Synergistic effects of asymmetrical dimethyl-L-arginine accumulation and endothelial progenitor cell deficiency on renal function decline during a 2-year follow-up in stable angina

Andrzej Surdacki1, Ewa Marewicz2, Ewa Wieczorek-Surdacka3, Tomasz Rakowski1, Grzegorz Szastak1, Julisz Pryjma2, Dariusz Dudek1 and Jacek S. Dubiel1

12nd Department of Cardiology 2Department of Immunology and 3Department of Nephrology, Jagiellonian University, Cracow, Poland

Correspondence and offprint requests to: Andrzej Surdacki; E-mail: surdacki.andreas@gmx.net

**Background.** Renal insufficiency predisposes to coronary artery disease (CAD), but also CAD and traditional risk factors accelerate renal function loss. Endothelial progenitor cell (EPC) deficiency and elevated asymmetrical dimethyl-L-arginine (ADMA), an endogenous nitric oxide (NO) formation inhibitor, predict adverse CAD outcome. Our aim was to assess changes in estimated glomerular filtration rate over time (ΔeGFR) in relation to baseline EPC blood counts and ADMA levels in stable angina.

doi: 10.1093/ndt/gfp439
Advance Access publication 3 September 2009

Received for publication: 10.11.09; Accepted in revised form: 22.1.10

© The Author 2009. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved.
For Permissions, please e-mail: journals.permissions@oxfordjournals.org
Methods. Eighty non-diabetic men with stable angina were followed up for 2 years after elective coronary angioplasty. Exclusion criteria included heart failure, left ventricular systolic dysfunction, eGFR <30 ml/min/1.73 m² and coexistent diseases. Those with cardiovascular events or ejection fraction <55% during the follow-up were also excluded. A baseline blood count of CD34+/kinase-insert domain receptor (KDR)+ cells, a leukocyte subpopulation enriched for EPC, was quantified by flow cytometry (percentage of lymphocytes).

Results. A synergistic interaction ($P = 0.015$) between decreased CD34+/KDR+ cell counts and increased plasma ADMA, but not symmetrical dimethyl-L-arginine, was the sole significant multivariate $\Delta$eGFR predictor irrespective of baseline eGFR. $\Delta$eGFR was depressed in the simultaneous presence of high ADMA (>0.45 μmol/l, median) and low CD34+/KDR+ cell counts (<0.035%, median) compared to either of the other subgroups ($P = 0.001–0.01$). $\Delta$eGFR did not correlate with traditional risk factors, angiographic CAD extent, levels of C-reactive protein and soluble vascular cell adhesion molecule-1.

Conclusions. Elevated ADMA and EPC deficiency may synergistically contribute to accelerated renal function decline in stable angina. This could result from the impairment of the EPC-dependent endothelial renewal in the kidney, an NO-dependent process.

Keywords: asymmetrical dimethyl-L-arginine; endothelial progenitor cells; renal function decline; stable angina

Introduction

Chronic kidney disease (CKD) predisposes to atherosclerotic cardiovascular disease via a corollary of both traditional and non-traditional risk factors [1,2]. Moreover, CKD patients are exposed to a high mortality risk irrespective of the presence of pre-existing established cardiovascular disease [2–4]. The relationship between CKD and atherosclerotic cardiovascular disease appears bidirectional as cardiovascular disease by itself [5], and some well-recognized risk factors (hypertension, diabetes, obesity, dyslipidaemia) accelerate renal function decline in addition to ageing [6–9].

Asymmetrical dimethyl-L-arginine (ADMA), an endogenous nitric oxide (NO) synthesis inhibitor, is associated with cardiovascular risk factors, endothelial dysfunction [10,11], early atherosclerosis [12] and adverse outcome in coronary artery disease (CAD) [13,14] and may be also involved in the interrelations between CKD and cardiovascular disease. In agreement with this concept, in non-dialyzed CKD patients elevated ADMA levels were linked to preclinical atherosclerosis [15], accelerated deterioration of renal function [16,17] and excessive cardiovascular mortality [18].

