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Serum uromodulin is associated with but does not predict type 2 diabetes in elderly KORA F4/FF4 study participants

Cornelia Then[1,2], Holger Then[3], Christa Meisinger[4,5], Margit Heier[6], Annette Peters[6,7], Wolfgang Koenig[8,9,10], Wolfgang Rathmann[11], Jürgen Scherberich[12], Jochen Seissler[1,2]

[1] *Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, LMU München, Germany;*

[2] *Clinical Cooperation Group Diabetes, Ludwig-Maximilians-Universität München and Helmholtz Zentrum München, Munich, Germany;*

[3] *Freie Waldorfschule Augsburg, Germany;*

[4] *Independent Research Group Clinical Epidemiology, Helmholtz Zentrum München – German Research Center for Environmental Health (GmbH), Neuherberg, Germany;*

[5] *Chair of Epidemiology at UNIKAT Augsburg, Ludwig-Maximilians-Universität München, Munich, Germany;*

[6] *Institute of Epidemiology, Helmholtz Zentrum München – German Research Center for Environmental Health (GmbH), Neuherberg, Germany;*

[7] *Research Unit of Molecular Epidemiology, German Research Center for Environmental Health, Neuherberg, Germany;*

[8] *Institute of Epidemiology and Biostatistics, University of Ulm, Ulm, Germany;*

[9] *Deutsches Herzzentrum München, Technische Universität München, Munich, Germany;*

[10] *DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany;*

[11] *German Diabetes Center, Leibniz Institute at Heinrich Heine University Düsseldorf, Institute of Biometrics and Epidemiology, Düsseldorf, Germany;*

[12] *Klinikum München-Harlaching, Teaching Hospital of the Ludwig-Maximilians-Universität, Munich, Germany.*

ORCiD numbers:

0000-0001-5180-1973

Then

Cornelia

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Aims Serum uromodulin has recently emerged as promising biomarker for kidney function and was suggested to be associated with type 2 diabetes (T2D) in coronary patients. Here, we analyzed the association of serum uromodulin with T2D in the population-based KORA F4/FF4 study.

Methods In 1119 participants of the KORA F4 study aged 62 - 81 years, serum uromodulin was measured and the association of serum uromodulin with T2D was assessed using logistic and linear regression models stratified for sex. After a mean follow-up time of 6.5 years, 635 participants where reevaluated. Glucose tolerance status was determined by oral glucose tolerance test at baseline and at the follow-up examination except in cases of known T2D.

Results Serum uromodulin was inversely associated with T2D in the crude analysis and after adjustment for age and BMI in men ($p < 0.001$) and in women ($p < 0.05$). After further adjustment for estimated glomerular filtration rate, serum uromodulin was significantly inversely associated with T2D in men ($p < 0.001$), but not in women. Serum uromodulin was

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not associated with prediabetes after multivariate adjustment and did not predict T2D in men or in women after the follow-up time of 6.5 ± 0.3 years.
Conclusions In participants of the KORA F4 study, serum uromodulin is independently associated with T2D in men, but is no predictor of future development of T2D.

In the population-based KORA F4 study, serum uromodulin was measured using an enzyme-linked immunosorbent assay kit and found to be inversely associated with T2D, but did not predict T2D.

Introduction

Type 2 diabetes mellitus (T2D) entails a roughly doubled cardiovascular risk (1), but the link between metabolic and vascular disturbances is still incompletely understood and very little is known about potentially protective factors, one of which might be the glycosylphosphatidylinositol-anchored protein uromodulin. Uromodulin is synthesized in tubular cells of the ascending limb of Henle´s loop and released into the urine by proteolytic cleavage in an amount of 75 - 200 mg/24 hours (2–4). In the urinary tract, the highly abundant uromodulin exerts anti-lithogen, anti-infective and immunomodulatory functions (5–12). The relevance of uromodulin for kidney integrity becomes obvious in case of mutations of the uromodulin-coding gene leading to severe kidney damage, such as cystic kidney disease, recurrent urinary tract infections, familial juvenile hyperemic nephropathy and congenital nephrolithiasis (4,7,9,13–15). Beside these severe uromodulin defects, even small changes in uromodulin concentration and/or function, caused for instance by uromodulin loci variants, may provoke and/or accelerate kidney disease (16–22). Vice versa, kidney disease with loss of uromodulin-producing cells due to other reasons entails decreased uromodulin secretion and might thus aggravate the decline of kidney function (23,24).

