td>
<td>0.96 ± 0.20</td>
<td>0.900</td>
</tr>
<tr>
<td>sRAGE, pg/ml</td>
<td>3,069 ± 1,352 (n = 43)</td>
<td>3,528 ± 1,706 (n = 27)</td>
<td>0.205</td>
</tr>
<tr>
<td>Belcaro &gt;II, n</td>
<td>66 (71.7%)</td>
<td>32 (68.1%)</td>
<td>0.654</td>
</tr>
</tbody>
</table>

Unless otherwise indicated the data are expressed as means \(±\) SD. Atherogenic index of plasma = Log (triglycerides/HDL); non-HDL-cholesterol = total cholesterol-HDL-cholesterol; ADMA = asymmetric dimethyl L-arginine; sRAGE = soluble receptors for advanced glycation end products. Body mass index calculated as weight (kg)/height (m)\(^2\).

**Fig. 1.** Prevalence of advanced atherosclerosis expressed as Belcaro score in men and women undergoing kidney transplantation. Values are percentages.
The following variables were put in the model: age, sex, smoking status, duration of hemodialysis, presence of diabetes mellitus, presence of hypolipemic therapy, body mass index, plasma triglycerides, AIP, plasma albumin, plasma asymmetric dimethyl L-arginine. Because of the low numbers of women with diabetes and available sRAGE, we could not include their data in the statistical model. The strongest predictors for advanced atherosclerosis were age, history of smoking, presence of diabetes mellitus and triglycerides (table 3).

**Discussion**

Based on our results, in addition to traditional cardiovascular factors such as age, history of smoking, and the presence of diabetes mellitus, higher plasma triglycerides were found to be strong and on the other risk factors independent predictors for advanced atherosclerosis.

Triglycerides and AIP expressed as log (triglycerides/HDL) reflects the 'atherogenic' profile of plasma in addition to LDL-cholesterol, which is still the main target in most of interventional studies using hypolipemic drugs. The atherogenic profile of plasma lipoproteins is characterized by an elevated concentration of plasma triglycerides and by a predominance of small dense LDL- and low HDL-cholesterol [31]. As cardiovas-
cular diseases remain the leading cause of death in pa-
tients with chronic kidney disease including renal trans-
plant recipients, management of dyslipidemia is of great
importance to prevent cardiovascular complications.
However, in the already mentioned large prospective
clinical trials the treatment focused on LDL-cholesterol
failed to significantly decrease the main cardiovascular
events [15–17]. Therefore, targeting treatment more ag-
gressively also on high triglycerides and low HDL-chole-
terol could be a more effective approach, especially in pa-
tients with end-stage renal failure and in women, in
whom triglycerides and HDL could be more important
than in men [32–34]. Looking at the data from our group,
mean LDL-cholesterol was only slightly elevated above
the recommended levels, undoubtedly thanks to frequent
hypolipemic treatment especially in patients with ad-
vanced atherosclerosis and preexisting cardiovascular
disease. However, in addition to aggressively lowering
LDL, the removal of residual risk caused by higher tri-
glycerides and low HDL-cholesterol seems to be manda-
tory in these patients, especially in women. In population
studies it has been shown that especially younger women
are more sensitive to the atherogenicity of high triglycer-ides and low HDL-cholesterol [33]; this fact could also be
true for the population of patients with ESRD. Our results
thus support the observation that renal dyslipidemia is
characterized by accumulation of intact and partially
metabolized triglyceride-rich lipoproteins with proather-
erogenic potential [35]; in addition, this potential was
found to be higher only in the women of our study.

In unadjusted analyses, only age was strongly associ-
ated with advanced atherosclerosis both in men and
women suffering from ESRD and undergoing kidney
transplantation. While smoking, diabetes mellitus, hy-
polipemic treatment, body mass index, albumin and
sRAGE were associated with advanced atherosclerosis in
men, in women the duration of hemodialysis, triglycer-ides, and AIP were found to be associated with advanced
atherosclerotic changes. While in men no strong associa-
tion between sRAGE and all the other risk factors under
study was found with intima-media thickness of the ca-
rotid arteries [36]. This discrepancy could be partly ex-
plained by a methodological approach: in our study we
focused on more advanced stages of atherosclerosis.
Therefore, ADMA could be more related to less advanced
atherosclerotic changes and their progression and less re-
lated to the already developed advanced atherosclerotic
plaques. In addition, we did not find any strong correla-
tion between ADMA levels and other risk factors under
study. After reviewing the available literature, in patients
with ESRD we found the plasma concentration of ADMA
to be mostly in the range of 1–2.5 µmol/l. ADMA levels
in our population were at the lower border of this range
(around 1 µmol/l). The cause for this finding could be
intensive treatment with cardiovascular drugs, which

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Marečková/Lansk
was rather high in our population before transplantation (antihypertensive drugs in 80% and lipid-lowering drugs in 40% of patients). The variation in ADMA levels immediately after transplantation as already reported [30] could also be a reason for false-negative results regarding the correlation between ADMA levels and cardiovascular risk factors under study. However, we did not find any significant difference between ADMA levels obtained 2 days and 3 months after transplantation in 76 patients. Therefore, the different results observed in our study could rather be caused by a different population of patients of different ethnic origin and with different status/treatment before transplantation (inclusion of only living donors by Yilmaz et al. [30]). In addition, the use of different laboratory methodologies could be also of importance.

In general, strong evidence exists that cardiovascular risk factors and their impact could qualitatively and quantitatively differ between men and women with ESRD [27]. Similar evidence was observed in our study: predictors of advanced atherosclerosis between men and women were different, despite the similar age of both groups. A surprising finding was the association between the duration of hemodialysis and advanced atherosclerotic changes in women only; in addition, in women, the duration of hemodialysis was strongly associated with AIP. However, whether the deleterious effects of hemodialysis can be mediated through impaired lipid metabolism in women could not be established based on our data, and longitudinal studies should address this question.

Another important finding in our study was the very high prevalence of advanced stages of atherosclerosis in carotid and femoral arteries, putting in question the frequently used intima-media thickness measurements in this high-risk population. In addition, the prevalence of advanced atherosclerosis was the same in men and women of similar age in our study, despite the fact that in the general population women develop cardiovascular disease 10–20 years later than men.

The main limitation of our study is its cross-sectional design which did not allow us to assess the cause and effect relationship. Also the relatively low number of women could be a cause of the observed differences between both genders in statistical associations of different cardiovascular risk factors with advanced atherosclerosis. The strengths of our study are the specific population of patients with ESRD undergoing kidney transplantation, the gender-oriented approach, and the assessment of not only traditional but also newly discussed risk factors, including newer lipid profile parameters, and the assessment of their association with advanced atherosclerosis not only in carotid but also in femoral arteries.

**Conclusion**

Apart from traditional cardiovascular risk factors such as age, smoking and diabetes mellitus, plasma triglycerides were found to be strong and independent predictors of advanced atherosclerosis in men and women with ESRD undergoing renal transplantation and treated frequently with antihypertensive and hypolipemic drugs. Based on our results, sRAGE in men and AIP in women deserve attention as potential newer risk factors for atherosclerosis.

**References**


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