In stable CAD, Thum et al. [19] reported progressive rises in ADMA levels coupled with decreasing blood counts of bone marrow-derived endothelial progenitor cells (EPC), whose mobilization and functional capacity are controlled by NO [20]. We have recently described the association between mild-to-moderate renal insufficiency accompanying stable angina and depressed numbers of CD34/kinase-insert domain receptor (KDR) double-positive cells (CD34+/KDR+ cells), a leukocyte subpopulation enriched for EPC [21]. Blood CD34+/KDR+ cells deficiency, like ADMA accumulation, relates to adverse prognosis [22,23], endothelial dysfunction [24] and preclinical atherosclerosis [25,26].

The L-arginine–NO pathway and the EPC-dependent endothelial renewal contribute to the maintenance of renal vascular integrity in experimental models of CKD [27,28] and glomerulonephritis [29–31], respectively. To the best of our knowledge, effects of EPC deficiency on renal function decline have not been studied so far in a clinical setting. Our aim was to verify the hypothesis that changes in estimated glomerular filtration rate over time ($\Delta$eGFR) might be related to CD34+/KDR+ cell counts and ADMA levels in optimally treated non-diabetic men with stable angina.

Subjects and methods

Patients

Eighty men with stable angina hospitalized in our centre for a planned coronary angiography were included in the final analysis. All the patients exhibited significant obstructive CAD defined as the presence of a diameter stenosis of ≥70% of at least one major epicardial artery segment. During the same hospitalization, the subjects underwent a complex elective coronary angioplasty and were followed up for 2 years after discharge.

As previously described in detail [21], exclusion criteria included diabetes, proteinuria, eGFR <30 ml/min per 1.73 m² body-surface area, any surgery within past 6 months, left ventricular ejection fraction <55% (by ultrasound), heart failure, hypertension uncontrolled adequately by drugs, overt extracoronary atherosclerosis, chronic coexistent infections within the previous two months, significant abnormalities in routine laboratory assays and any chronic non-cardiovascular medication. All patients were receiving low-dose aspirin, angiotensin-converting enzyme inhibitors (ACEI) and statins for ≥3 preceding months.

Those with contrast-induced nephropathy, cardiovascular events (hospitalization due to acute myocardial infarction, heart failure, stroke, or urgent coronary revascularization), any major surgery, ejection fraction <55%, discontinuation of ACEI or statins and newly diagnosed chronic coexistent abnormalities during the follow-up were also excluded.

The study was conducted in compliance with the Declaration of Helsinki; the Bioethical Committee of our university approved the protocol and the patients gave informed consent.

Blood samples for extended biochemical assays and fluorescence-activated cell sorter analysis were taken from an antecubital vein after an overnight fast at routine blood sampling 0–2 days before the planned angiography. Plasma and serum were separated and stored at −70°C until assayed. Blood samples for serum creatinine were also drawn under similar conditions on the occasion of routine assays at a control visit after 24 ± 1 months; eGFR was calculated according to the four-variable equation of the Modification of Diet in Renal Disease Study Group [32] and $\Delta$eGFR was computed.

Angiographic CAD quantification

Analysis of coronary angiogram (Philips Integris HM 3000) included the number of main coronary vessels with luminal diameter narrowings ≥70%, maximal percent diameter stenosis and CAD extension score calculated according to Sullivan et al. [33] and expressing a proportion of the visible coronary arterial tree with angiographically detectable atheroma.

