REPRODUCING HUMAN DIABETIC NEPHROPATHY IN A NOVEL OBESITY-DRIVEN ANIMAL MODEL

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BACKGROUND AND AIMS

The pathogenesis of diabetic nephropathy (DN) is not completely known. This could be related with a lack of pre-clinical models. Current animal models, mostly genotypic and monogenic, do not fully reflect diabetic organ damage. In previous studies of our group, we observed that Tacrolimus (TAC) induced a beta-cell toxicity in the context of obesity that resembles the pathogenesis of diabetes. Herein, we aim to evaluate the organ damage, specifically DN, in the same animal model.

MATERIAL AND METHODS

26 Sprague Dawley male rats were fed with high fat diet to induce obesity and metabolic syndrome (MS) during 30 days. Then, animals were randomized to TAC or placebo during 6-9 months. The first 15 days animals were treated daily with a dose of 0.5 mg/kg. The next 30 days, animals were treated 3 times/week with 0.5 mg/kg of TAC. Then, until month 6 animals were treated 2 times/week with 0.5 mg/kg. At months 6 to 9, the dose used was 0.5 mg/kg 1 times/week. Animals continued with HFD until the end. Weight control was performed weekly. Blood levels of TAC were measured every month. Hyperglycemia and insulin resistance were analysed regularly with fasting glucose, intraperitoneal glucose tolerance test (IPGTT) and insulin tolerance test (ITT). Glomerular filtration

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rate (GFR) was measured by iohexol-DBS plasma clearance. Urine at 24 hours was collected to analyse albuminuria and proteinuria. At the endpoint, renal morphology and histology was analysed.

RESULTS

Animals treated with TAC developed diabetes at baseline and after glucose load since day 15 to 9 months. In the pancreas, diabetic animals on TAC showed characteristics similar to those observed in diabetic patients (e.g. decrease in islet number and area, fibrosis, disbalance in alpha/beta cells number) (data not shown). Blood levels of TAC at 24h were 7.5 ± 2.4 ng/mL the first 15 days, 5.1 ± 1.8 ng/mL on month 1, 4.3 ± 1.4 ng/mL on month 3, 4 ± 1.6 ng/mL on month 6 and 0.9 ± 0.2 ng/mL on month 9. Animals increased the GFR after 30 days of HFD. Then, GFR continue to increase up to 6 months. From 6 months on, GFR started to decline. Animals on TAC showed higher GFR than control. In the kidney, diabetic animals on TAC showed increased glomerular area ($p \leq 0.0001$), mesangial expansion ($p \leq 0.0001$) and fibrosis intraglomerular ($p \leq 0.0002$) and peritubular ($p \leq 0.0001$), a higher proportion of glomeruli with nodular sclerosis ($p \leq 0.0043$), increased cortical expression of inflammatory markers TNF-α y MCP-1 ($p \leq 0.0001$), and increased proteinuria levels.

CONCLUSION

In an animal model of diabetes induced by Tacrolimus in a context of we observed markers of diabetic kidney disease: hyperfiltration and GFR decline, proteinuria, increased mesangial expansion, fibrosis, increased inflammatory markers and nodular sclerosis. This model can be used for studying the pathogenesis of DKD and as a platform for testing new drugs.

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EXERCISE AND PREDIABETES AFTER RENAL TRANSPLANTATION: EXPRED-II STUDY

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INTRODUCTION

Prediabetes after renal transplantation is the main risk factor for post-transplant diabetes (PTDM). In the general population, exercise prevents the progression from prediabetes to diabetes. In renal transplant patients, this effect is unknown.

METHODOLOGY

This was a randomized clinical trial including renal transplant patients after 12 months with prediabetes, who were able to perform exercise. Participants were randomized to either standard lifestyle recommendations (control group) or an individualized exercise program. The intervention consisted of 30 minutes of aerobic exercise, five times per week, with the possibility of increasing to 60 minutes and/or combining it with resistance exercises. In parallel, an adherence plan was implemented, including phone calls, follow-up visits, and monitorization of physical activity through an activity tracker. Every three months, oral glucose tolerance tests (OGTT) were performed, and fasting glucose, body weight, blood pressure, and lipid profile were assessed (analytics). The total study duration was 12 months. The expected outcome was the reversibility from prediabetes to normoglycemia. Based on previous studies conducted by the group (EXPRED I)[1], a sample size of 50 participants (25 per group) was calculated.

