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This is the accepted version of a paper published in *Diabetes Research and Clinical Practice*. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the original published paper (version of record):

Carlsson, A., Calamia, M., Risérus, U., Larsson, A., Helmersson-Karlqvist, J. et al. (2014)
Kidney injury molecule (KIM)-1 is associated with insulin resistance: Results from two
community-based studies of elderly individuals.
Diabetes Research and Clinical Practice, 103(3): 516-521
<http://dx.doi.org/10.1016/j.diabres.2013.12.008>

Access to the published version may require subscription.

N.B. When citing this work, cite the original published paper.

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Kidney Injury Molecule (KIM)-1 is associated with insulin resistance: results from two community-based studies of elderly individuals

*Axel C Carlsson^{1,2}, *Michael Calamia³, Ulf Risérus⁴, Anders Larsson⁵, Johanna Helmersson-Karlqvist⁵, Lars Lind⁵, and **Johan Ärnlöv^{2,6}

¹Centre for Family Medicine, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, Sweden

²Department of Public Health and Caring Sciences/ Section of Geriatrics Uppsala University, Uppsala Sweden

³Landstinget Dalarna, Falun, Sweden

⁴Department of Public Health and Caring Sciences/ Section of Clinical Nutrition and Metabolism, Uppsala University, Uppsala Sweden

⁵Department of Medical Sciences, Uppsala University Hospital, Uppsala, Sweden

⁶School of Health and Social Studies, Dalarna University, Falun, Sweden

*Contributed equally

**Corresponding author: Johan Ärnlöv, Department of Public Health and Caring Sciences/Geriatrics, Uppsala Science Park, SE-75185 Uppsala, Sweden

Fax: +46-18-6117976; phone: +46-70-6077703

E-mail: johan.arnlov@pubcare.uu.se

Words in summary: 209

Number of words in main text: 1852 (excluding tables and references)

Tables: 2

References: 25

Summary

Background and Objectives Insulin resistance has been shown to be closely associated with glomerular filtration rate and urinary albumin/creatinine ratio, even prior to the development of diabetes. Urinary kidney injury molecule 1 (KIM-1) is a novel, highly specific marker of kidney tubular damage. The role of insulin resistance in the development of kidney tubular damage is not previously reported. Thus, we aimed to investigate the associations between insulin sensitivity (assessed by HOMA) and urinary KIM-1.

Design, setting, participants and measurements Two community-based cohorts of elderly individuals were investigated: Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS, n=701; mean age 75 years, 52 % women); and Uppsala Longitudinal Study of Adult Men (ULSAM, n=533; mean age 78 years).

Results Lower insulin sensitivity was associated with higher urinary KIM-1 in both cohorts after adjustments for age, BMI, blood pressure, antihypertensive treatment, glomerular filtration rate, and urinary albumin-creatinine ratio (PIVUS: regression coefficient for 1-SD higher HOMA-IR 0.11, 95% CI 0.03-0.20, p=0.009, and ULSAM: 0.11, 95% CI 0.02-0.19, p=0.02). Results were similar in individuals without diabetes, with normal kidney function and normo-albuminuria.

Conclusions Our findings in elderly individuals support the notion that the interplay between an impaired glucose metabolism and renal tubular damage is evident even prior to the development of diabetes and overt kidney disease.

Key words: diabetes; blood glucose; microalbuminuria; glomerular filtration; kidney injury

Introduction

A long duration of elevated blood glucose levels (i.e. poorly controlled diabetes) is considered the major underlying mechanism causing diabetic nephropathy and chronic kidney disease [12]. Interestingly, the interplay between a disturbed glucose metabolism and kidney damage appears to be bi-directional; individuals with micro-albuminuria are at an increased risk of developing diabetes [3, 13]. Other aspects of glucometabolic derangements than diabetes have also been suggested to be of importance for the development of kidney damage. In particular, insulin resistance has been shown to be closely associated with the two major indices of kidney damage and dysfunction used in clinical practice, glomerular filtration rate (GFR) and urinary albumin/creatinine ratio (ACR), even prior to the development of diabetes [13, 15].

Both GFR and ACR have limitations as biomarkers as they both mainly reflect an underlying disease process that already is well established [4]. In order to better identify individuals with an increased risk for chronic kidney disease, there is need for biomarkers that may detect early signs of kidney damage. Urinary kidney injury molecule 1 (KIM-1) is a novel and promising marker of renal tubular damage [22]. KIM-1 levels rise quickly in various forms of acute kidney injury but recent studies also show that it also is a relevant marker for chronic kidney damage that precedes the deterioration of kidney function [16]. A recent study reported elevated KIM-1 levels in diabetes patients with normo-albuminuria [14], indicating that renal tubular damage may be involved in early stages of the development of diabetic nephropathy. Yet, the association between insulin sensitivity and kidney tubular damage has not been reported previously.