Flow cytometry

As previously described [21,23,34], 100 μl of blood was incubated in the dark (<60 min. after venopuncture) with mouse monoclonal antibodies...
against human KDR (Sigma, St Louis, MO, USA) followed by rabbit fluoroescin isothiocyanate (FITC)-labelled secondary antibodies (Dako, Denmark) and phycoerythrin (PE)-conjugated mouse monoclonal antibodies against human CD34 (Becton Dickinson, Franklin Lakes, NJ, USA). Control blood samples were incubated with mouse isotype-matched antibodies (IgG1-FITC and IgG2a-PE, yl/y2a Simultest, Becton Dickinson). Following lysis of erythrocytes, data acquisition was performed on a flow cytometer (FACScan, Becton Dickinson GmbH, Heidelberg, Germany) including 100 000 events. The CD34+/KDR+ cell count was expressed as a percentage of peripheral blood mononuclear cells (PBMC) in a pre-specified lymphocyte gate [21–23,34]. In our hands, the method exhibited a high reproducibility, quantified as a close within-subject correlation ($r = 0.89, P < 0.001$) obtained for CD34+/KDR+ cell numbers measured twice for the same 10 patients from two separate blood samples drawn under similar conditions [21].

**Biochemical assays**

Plasma ADMA and symmetrical dimethyl-l-arginine (SDMA) were measured by means of commercially available enzyme-linked immunoadsorbent assays (DLD Diagnostika GmbH, Hamburg, Germany). The lower detection limit was 0.05 μmol/l for both analytes and intra-assay and inter-assay coefficients of variation averaged 7.5 and 10.3% (ADMA) and 6.1 and 9.8% (SDMA), respectively.

Plasma levels of soluble vascular cell adhesion molecule-1 (sVCAM-1) were measured by an enzyme-linked immunoadsorbent assay (R&D Systems, Minneapolis, MN, USA), serum high-sensitivity C-reactive protein and homocysteine with chemiluminescent immunoassay systems (Immulumite 1000 and Immulite 2000, DPC, Flanders, NJ, USA) and creatinine by the modified Jaffe method (Roche Hitachi 911 analyzer, Roche Diagnostics, F. Hoffmann-La Roche, Basel, Switzerland).

**Statistical analysis**

Data are presented as means ± SD for continuous variables with normal distribution, medians and interquartile ranges (25th–75th percentile) for not normally distributed parameters (CD34+/KDR+ cell counts, high-sensitivity C-reactive protein, homocysteine, sVCAM-1) and counts (proportions) for categorical variables. Univariate correlations were estimated by Pearson’s correlation coefficients ($r$). Logarithmic transformation was applied, if necessary to obtain a normal distribution. As in three patients, the CD34+/KDR+ cell counts equalled 0, the logarithmic transformation consisted in the computation of log [raw value (%) + 0.01].

Since bivariate scatterplots suggested that the effects of ADMA or CD34+/KDR+ cell counts on ΔeGFR were modified by the levels of the other variable, two-way analysis of variance (ANOVA) was used to estimate this interaction with ΔeGFR as a dependent variable and two independent predictor variables (ADMA and CD34+/KDR+ cell counts) as factors categorized with the reference to the respective medians. A P-value ≤0.05 was considered significant. Post hoc intergroup differences were assessed by Tukey’s honestly significant difference test.

In order to identify independent ΔeGFR determinants, backward stepwise multiple linear regression was used with ΔeGFR as a dependent variable and a ridge regression option due to the relationship between some independent variables. Only variables for which the $P$-values in a univariate analysis did not exceed 0.15 were taken into account in the multiple regression. We have also included an interaction term that was set to 1 in the subjects who exhibited the coincidence of plasma ADMA over its median (0.45 μmol/l) and CD34+/KDR+ cell counts below the respective median (0.035%) being equal to 0 in the remainder. Additionally, as an adjustment for baseline values of a variable may produce a measurement error-dependent bias when looking for determinants of changes in the variable over time [35,36], two regression models were constructed either excluding (model 1) or including (model 2) baseline eGFR.

**Results**

**Patient characteristics**

The baseline characteristics of the study patients, who were included into the final analysis, are shown in Tables 1 and 2. Baseline eGFR and ΔeGFR averaged 69 ± 12 and 0.5 ± 3.3 ml/min/1.73 m², respectively.