Other circumstances may also influence uromodulin secretion. A decreased urinary uromodulin was described in diabetic patients (25,26). In diabetes, urinary uromodulin may additionally feature an altered glycation pattern, possibly influencing its functionality (27). Recently, a decreased serum uromodulin (sUmod) was described in diabetic patients with coronary heart disease (28). These observations suggest a link between diabetes and uromodulin. However, the causal nature of the relation of circulatory uromodulin and diabetes remains to be clarified.

The presence of uromodulin in serum has long been recognized (29), but has gained little interest up to recently. Uromodulin concentration in serum is about 1000fold lower than in the urine (30). Nevertheless, sUmod does not seem to be a “byproduct” only. Uromodulin is actively secreted by endocytotic vesicles from the basolateral side of tubular cells into the interstitial space and circulation (30–32). The physiological functions and significance of uromodulin in the circulation remain largely unknown. Since T2D is often associated with kidney disease, we here aimed to assess the association of sUmod with T2D and its predictive value for T2D in the population-based KORA F4/FF4 cohort.

Methods

Study participants

The KORA (Cooperative Health Research in the Region of Augsburg) S4/F4/FF4 cohort study originally involved 4,261 participants from the general community in the health survey S4 (1999–2001). Follow-up examinations took place 2006–2008 (KORA F4 with 3,080 participants) and 2013–2014 (KORA FF4 with 2,279 participants). The loss of participants from S4 to FF4 was due to participants’ death (455), relocation (296), refusal (570), illness or lack of time (504) and no contact possible (157). Recruitment and eligibility criteria for the KORA studies have been described previously (33). The study design, standardized sampling methods and data collection (medical history, medication, anthropometric measurements,

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blood pressure) have been described in detail elsewhere (34,35). All study participants gave written informed consent. The study was approved by the Ethics Committees of the Bavarian Medical Association and the Bayerische Landesärztekammer in adherence to the declaration of Helsinki and Istanbul. In 1119 randomly selected participants aged 62 - 81 years in the KORA F4 cohort, sUmod was measured. Criteria for a pre-known diagnosis of diabetes mellitus were a validated medical diagnosis or current use of glucose-lowering agents. After an overnight fasting period, all non-diabetic participants underwent a standard 75 g oral glucose tolerance test. Newly diagnosed diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and normal glucose tolerance (NGT) were defined according to the 1999 World Health Organization diagnostic criteria based on both fasting and post-challenge glucose values (T2D: ≥ 7.0 mmol/l fasting and/or ≥ 11.1 mmol/l 2-h glucose; IFG: ≥ 6,1 mmol/l and < 7,0 mmol/l; IGT: ≥ 7.8 - < 11.1 mmol/l 2-h glucose). Prediabetes was defined as IFG and/or IGT (2-h glucose ≥ 7.8 - < 11.1 mmol/l). Arterial hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or known hypertension with use of anti-hypertensive drugs. Of the 1119 participants with sUmod measurements in KORA F4, 130 died and 354 could not be contacted or declined participation in the FF4 survey. Thus, the study sample in the FF4 examination comprised 635 participants. The follow-up time amounted to 6.5 ± 0.3 years.