In the present study we hypothesized that there is an interplay between impaired insulin sensitivity and kidney tubular damage even prior to the development of diabetes or overt kidney disease. Consequently, we aimed at investigating associations between insulin

sensitivity assessed by Homeostasis Model Assessment (HOMA) [24], and urinary KIM-1 in two independent community-based cohorts of elderly individuals with pre-specified subgroup analyses in non-diabetics without kidney disease.

Methods

Study samples

The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)

All 70-year old men and women living in Uppsala, Sweden, between 2001-2004 were eligible for the PIVUS study (described in detail on <http://www.medsci.uu.se/pivus/pivus.htm>) [11].

Of 2025 invited individuals, 1016 agreed to participate. In the present study the second examination cycle of PIVUS was used (2006-2009) when participants were 75 years old. Of 964 invited participants, 827 participated (86%). Of these, 53 participants were excluded due to missing data on urinary KIM-1 or co-variates. We also excluded 73 participants on anti-diabetic medication as this treatment may influence the HOMA-estimate, leaving 701 as the present study sample.

The Uppsala Longitudinal Study of Adult Men (ULSAM)

The ULSAM study was initiated in 1970. All 50-year-old men, born in 1920-24 and living in Uppsala, Sweden, were invited to a health survey, focusing at identifying cardiovascular risk factors (described in detail on <http://www.pubcare.uu.se/ULSAM>) [8]. These analyses are based on the fourth examination cycle, when participants were approximately 77 years old (1998-2001). Of 1398 invited men, 838 (60%) participated. Of these, 256 were excluded due to missing data on urinary KIM-1 or covariates. We additionally excluded 49 participants on anti-diabetic medication, leaving 533 participants as the present study sample.

All participants in both studies gave written informed consent and the Ethics Committee of Uppsala University approved the study protocols. The study was conducted according to the Declaration of Helsinki.

Baseline investigations

The investigations in PIVUS and ULSAM were performed using similar standardized methods, including anthropometrical measurements, blood pressure, blood sampling, and questionnaires regarding socioeconomic status, medical history, smoking habits, medication and physical activity level [8, 11]. Venous blood samples were drawn in the morning after an overnight fast and stored at -70°C until analysis. In the PIVUS cohort a spot sample of morning urine was used for analyses. In ULSAM a 24-hour collection of urine was used. Urinary KIM-1 levels (the concentration of the cleaved extracellular KIM-1 domain) were analyzed with the commercial sandwich ELISA kit, (DY1750 R&D Systems, Minneapolis, MN, USA). The assay was run in singlicate. The total CVs of the assay was approximately 7% at the local laboratory. Urinary KIM-1 was, additionally, adjusted for urinary creatinine (Abbott, Abbot Park, IL, USA). Cystatin C-based GFR was estimated as previously described.[10] Urine albumin was measured by nephelometry (Urine albumin, Dade Behring, Deerfield IL, USA) using a Behring BN ProSpec® analyzer (Dade Behring), and creatinine related urine albumin (ACR) was calculated. Markers of inflammation and oxidative stress were analyzed as previously described [1, 2].

HOMA-IR was calculated as per the formula (fasting plasma insulin (mU/L) x fasting plasma glucose (mmol/L))/22.5 [24]. Diabetes mellitus was defined as fasting plasma glucose ≥ 7.0 mmol/l (≥ 126 mg/dl) [25].

Statistical analysis

Linear regression analyses were used to assess cross-sectional associations with urinary KIM-1 levels as dependent variable (logarithmically transformed to promote a normal distribution) and HOMA-IR levels as the independent variable. The following multivariable models were used:

A-age and gender (PIVUS).

B-anthropometric (age, gender (PIVUS), and BMI), was controlled for to rule out that the association between obesity and insulin resistance mediates the association between tubular damage and insulin resistance.

C-hypertension (age, gender, systolic blood pressure, and antihypertensive treatment), was controlled for to rule out the possibility that damages due to elevated blood pressure or history of hypertension mediates the association between tubular damage and insulin resistance.

D-renal model (age, gender, GFR, and ACR), to ascertain that the association between tubular damage and insulin resistance is independent of the clinically used markers of kidney damage.

E-combined (all covariates in models A-D).

In the ULSAM-cohort, we also performed an additional model where different markers of inflammation and oxidative stress (plasma c-reactive protein (CRP), plasma interleukin (IL)-6, plasma serum amyloid A (SAA), urinary 15-keto-dihydro-PGF_{2α} (reflecting COX-mediated inflammation) and F₂-isoprostanes (reflecting oxidative stress) were added to multivariable model E to control for the possibility that novel markers of inflammation or oxidative stress that are thought to be associated with nephropathy mediates the association between tubular damage and insulin resistance.