**Correlates of ΔeGFR and baseline eGFR**

ΔeGFR correlated to plasma ADMA ($r = -0.25, P = 0.03$) and CD34+/KDR+ cell counts ($r = 0.23, P = 0.04$), but not CD34+ cell counts ($r = 0.05, P = 0.6$), at the beginning of the follow-up.

Baseline eGFR correlated to plasma SDMA ($r = -0.61, P < 0.001$), CAD extension score ($r = -0.30, P = 0.007$), homocysteine ($r = -0.29, P = 0.009$), CD34+/KDR+ cell numbers ($r = 0.25, P = 0.03$) and sVCAM-1 ($r = -0.23, P = 0.04$).
There were insignificant tendencies towards correlations among \( \Delta \text{eGFR} \) and baseline eGFR \((r = 0.20, P = 0.08)\), HDL cholesterol \((r = 0.19, P = 0.10)\) and SDMA concentrations \((r = -0.17, P = 0.13)\), as well as between baseline eGFR and ADMA concentrations \((r = -0.20, P = 0.08)\) and haemoglobin \((r = 0.17, P = 0.14)\).

### Correlates of plasma ADMA, SDMA and CD34+/KDR+ cell counts

Besides \( \Delta \text{eGFR} \) and baseline eGFR, as mentioned above, plasma ADMA and CD34+/KDR+ cell numbers were not significantly correlated with other variables. CD34+/KDR+ cell counts exhibited only an insignificant relationship with sVCAM-1 \((r = -0.21, P = 0.06)\) and the CAD extension score \((r = -0.18, P = 0.10)\). ADMA levels and CD34+/KDR+ cell counts were mutually unrelated \((r = -0.04, P = 0.7)\) (Figure 1).

In addition to eGFR, SDMA levels correlated significantly to CAD extension score \((r = 0.34, P = 0.002)\), homocysteine \((r = 0.31, P = 0.005)\), CD34+/KDR+ cell numbers \((r = -0.27, P = 0.02)\) and sVCAM-1 \((r = 0.22, P = 0.05)\).

### A synergistic ADMA−CD34+/KDR+ cells counts interaction with regard to \( \Delta \text{eGFR} \)

Two-way ANOVA revealed a significant interaction \((P = 0.015)\) between ADMA levels and CD34+/KDR+ cell numbers with regard to \( \Delta \text{eGFR} \). \( \Delta \text{eGFR} \) was significantly lower in the simultaneous presence of high ADMA (>0.45 \( \mu \text{mol/l} \), median) and low CD34+/KDR+ cell counts (<0.035%, median) as compared to either of the other subgroups (Figure 2A). No such interaction \((P = 0.5)\) by ANOVA was observed between plasma SDMA and CD34+/KDR+ cell counts; accordingly, \( \Delta \text{eGFR} \) was similar across analogous subgroups created on the basis of cut-off values corresponding to respective medians (0.63 \( \mu \text{mol/l} \) for SDMA and 0.035% for CD34+/KDR+ cell counts) (Figure 2B).

### Multivariate determinants of \( \Delta \text{eGFR} \)

Multiple regression revealed the ADMA−CD34+/KDR+ cell counts interaction term as the sole independent predictor of \( \Delta \text{eGFR} \). This was observed irrespective of the inclu-
sion (model 1) or exclusion (model 2) of baseline eGFR as an independent variable (Table 3). The regression results did not change significantly after setting cut-off values for the interaction term at the upper-third of plasma ADMA and the lower-third of CD34+/KDR+ cell counts ($\beta = -0.33 \pm 0.10, P = 0.001$ for the interaction term).

**Discussion**

Our salient finding consists of synergistic contributions of elevated plasma ADMA and depressed CD34+/KDR+ cell counts to renal function decline in non-diabetic men with stable angina receiving an optimal complex therapy according to current practice guidelines.

Although both ADMA accumulation and CD34+/KDR+ cells deficiency were more pronounced in CAD subjects with preexisting mild-to-moderate renal insufficiency, their effects on further renal deterioration appeared independent of the initial renal function. Moreover, the effect was specific for ADMA, being unrelated to SDMA or sVCAM-1 levels, despite the fact that the latter biomarkers, not ADMA, were significant correlates of baseline eGFR and/or angiographic CAD extent.