RESULTS

Ad interim analysis of 23 patients (46% of the original sample) who completed 12 months of follow-up showed that the reversibility of prediabetes in the exercise group was 70% (7 out of 10) compared

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with 15% (2 out of 13) in the control group (70% vs. 15%; p = 0.012). **Therefore, the study was interrupted early due to efficacy.**

In the exercise group a significant reduction was observed in weight 81 ± 19 to 72 ± 13 Kg *(p<0.01),* waist perimeter 103 ± 14 to 93 ± 11 cm *(p<0.01)* and triglycerides 128 ± 47 to 93 ± 28 mg/dL *(p<0.01)*. The mean adherence rate was 74 ± 16 %. In the control group, no significant changes were observed.

CONCLUSIONS

Exercise is effective and safe for reverting prediabetes in renal transplant patients at risk of PTDM. A supervised and personalized adherence protocol was essential. Long-term studies with exercise in nephrology care are needed, particularly in renal transplant recipients.

GROUP	**EXERCISE (*N=10*)**		**CONTROL (*N=13*)**	
Follow-up	**M0**	**M12**	**M0**	**M12**
Glucose 0'	111 ± 22	98 ± 16	97 ± 14	102 ± 12
Glucose 120'	185 ± 68	147 ± 69	148 ± 46	163 ± 54
Weight	81 ± 19	72 ± 13*	82 ± 13	82 ± 14
Triglycerides	128 ± 47	93 ± 28*	120 ± 42	120 ± 56

Note: * (p<0.05)

1. Morales Febles R, Marrero Miranda D, Jiménez Sosa A, et al. Exercise and Prediabetes After Renal Transplantation (EXPRED-I): A Prospective Study. *Sports Med Open*. 2023;9(1):32. Published 2023 May 18. doi:10.1186/s40798-023-00574-8

THERAPEUTIC EXERCISE AND RENAL DISEASE: ETER STUDY

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INTRODUCTION

Obesity and metabolic syndrome (MS) are risk factors for the progression of kidney damage in individuals with chronic kidney disease (CKD) of various etiologies, including kidney transplantation. Therapeutic exercise is an effective and valuable tool for managing obesity and MS in the general population. However, the potential renoprotective effect of weight reduction and improvement of MS through exercise in patients with CKD remains unknown.

OBJECTIVES

In a group of patients with CKD and obesity/metabolic syndrome, we will evaluate the effect of exercise on (i) metabolic parameters: weight reduction and improvement of metabolic syndrome traits, and (ii) renal parameters: reduction of albuminuria/proteinuria, changes in measured renal function and renal reserve (RR), as well as improvement in renal perfusion and oxygenation assessed by metabolic MRI.

PROTOCOL DESCRIPTION

The ETER study is an exploratory interventional study in which patients with CKD of various etiologies (including kidney transplant recipients) with overweight/obesity and metabolic syndrome or type 2 diabetes will undergo a therapeutic exercise program.

There is no prior evidence to calculate sample size; therefore, we will analyze a group of 144 patients based on our preliminary data, divided into three subgroups of CKD: (A) GFR >30 mL/min, (B) GFR <30 mL/min and (C) kidney transplant recipients. Ad interim analyses will be conducted regularly, every 6 months or after every 30 enrolled patients, to assess the expected response.

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Individualized exercise program consists of a combination of incremental aerobic (from 30 min/day to 80 min/day) + resistance exercise based on previous physical capacity. Simultaneously, an adherence protocol incorporating new technologies will be implemented (APP + activity tracker). The intervention will last 24 months, divided into an acute phase (0–6 months) and a chronic phase (6–24 months).

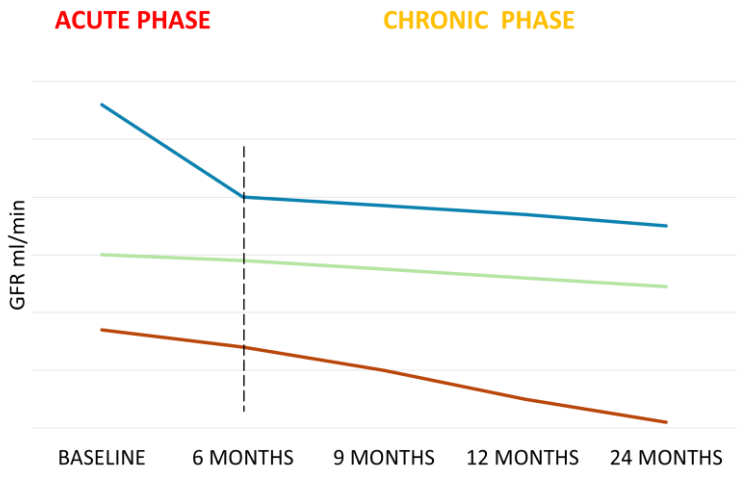
Outcomes: changes in MS, measured renal function renal reserve, renal perfusion and oxygenation (MRI), and albuminuria/proteinuria will be assessed every 3 months during the acute phase and every 6 months during the chronic phase.