Laboratory measurements

Blood was collected after an overnight fast of at least eight hours without stasis, and the samples were kept at 4°C until centrifugation. Serum samples were stored at -80°C until assayed. Except for 2-h glucose, all blood parameters were determined in fasting blood samples. Measurements of serum creatinine and cystatin C were performed as described elsewhere (36). Glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2009) based on serum creatinine (eGFRcr), cystatin C (eGFRcc) or both parameters (eGFRcrcc), respectively. SUmod was determined using the commercially available uromodulin enzyme-linked immunosorbent assay kit (Euroimmun AG, Lübeck, Germany) with a lower detection limit of 2 ng/ml, an intraassay precision of 1.8 - 3.2 % and an interassay precision of 6.6 %. The measurement procedure was performed as described previously (32).

Statistical Analyses

Characteristics of the study participants were compared between men and women using t-tests in case of normally distributed variables. For skewedly distributed variables, Mann-Whitney U-tests were performed. Chi-square tests were used to compare binomial proportions. The associations of sUmod with the outcomes of interest were assessed in logistic regression models in case of categorical dependent variables and in linear regression models in case of continuous dependent variables, respectively. SUmod was deployed as independent variable. In multinomial logistic and linear regression analyses, the association of sUmod with the respective dependent variables was adjusted for confounders as indicated for each observation. The models were fitted for the whole study group and for women and men. Participants with missing covariables were excluded from the respective analyses. The number of participants finally included in the respective fully adjusted model is given for each analysis. The level of statistical significance was set at 5 %. All calculations were performed using the statistical environment R, version 3.4.4.

Results

Study population characteristics

Baseline characteristics of the study population stratified for sex are shown in table 1. Men had an adverse metabolic and cardiovascular risk profile compared to women, including

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significantly higher waist circumference, systolic and diastolic blood pressure, triglycerides, lower HDL cholesterol and a higher proportion of subjects with T2D. However, women in the current study group had a higher BMI, LDL cholesterol and hsCRP. Women displayed significantly higher sUmod levels than men.

Association of sUmod with sex, age, height, weight and BMI

The association of sUmod with sex was highly significant ($p < 0.001$) and largely independent of possible confounders (table 2). SUmod declined with advancing age. This inverse association was attenuated after correction for eGFR, but remained significant ($p < 0.001$; table 2). Adjustments for other possible confounders did not further substantially weaken the association of age and decreased sUmod. SUmod was not associated with height after correction for age in men or women (data not shown), whereas weight was inversely related to sUmod in both sexes in the crude analysis and after adjustment for age (men: -0.17 ± 0.04; women: -0.26 ± 0.05, $p < 0.001$ for both observations). Further, sUmod correlated inversely with BMI in the total study cohort, in men and in women without and with adjustment for age (total cohort: -0.23 ± 0.03; men: -0.18 ± 0.04; women: -0.26 ± 0.05; $p < 0.001$ for each observation).

Association of sUmod with prediabetes, diabetes mellitus and parameters of glucose regulation

Study participants with prediabetes or T2D displayed lower sUmod levels compared to subjects with normal glucose tolerance (figure 1). SUmod was inversely associated with prediabetes in the total study cohort and in men, but not in women (table 3). After adjustment for age, sex and BMI, the associations of sUmod with prediabetes were no longer significant. SUmod correlated inversely with T2D in the total cohort, in men and in women without adjustment and after adjustment for (sex,) age and BMI (table 3). However, in women, further adjustment for eGFR attenuated the association to non-significance.

After adjustment for age, (sex,) BMI and eGFR, sUmod was inversely associated with HbA1c as continuous variable in the total study cohort (coefficient -0.09 ± 0.03; $p = 0.003$) and in men (-0.14 ± 0.05; $p = 0.005$), but not in women (-0.053 ± 0.06; $p = 0.13$). Compatible with the lacking association of sUmod with prediabetes, the relation of sUmod with moderately elevated HbA1c levels in the prediabetic range (39 – 46 mmol/mol (5.7 - 6.4 %)) was not significant in women and no longer significant in the total study cohort and in men after adjustment for age and BMI. HbA1c values in the diabetic range (≥ 48 mmol/mol (6.5%)) were inversely associated with sUmod in the total cohort and in men after adjustment for age, BMI and eGFR. In women, the inverse relation of sUmod and HbA1c values ≥ 48 mmol/mol (6.5%) was no longer significant after adjustment for age and BMI (table 1 in (37); DOI 10.5282/ubm/data.142).