This supports the hypothesis by Kielstein and Sydow that ADMA may contribute to both coronary and renal pathology [37], extending earlier clinical reports on the relevance of ADMA for renal function loss in CKD over a wide range of eGFR [16,17] and suggesting a complementary role of EPC deficiency. Additionally, our results provide a clinical argument in favour of the experiment-based concept [27–31] of the importance of bone marrow-derived cells for the maintenance of vascular integrity also within the kidney.

**Beneficial effects of EPC in experimental kidney damage**

Bone marrow-derived EPC have been shown to contribute to endothelial repair not only in balloon-induced arterial injury [38] or atherosclerosis-prone apolipoprotein E-deficient mice [39], but also within glomeruli in experimental glomerulonephritis [29,30]. Moreover, intrarenal infusion of *in vitro*-differentiated EPC attenuated endothelial damage and mesangial activation in experimental glomerulonephritis [31]. This might reflect generalized beneficial effects of EPC on the endothelium, as evidenced earlier from the ability of systemic infusions of cultured spleen-derived EPC from wild-type animals to persistently correct endothelial dysfunction in apolipoprotein E-deficient mice [39].

A simple application of the results obtained in experimental glomerulonephritis studies to CKD is not justified. However, the participation of EPC in the on-going renewal of endothelial lining has been demonstrated in the kidney [29,40]. Additionally, on the basis of the chronic hypoxia, hypothesis of progressive tubulointerstitial injury in CKD [41] and the preferential ability of erythropoietin (locally secreted within the renal cortex) to stimulate the EPC homing-dependent neovascularization within ischemic areas [40], it can be hypothesized that the role of EPC, with regard to renal integrity, might be even accentuated in CKD.

**Contribution of intrarenal NO bioavailability to the maintenance of renal function**

Irrespective of the hypothetical contribution of EPC to renal integrity, the role of intrarenal NO bioavailability and endothelial renewal for long-term maintenance of renal function in CKD appears well established, which implies the relevance of ADMA generation. In the 5/6 nephrectomized rat, a classic model of progressive CKD, chronic blockade of NO generation potentiated glomerular hypertension and endothelial cell loss associated with an impaired endothelial proliferative activity within glomeruli and peritubular capillaries with consequent augmentation of glomerulosclerosis, interstitial fibrosis, proteinuria and creatinine retention [27,28]. In another study, the animals with more pronounced baseline acetylcholine-induced vasodilation of small intrarenal arteries (partially NO-dependent) exhibited a better renal function and developed less proteinuria after 5/6 subtotal nephrectomy [42]. Finally, in the same remnant kidney model, overexpression of dimethyl-l-arginine dimethylaminohydrolase, an enzyme metabolizing ADMA and colocalizing with NO synthases in the kidney [43], abolished the progressive loss of glomerular capillaries, glomerulosclerosis [44] and tubulointerstitial fibrosis [45], which preserved eGFR and prevented proteinuria independently of the blood pressure-lowering effect [44,45].

Keeping in mind the ability of ADMA to antagonize angiogenesis and arteriogenesis [46] and to inhibit EPC proliferation and differentiation [19], the interference of ADMA with the intrarenal L-arginine–NO pathway might produce the disequilibrium between endothelial damage and regeneration in addition to direct ADMA effects on glomerular haemodynamics [47], thus mechanistically linking ADMA to renal function loss [16,17].

Admittedly, the presence of a correlation does not imply a cause-and-effect relationship. Accordingly, accelerated renal function decline, elevated ADMA and CD34+/KDR+ cell deficiency might have resulted from a common cause, e.g. generalized atherosclerosis (including also the renal vasculature), renal insufficiency, endothelial dysfunction or heart failure [10–12,15,21,24,36]. Non-invasive indices of preclinical atherosclerosis, previously shown to be associated with higher ADMA levels [12,15] and lower CD34+/KDR+ cell counts [25,26], were recently identified as predictors of rapid renal function loss [36].