We also performed the above analyses in a pre-specified subgroup with participants without diabetes, with normal GFR (>60 ml/min/1.73m²) and normal ACR (<3 mg/mmol). Possible multiplicative interactions with gender were also explored in PIVUS. The statistical software package STATA 11.2 (Stata corp, college Station, TX) was used.

RESULTS

Baseline characteristics

Baseline characteristics are presented in Table 1.

Linear regression models

Higher HOMA, reflecting lower insulin sensitivity, was significantly associated with higher urinary KIM-1 in all multivariable models (Models A-E, Table 2).

Higher HOMA was also significant in ULSAM in a model adjusted for different markers of inflammation and oxidative stress, 0.095 (95% CI 0.0068-0.18), $p=0.035$ (data not shown).

Subgroup, multiplicative interactions and additional analyses

The association was similar (albeit of borderline-significance in ULSAM) in sub-group analyses in individuals without diabetes, with normal GFR and ACR (PIVUS: $n=377$, Model E, multivariable regression coefficient for 1 SD increase in HOMA 0.15, (95% CI 0.03-0.28, $p=0.01$), and; ULSAM, $n=349$, 0.15 (95 % CI -0.01-0.31, $p=0.06$). There was no effect modification by gender in PIVUS (p for interaction 0.18).

Discussion

In two community-based samples of elderly, insulin sensitivity was inversely and independently associated with urinary KIM-1 concentrations. These associations were still significant after adjustments for age, gender, anthropometry, and blood pressure levels. Importantly, results were similar in subgroup analyses in participants without diabetes, with no other signs of kidney damage or dysfunction even after adjustment for GFR and ACR. Thus, our findings support the notion that the interplay between insulin resistance and renal tubular damage is evident even prior to the development of diabetes and overt kidney disease

Comparisons with previous studies

Studies have shown that individuals with impaired insulin sensitivity have a faster regression of GFR than individuals with normal insulin sensitivity [15], and ACR has been shown to be higher in insulin resistant individuals [13]. Early renal tubular damage biomarker levels (including urinary KIM-1 levels) are elevated in patients with diabetes, even in those with normoalbuminuria [4, 18]. Interestingly, regression of diabetic nephropathy has been shown to be associated with reduced levels of urinary KIM-1 as well [23]. However, no previous study has reported the association between impaired insulin sensitivity and KIM-1.

Possible mechanisms for observed associations

Impaired insulin sensitivity and compensatory hyperinsulinemia have been suggested to contribute to development of renal injury by promotion of mitogenic and fibrotic processes via different pathophysiologic pathways such as activation of insulin-like growth factor-1, transforming growth factor- β , endothelin-1, and the renin-angiotensin-aldosterone system [19]. Moreover, insulin resistance is closely associated with oxidative stress [17], pro-inflammatory cytokines and adipokines [9], which also could promote renal injury. But the opposite chain of events is also possible; an increased inflammatory activity due to ongoing

kidney damage could also impair insulin sensitivity [6]. In the present study the associations between insulin sensitivity and urinary KIM-1 was essentially unaltered after adjustment for various markers of inflammatory and oxidative stress but we cannot rule out that there may be substantial residual confounding given the complexity of these processes.

Insulin resistance is associated with several cardiovascular risk factors (e.g. hypertension) that have been associated with micro-albuminuria [13], and reduced GFR [7]. The fact that insulin sensitivity remained significantly associated with KIM-1 in all multivariable models suggests that confounding by these factors does not explain our findings. Interestingly, the association appeared similar after adjustment for ACR and GFR, even in individuals with ACR and GFR in the normal range. Thus, the previously proposed relationship between insulin resistance, micro-albuminuria [13] and low GFR [15] are unlikely mediators of the present association. Another explanation for the present findings could be that renal insufficiency suppresses renal clearance of insulin, resulting in higher circulating levels of insulin and consequently a higher HOMA. We were unable to evaluate the potential influence of reduced renal clearance of insulin, but the similar results observed in individuals with normal renal function indicate that a reduced renal clearance is not a likely explanation.

Clinical implications

The prevalence of insulin resistance is ~30% in the US, and its presence increases the risk of kidney failure [20]. Tubulointerstitial injury is present in all forms of chronic kidney disease and is thought to be a better predictor of disease progression and long-term prognosis than is the severity of damage to glomeruli [7, 16]. By measuring KIM-1, this “tubular phase” of renal damage could be detected before the development of albuminuria, the currently used marker of early diabetic nephropathy [18]. However, the clinical relevance of such an

approach remains to be evaluated. Previous studies showed antihypertensive treatment with RAS-inhibition or diuretics lowers urinary levels of KIM-1 [5, 21]. However, whether this effect on KIM-1 levels corresponds to a decreased risk for diabetic nephropathy is unknown.