SUmod was associated with a lower fasting glucose and a lower insulin resistance as determined by HOMA-IR. In women, the association with HOMA-IR was attenuated to non-significance after adjustment for age and BMI. After adjustment for age, BMI and eGFR, fasting insulin was weakly, but significantly inversely associated with sUmod in men, but not in women, whereas a relation of proinsulin with sUmod could not be established after correction for age, sex, BMI and eGFR (table 2 in (37); DOI 10.5282/ubm/data.142).

SUmod was inversely related to hsCRP in men after adjustment for age, BMI and eGFR (-0.10 ± 0.04; $p < 0.05$). In women, hsCRP and sUmod correlated without correction for confounders, but not after multivariate adjustment (data not shown). The risk reduction for T2D in study participants with higher sUmod values was largely independent of hsCRP, as correction for hsCRP did not change the level of significance (table 3).

Lacking association of sUmod with T2D in follow-up

SUmod was no predictor for prediabetes or T2D in men or in women after multivariate adjustment in the follow-up examination after 6.5 ± 0.3 years (OR for T2D in men: 1.35, 95%

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CI 0.87 – 2.11; women: OR 0.77, 95% CI 0.51 – 1.17; table 4). Fittingly, HbA1c (men: -0.001 ± 0.046; women: -0.071 ± 0.038), fasting glucose (men: 0.056 ± 0.049; women: -0.031 ± 0.038), fasting insulin (men: -0.119 ± 0.064; women: -0.073 ± 0.044) and HOMA-IR (men: -0.070 ± 0.059; women: -0.052 ± 0.033) where not significantly associated with baseline sUmod in men or in women in the follow-up survey after adjustment for age, BMI, eGFR and the respective baseline parameters.

Discussion

This is the first study showing the association of sUmod with T2D in a population-based cohort. Our results describing a strong link of T2D with sUmod are in line with previous studies that predominantly involved participants with kidney and/or coronary disease (28,38). In contrast to previous data (28), we here also show an association of sUmod with HOMA-IR and fasting insulin. The stratification for sex in our study revealed a highly significant association of sUmod with T2D in men, but not in women. To our knowledge, a different association of uromodulin and T2D depending on sex has not yet been described. Another important finding of our study is that sUmod is not an independent marker of prediabetes either defined by increased fasting glucose, impaired glucose tolerance and/or moderately increased HbA1c levels. In our cohort, prediabetic participants were asymptomatic and mainly detected by a screening test. Thus, the majority of prediabetic individuals may not have developed diabetic nephropathy, which may explain the unchanged uromodulin serum levels.

The current data clearly demonstrate that sUmod is no predictor of future prediabetes or T2D, which is in line with the lacking significant association with prediabetes, but contradicts the results of Leiherer et al. (28) describing lower sUmod values in individuals developing diabetes within a follow-up time of 3.5 years. The discrepant results may arise from differences in the study populations (in the study of Leiherer et al., 55% of the participants suffered from significant coronary heart disease) and from the multivariate adjustments of the longitudinal analyses of our study. Regarding our current data, it can be largely excluded that sUmod plays a causative role in diabetes pathogenesis. The inverse association of sUmod with diabetes may be due to a suppression of uromodulin secretion. Experimental data investigating this possibility are currently lacking. Another possibility for the eGFR-independent relation of sUmod and diabetes is an early diabetes-related kidney affection that is underestimated by GFR calculations. In early kidney injury, sUmod decrease may precede the eGFR decline determined by the endogenous filtration markers creatinine or cystatin C, since a progressive nephron loss may initially be compensated by an increased hydraulic pressure and subsequent glomerular hyperfiltration (31,32). Therefore, in early kidney disease, correction for eGFR may not exclude that the sUmod decline is in fact primarily related to the reduction of nephron number. This presumption may be especially true for diabetic nephropathy, in which hyperfiltration is typical.