However, although in the present study angiographic CAD extent correlated to baseline eGFR and SDMA, as previously reported by Bode-Böger et al. [48], nevertheless, it was unrelated to $\Delta$eGFR. Moreover, $\Delta$eGFR did not correlate to baseline eGFR or plasma SDMA that, in addition to being a good marker of renal dysfunction [49], had previously been reported to directly impair endothelial NO formation [48] and stimulate reactive oxygen species generation in endothelial cells [48] and monocytes [50]. Additionally, the relationship with $\Delta$eGFR was absent of another biochemical marker of endothelial dysfunction, sVCAM-1, which had largely explained the adverse effect of mild-to-moderate renal insufficiency on cardiovascular mortality risk in a sample of the Hoorn Study patients [2]. This may suggest rather a causal connection between
Synergistic effects of asymmetrical dimethylarginine accumulation and endothelial progenitor cell deficiency on renal function decline

ΔeGFR, elevated ADMA and CD34+/KDR+ cell deficiency in the present study. Finally, none of our patients exhibited heart failure, the strongest determinant of eGFR decline in the Cardiovascular Health Study [36], and subjects with cardiovascular events during the follow-up had been a priori excluded from the analysis.

Prognostic implications of the association of lower ΔeGFR with elevated ADMA and depressed CD34+/KDR+ cell counts

That we focused on a relatively uniform group of treated non-diabetic CAD men indicates that the proposed hypothetical mechanisms might take place in the clinical reality. Worsening of eGFR over time independently predicted cardiovascular and all-cause mortality risk in the Cardiovascular Health Study patients irrespective of baseline eGFR or prevalent CAD [51]. Therefore, it can be speculated that accelerated eGFR decline may have contributed to excessive cardiovascular mortality risk previously demonstrated for elevated ADMA [13] and CD34+/KDR+ cell deficiency [22] in CAD, because those large studies [13,22] did not adjust for changes in eGFR during the follow-up. Deteriorating renal function may potentiate cardiovascular risk exacerbating not only hypertension, but also dyslipidaemia and inflammatory activation [52], and presumably the retention of putative pro-atherogenic compounds, such as ADMA.

Finally, nephroprotective effects of ACEI [53] and statins [54,55] in CAD may partially be due to their ability to lower ADMA levels [56] and/or to enhance EPC mobilization [34,57]. The optimal medical therapy, adequate blood pressure control and complex revascularization might have accounted for a weak tendency to rises in eGFR in our study, instead of the expected age-related decline. On the other hand, our findings are compatible with improvements in average eGFR during a 5-year follow-up in the Treating to New Targets study revascularized stable CAD patients on atorvastatin at on-treatment LDL cholesterol levels comparable to those measured in our subjects [55].

In summary, elevated ADMA and EPC deficiency may synergistically contribute to accelerated renal function decline in stable angina. This could result from the impairment of the EPC-dependent endothelial renewal in an kidney, a NO-dependent process.

Limitations of the study

A major drawback of the present study concerns the therapeutic interventions in the study group. However, all patients were receiving medications known to affect ΔeGFR, EPC mobilization and/or ADMA levels—ACEI [53,56,57] and statins [34,54,55]—for ≥3 months prior to the time of enrolment and the therapeutic regimen was maintained after discharge from our centre. Secondly, a complex elective percutaneous coronary revascularization was performed at the beginning of the follow-up; nevertheless, those with evidence of contrast nephropathy were excluded. Thirdly, a history of hypertension was present in ~3/4 of the patients studied; nevertheless, neither baseline blood pressure nor the use of additional antihypertensive drugs exhibited any relationship with ΔeGFR.

Another methodological shortcoming is the lack of confirmation of our flow cytometry results by in vitro EPC culture assays. However, CD34+/KDR+ cell depletion was associated with adverse prognosis [22,23] and endothelial dysfunction [24] in CAD. Additionally, CD34+/KDR+ cell numbers correlated inversely to preclinical atherosclerosis [25,26], whereas the other five subpopulations of EPC-related cells identified by flow cytometry showed no association with carotid intima–media thickness [25].