Strengths and limitations

Strengths of our investigation include the validation of our findings in an independent cohort and the detailed characterization of study participants. To our knowledge the PIVUS and ULSAM cohorts are the largest community-based samples with data on urinary KIM-1.

Limitations include the unknown generalizability to other age-, and ethnic groups.

Furthermore, no conclusions regarding causality should be drawn from our cross-sectional observational data. Moreover, in our study, the cross-sectional regression and correlation estimates indicate that the magnitude of the association between insulin resistance and urinary KIM-1 may be modest, even though it was statistically significant in all models in both cohorts. It is possible that the strength of the associations may have been diluted by the use of HOMA rather than the gold standard method of estimating insulin sensitivity. Still, we would like to emphasize that no firm conclusions regarding effect size should be drawn from our cross-sectional observational data. Additional intervention trials are needed to properly investigate these issues.

In summary, data from two independent community-based studies of elderly, consistently demonstrates an independent association between decreased insulin sensitivity and renal tubular damage as assessed by urinary KIM-1. The clinical value of urinary KIM-1 as a marker of cardiorenal and metabolic risk needs to be evaluated further in prospective studies.

Acknowledgements

This study was supported by The Swedish Research Council (2006-6555), Swedish Heart-Lung foundation, Thuréus foundation, the Marianne and Marcus Wallenberg Foundation, Dalarna University and Uppsala University. The funding sources did not play any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Dr. Ärnlov is the guarantor of this work, had full access to all the data, and takes full responsibility for the integrity of data and the accuracy of data analysis.

Author contributions

Author contributions: J.Ä. researched data, edited manuscript, contributed to discussion, provided funding. A.C.C. and M.C. wrote manuscript, researched data, contributed to discussion. L.L. reviewed manuscript, contributed to discussion. A.L. reviewed manuscript, contributed to discussion. J.H-K. reviewed manuscript, contributed to discussion.

The authors of this manuscript have no conflict of interest to disclose.

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Table 1 Baseline characteristics of PIVUS and ULSAM

| Variable | PIVUS | ULSAM |
|---|-------------|-------------|
| Number of subjects | 701 | 533 |
| Female no. (%) | 362 (52%) | 0 |
| Age (years) | 75.3 ± 0.2 | 77.7 ± 0.8 |
| HOMA | 1.67 ± 1.41 | 1.7 ± 2.6 |
| Urinary KIM-1/creatinine (ng/mmol) | 101 ± 73 | 96 ± 87 |
| Glomerular filtration rate (ml/min/1.73m ²) | 68 ± 19 | 74 ± 17 |
| Body mass index (kg/m ²) | 26 ± 4 | 26 ± 3 |
| Systolic blood pressure (mmHg) | 148 ± 19 | 150 ± 21 |
| Serum interleukin-6 (ng/L) | na | 3.8 ± 2.6 |
| Serum amyloid A protein (mg/L) | na | 10.9 ± 40.5 |
| high sensitivity C-reactive protein (mg/L) | na | 3.92 ± 7.1 |
| Urine F ₂ -isoprostane (nmol/mmol) | na | 0.20 ± 0.09 |
| Urine 15-keto-dihydro-PGF ₂ α (nmol/mmol) | na | 0.32 ± 0.18 |
| Antihypertensive treatment – no (%) | 317 (45%) | 245 (46%) |
| Diabetes no (%) | 32 (5) | 31 (6) |

Data are mean ± standard deviation for continuous variables and n (%) for categorical variables

Table 2 The Association of Insulin Sensitivity (HOMA) and kidney tubular damage (urinary KIM-1/creatinine) in ULSAM and PIVUS: Multivariable linear regression

| Study | Model | B coefficient (95% CI) | p |
|---------------------|--------------|-----------------------------------|----------|
| <u>PIVUS</u> | A | 0.11 (0.03-0.18) | 0.005 |
| | B | 0.11 (0.02-0.19) | 0.01 |
| | C | 0.11 (0.04-0.19) | 0.003 |
| | D | 0.10 (0.21-0.17) | 0.009 |
| | E | 0.11 (0.31-0.20) | 0.009 |
| <u>ULSAM</u> | A | 0.11 (0.02-0.19) | 0.01 |
| | B | 0.11 (0.02-0.20) | 0.02 |
| | C | 0.10 (0.02-0.19) | 0.02 |
| | D | 0.09 (0.01-0.17) | 0.03 |
| | E | 0.11 (0.02-0.19) | 0.02 |

Data are regression coefficients of for 1-standard deviation higher HOMA as explanatory variable of 1-standard deviation higher urinary KIM-1/creatinine. Model A is adjusted for age and sex, model B is adjusted for age, sex is and BMI, Model C adjusted for age, sex, systolic blood pressure (hypertension, blood pressure medication), model D is adjusted for age, sex and impaired renal function (GFR and ACR), model E is adjusted for all covariates in models A-D.