In our cohort aged 62 - 81 years, sUmod was lower in older participants. The decline of uromodulin with advancing age is well known (32,39,40) and mostly attributed to a declining kidney function and reduction of nephron number at higher age. In our study, eGFR reduction only partially explained the age-related sUmod decrease. Altogether, the attribution of sUmod values to nephron mass as only determinant remains open to further study considering the lacking association of sUmod with height, the inverse relation to weight and the considerably higher sUmod levels in women compared to men in our study population. Although sex-related data regarding nephron numbers in healthy women and men are lacking, higher sUmod in women is probably not due to a (relatively) higher nephron mass. Rather, hormonal and receptor-related factors may be involved. We assume that higher sUmod values in women may mirror a sex-related nephroprotective role of the molecule,

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since women suffering from chronic kidney disease reach end-stage renal disease 3 - 5 years later than men (41). However, our data suggest that sUmod is also subjected to regulation processes beside kidney mass and function. SUmod joins various other, well-known metabolic parameters featuring more favorable profiles in women than in men. Interestingly, the inverse association of sUmod with prediabetes, T2D, HbA1c, fasting insulin and insulin resistance was stronger in men than in women. The reasons for sex-related differences in the link between sUmod and T2D are unknown. Since women have generally higher sUmod values, the possible suppressive effect of diabetes may be less obvious. Not only uromodulin quantity might be influenced by hormonal parameters, but also uromodulin function. For example, uromodulin isolated from the urine of pregnant women has different immunomodulatory properties compared to uromodulin from men and non-pregnant women, probably due to an altered uromodulin glycosylation state (42). Whether such differences are also detectable in sUmod remains to be clarified.

Overall, the physiological functions of uromodulin in the circulation and thus possible causal interferences of a reduced sUmod in diabetes with outcome are largely unknown. Similar to known uromodulin capacities in the urine, immunomodulatory properties in the blood stream have been proposed (43–46). Uromodulin receptors in the body remain to be determined for the most part, but possibly include Toll-like receptor 4, via which uromodulin may activate myeloid dendritic cells (47). In the current study, sUmod correlated inversely with hsCRP in men, but not significantly in women after multivariate adjustment. Since two studies involving patients admitted for coronary angiography detected an inverse association of sUmod and cardiovascular events and mortality (48,38), it is tempting to speculate that sUmod is one link between diabetes and cardiovascular complications. Another possibility is that very early kidney affection is not adequately assessable to date and plays a more prominent role for cardiovascular complications than previously assumed.

Study strengths and limitations

The major strengths of our study are the population-based design with a large, well-characterized community-based cohort and the follow-up time of 6.5 years. All participants without pre-diagnosed diabetes underwent an oral glucose tolerance test at baseline and in the follow-up examination. However, only participants aged 62 - 81 years were included, so that the relation of sUmod with metabolic disturbances in younger subjects remains to be confirmed.

Conclusions

To our knowledge, this is the first population-based study assessing the association of sUmod with T2D. The current data indicate that sUmod is a valuable biomarker for T2D in elderly individuals, but no predictor for future T2D, suggesting that the presence of T2D causes a decrease of uromodulin serum levels. Preclinical studies are needed to clarify the mechanistic basis of the reduced sUmod levels in T2D. Further clinical studies will determine, whether the reduced sUmod in T2D predicts diabetic nephropathy and cardiovascular complications in diabetic individuals.