Finally, we computed creatinine-based eGFR, whose accuracy has been challenged especially in subjects with normal or near-normal renal function [32]. Nevertheless, these errors were less likely to bias ΔeGFR than eGFR. Additionally, comparable results had been obtained for eGFR calculated from serum creatinine and cystatin C for prognostic effects of ΔeGFR [51] and its correlates [36] in the Cardiovascular Health Study.

Acknowledgements. This work was supported by research grants No. 2P05A01227 and N N402 300136 from the Polish State Committee for Scientific Research. An abstract based on a part of our data has been accepted as poster presentation during the European Society of Cardiology Annual Congress, Barcelona, 2009.

Conflict of interest statement. None declared.

References

29. Rookmaaker MB, Smits AM, Tolboom H et al.

30. Ikarashi K, Li B, Suwa M et al.


Influence of tonsillectomy on the progression of mesangioproliferative glomerulonephritis

Antonio Piccoli, Marta Codognotto, Maria-Grazia Tabbi, Enrico Favaro and Barbara Rossi

Department of Medical and Surgical Sciences, Nephrology Clinic, University of Padova, Padova, Italy

Correspondence and offprint requests to: Antonio Piccoli; E-mail: apiccoli@unipd.it

Abstract

Background. Little information is available about the efficacy of tonsillectomy on long-term renal survival of patients with primary IgA nephropathy (IgAN).

Methods. In this retrospective cohort study, we considered 61 patients with IgAN who had tonsillectomy (n = 15) or not (n = 46) and compared them with 121 control patients with mesangioproliferative glomerulonephritis (MesGN) free of IgA deposits, who had tonsillectomy (n = 49) or not (n = 72). We evaluated the progression from a normal function [estimated glomerular filtration rate 60–220 mL/min/1.73 m², chronic kidney disease (CKD) stage 1 and 2] to a moderate renal dysfunction in CKD stage 3, which was considered the outcome.

Results. The mean duration of follow-up was 250 months (12–300 months) in the whole group of 182 patients. The survival to progression to stage 3 was 88% after 10 years, 71% after 20 years and 53% after 25 years. It was 72% after 20 years in both groups. Tonsillectomy was not significantly associated with CKD progression. Significant prognostic factors were age (P = 0.01), initial CKD stage (P = 0.03), proteinuria (P = 0.03), persistent proteinuria (P < 0.001) and diastolic blood pressure (P = 0.01). In the multivariate analysis (Cox model), there was no significant effect of tonsillectomy adjusted for the type of glomerulonephritis, initial CKD stage, persistent proteinuria, diastolic blood pressure and age. Only persistent proteinuria adjusted for the other factors was significantly associated with CKD progression (hazard ratio of 6.2, 95% confidence interval 3.1–12.7, P < 0.001).

Conclusions. Tonsillectomy was not associated with a different progression rate of IgAN nor of MesGN after 20 years of follow-up.

Keywords: Chronic kidney disease; Glomerular filtration rate; IgA nephropathy; Mesangioproliferative glomerulonephritis; Proteinuria; Tonsillectomy

Introduction

Primary IgA nephropathy (IgAN) is the most common glomerular disease worldwide, yet there is no international consensus for its pathological or clinical classification. Recently, a new classification for IgA nephropathy tried to identify specific pathological features that would predict the risk of progression of the nephropathy independent of clinical features [1]. The derivation set was based on retrospective clinical data and renal biopsy material from 265 patients (206 adults and 59 children) collected from eight countries. The estimated glomerular filtration rate (eGFR) values were evenly distributed within stages 1, 2 and 3 of the Kidney Disease Outcomes Quality (KDOQI) classification of chronic kidney disease (CKD). Only 16 patients (6%) had previous tonsillectomy. Prospective long-term studies are needed to validate the new classification.