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Contribution statement:
Conception and design of the study: CM, MH, AP, WK, WR, J Scherberich and J Seissler; collection of data: CT, CM, MH, AP, WK, WR, J Scherberich and J Seissler; data analysis, interpretation of results, writing of the manuscript: CT, HT, J Seissler and J Scherberich; all authors revised the manuscript critically for important intellectual content and approved the final version. Guarantors: CT, J Seissler

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Corresponding author: Cornelia Then, MD, Medizinische Klinik und Poliklinik IV - Klinikum der Ludwig-Maximilians-Universität, Ziemssenstraße 1, 80336 München, Germany. Fax: 004989440054956; Phone: 004989440052111; E-mail: cornelia.then@med.uni-muenchen.de; reprint requests should be addressed to Cornelia Then

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The authors have nothing to disclose.

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Figure 1 SUmod levels according to glucose tolerance status. Given are medians, interquartile ranges and 10^{th} - 90^{th} percentiles. **p< 0.01; ***p< 0.001. Abbreviation: T2D: type 2 diabetes mellitus.

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Table 1 Characteristics of study participants [a]

	All subjects	Men	Women	p [b]
n	1119	569	550	
Age (years)	70.3 ± 5.5	70.4 ± 5.6	70.3 ± 5.4	n.s.[#]
BMI (kg/m^2)	28.7 ± 4.5	28.4 ± 3.9	29.0 ± 5.0	0.018[#]
Waist circumference (cm)	98.2 ± 12.2	102.8 ± 10.4	93.4 ± 12.0	<0.001[#]
Systolic blood pressure (mmHg)	128.5 ± 19.6	132.2 ± 19.2	124.8 ± 19.4	<0.001[#]
Diastolic blood pressure (mmHg)	74.0 ± 10.0	75.4 ± 10.3	72.5 ± 9.7	<0.001[#]
Arterial hypertension (%)	699 (62)	380 (67)	319 (58)	0.002[###]
HDL cholesterol (mmol/l)	1.45 ± 0.37	1.33 ± 0.33	1.57 ± 0.36	<0.001[#]
LDL cholesterol (mmol/l)	3.64 ± 0.93	3.52 ± 0.9	3.76 ± 0.95	<0.001[#]
Triglycerides (mmol/l)	1.27 (0.94; 1.77)	1.35 (0.94; 1.90)	1.23 (0.93; 1.66)	0.009[##]
Prediabetes (%)	290 (26)	151 (27)	139 (25)	n.s.[###]
Type 2 diabetes (%)	218 (19)	131 (23)	87 (16)	0.006[###]
HbA1c (mmol/mol)	38 (36; 41)	38 (36; 42)	38 (36; 41)	n.s.[##]
HbA1c (%)	5.6 (5.4; 5.9)	5.6 (5.4; 6.0)	5.6 (5.4; 5.9)	n.s.[##]
hsCRP (nmol/l)	14.7 (7.5; 30.4)	13.8 (7.0; 29.0)	15.9 (8.6; 32.3)	0.046[##]
eGFR (ml/min/1.73 m^2)	77.9 (67.2; 87.8)	79.1 (68.2; 87.4)	76.8 (66.0; 88.1)	n.s.[##]
Physically inactive [c] (%)	556 (50)	293 (51)	263 (48)	n.s.[###]
sUmod (ng/ml)	152.5 (110.4; 207.6)	138.6 (103.3; 187.6)	169.0 (120.4; 224.7)	<0.001[##]

[a] Means ± standard deviation, median (first quartile; third quartile), or proportion (%);
[b] The p value is related to the null hypothesis of no sex differences;
[c] Physically active: ≥ 1 hour sports/week in winter and summer;
[#] t-Test; [##] Mann-Whitney U-test; [###] Chi-square test; n.s. not significant

Table 2 Association of sUmod with age and sex: Results of multinomial linear/logistic regression models; n = 1065 in the fully adjusted model

Age	Sex (female)
Without adjustment	
-3.032 ± 0.392 ***	26.242 ± 4.336 ***
Adjustment for eGFR	
-1.666 ± 0.412 ***	26.900 ± 4.114 ***
Multivariate adjustment[1]	Multivariate adjustment[2]
-1.313 ± 0.418 **	23.723 ± 4.207 ***

[1] adjusted for sex, BMI, diabetes, hypertension, LDL, eGFR, hsCRP, myocardial infarction or stroke, smoking behavior, physical activity
[2] adjusted for age, BMI, diabetes, hypertension, LDL, eGFR, hsCRP, myocardial infarction or stroke, smoking behavior, physical activity
** p < 0.002; *** p < 0.001

Table 3 Relation of sUmod and prevalent prediabetes and T2D. Adjusted ORs (95% CI) for glucose regulation (prediabetes and T2D with normal glucose tolerance as reference) as dependent variable and sUmod as independent variable (per standard deviation): Results of multinomial logistic regression models; n (in the fully adjusted model: total cohort; men; women) = 872; 426; 446 for the analysis of prediabetes (prediabetes yes: 288; 150; 138); n (in the fully adjusted model: total cohort; men; women) = 797; 405; 392 for the analysis of T2D (T2D yes: 213; 129; 84)

	Prediabetes	T2D
Without adjustment		
Total study cohort	0.8 (0.69 - 0.92) *	0.55 (0.47 - 0.65) ***
Men	0.79 (0.65 - 0.98) *	0.55 (0.44 - 0.69) ***
Women	0.82 (0.66 - 1.01)	0.57 (0.44 - 0.73)***
Adjustment for age, (sex) and BMI		
Total study cohort	0.91 (0.78 - 1.07)	0.67 (0.56 - 0.81) ***
Men	0.88 (0.71 - 1.1)	0.63 (0.5 - 0.81) ***
Women	0.95 (0.76 - 1.2)	0.73 (0.55 - 0.97) *
Adjustment for age, (sex), BMI and eGFR		
Total study cohort	0.89 (0.75 - 1.05)	0.68 (0.56 - 0.82) ***
Men	0.83 (0.65 - 1.05)	0.62 (0.48 - 0.81) ***
Women	0.95 (0.75 - 1.21)	0.75 (0.56 - 1.01)
Adjustment for age, (sex), BMI, eGFR and hsCRP		

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Total study cohort	0.91 (0.77 - 1.08)	0.68 (0.56 - 0.83) ***
Men	0.84 (0.66 - 1.07)	0.63 (0.48 - 0.82) ***
Women	0.98 (0.77 - 1.24)	0.76 (0.56 - 1.01)

* $p < 0.05$; *** $p < 0.001$

Table 4 Relation of sUmod and incident prediabetes and T2D. Adjusted ORs (95% CI) for glucose regulation (prediabetes and T2D with normal glucose tolerance as reference) as dependent variable and sUmod as independent variable (per standard deviation): Results of multinomial logistic regression models

	Prediabetes	**T2D**	**Prediabetes or T2D**
Without adjustment			
Total study cohort	0.90 (0.69 - 1.18)	0.83 (0.64 - 1.08)	0.81 (0.66 - 1.00)
Men	0.97 (0.65 - 1.45)	1.07 (0.73 - 1.56)	0.85 (0.60 - 1.17)
Women	0.91 (0.62 - 1.34)	0.66 (0.45 - 0.96) *	0.88 (0.67 - 1.16)
Adjustment for age, (sex), BMI, eGFR and hsCRP			
Total study cohort	1.03 (0.77 - 1.38)	1.0 (0.75 - 1.35)	1.01 (0.80 - 1.27)
Men	1.03 (0.68 - 1.57)	1.35 (0.87 - 2.11)	1.00 (0.70 - 1.44)
Women	1.06 (0.7 - 1.6)	0.77 (0.51 - 1.17)	1.02 (0.75 - 1.39)
n [a]	112; 61; 51	72; 41; 31	184; 102; 82

* $p < 0.05$

[a] number of participants included in the fully adjusted model who met criteria (total cohort; men; women)

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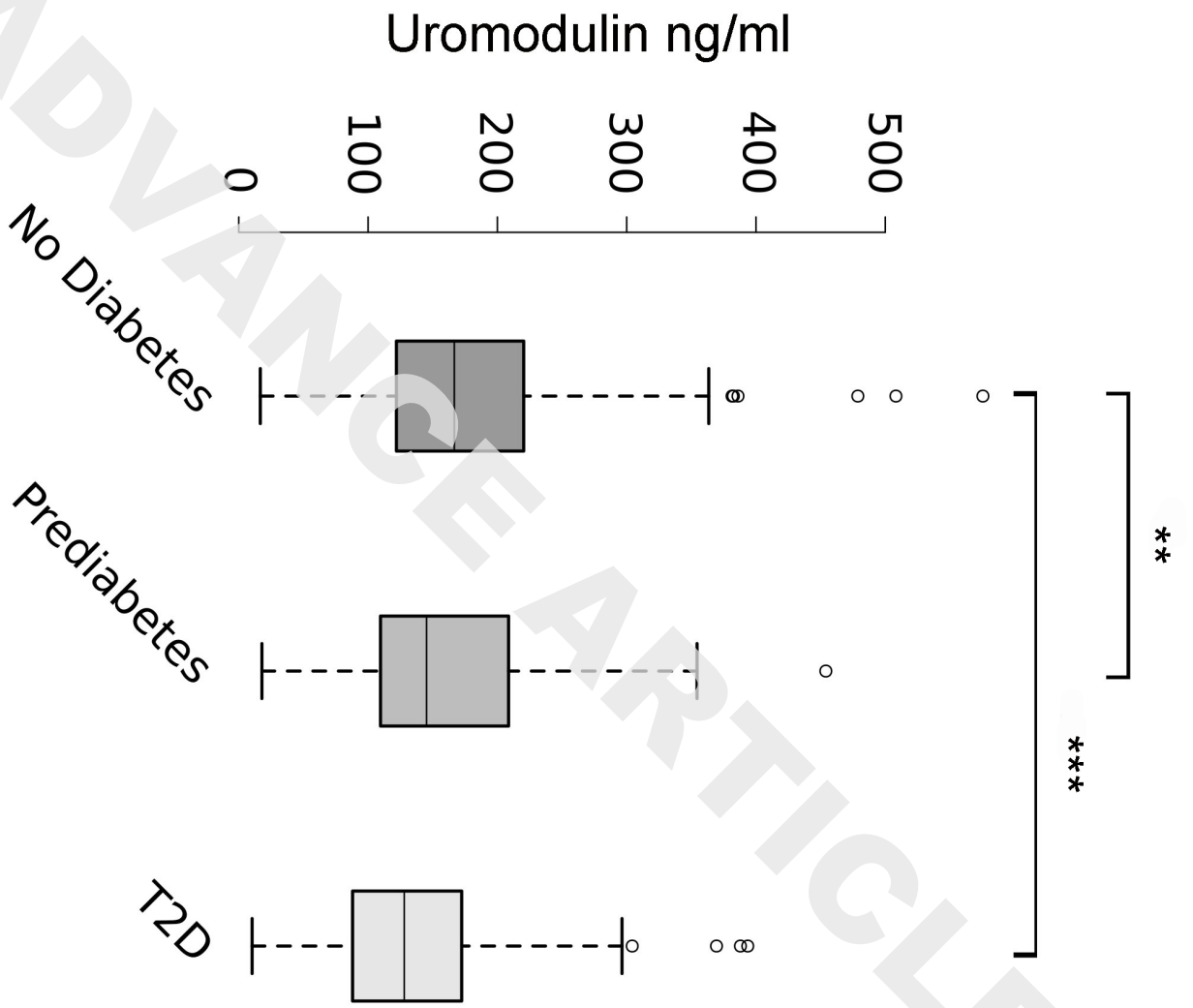

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