EXPECTED RESULTS

We foresee these possible evolutions:

(I) RESPONDERS to weight loss and MS (**blue:** a decrease in GFR in the acute phase, followed by a slow decline - **green:** no changes in the acute phase followed by mild GFR loss.)

(II) NON-RESPONDERS to weight loss and MS (**brown:** accelerated decline in renal function in both phases.)



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URINARY LIPIDOMICS: A NOVEL BIOMARKER OF RENAL DISEASE IN METABOLIC SYNDROME AND DIABETES?

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INTRODUCTION

The incidence of chronic kidney disease (CKD) is rising globally at an alarming rate, mirroring the obesity pandemic. Despite the strong association between these factors, a profound understanding of the underlying mechanisms and reliable biomarkers for CKD are currently lacking. While renal biopsies offer unique diagnostic value, they are rarely available in routine clinical practice due to their invasive nature. Instead, serum and urinary analyses are commonly employed to estimate tissue damage, yet they present several limitations. Therefore, a better understanding of the pathogenesis driving CKD in the context of obesity is crucial to facilitate the development of new therapeutic opportunities and identify more reliable biomarkers for the early and accurate detection of renal damage in patients at risk.

Dysregulation of the lipid metabolism leads to cellular injury and malfunctioning, commonly observed in metabolic syndrome (MS) and diabetes mellitus (DM). Given that lipids are involved in essential cellular pathways, such as energy production, signalling and membrane dynamics, alterations in their metabolism may have deleterious consequences. Particularly, fatty acids participate in the synthesis of ATP in the mitochondria but also regulate inflammatory processes and the fusion/fission pathways required by organelles to function.

OBJECTIVES

Accumulating evidence suggests that renal lipotoxicity may play a crucial role in the progression of the disease, resulting in chronic kidney damage and end-stage kidney disease (ESKD). Currently, these pathways are poorly understood. Clarifying the underlying mechanisms is essential to uncover new therapeutic strategies and identify novel biomarkers.

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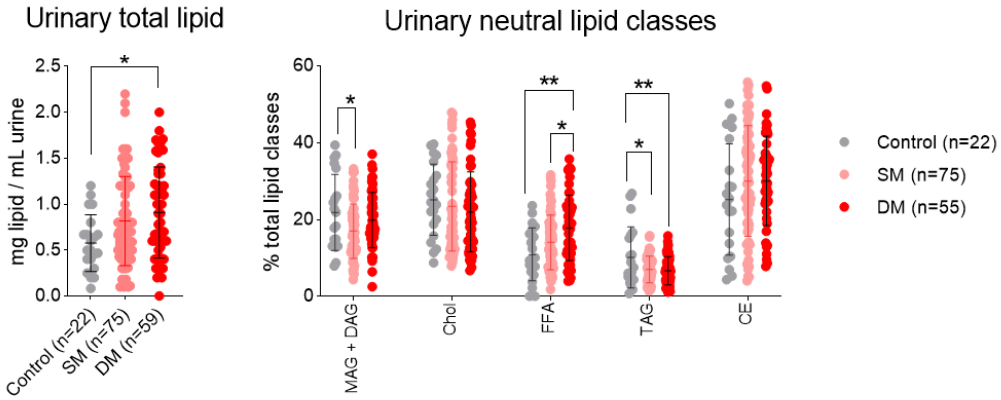
PROTOCOL DESCRIPTION

In this study, we performed lipid analyses of urinary samples from lean (Control), metabolic syndrome (MS) and diabetes mellitus (DM) from the European Nephrectomy Biobank (ENBiBA) to identify alterations in the lipid metabolism that may reflect the renal condition of the patients. For that purpose, we used chloroform/methanol for lipid extraction. Total lipid was determined gravimetrically, lipid classes were measured by high performance thin-layer chromatography (HPTLC) and the fatty acid profile was determined by TLC and GC-MS/MS.

RESULTS



FFA=free fatty acids, MAG=monoacylglycerol, DAG=diacylglycerol, TAG=triacylglycerol, CE=cholesteryl ester. *, p<0.05; **, p<0.01; ***, p<0.001. One-way ANOVA statistical tests.

CONCLUSIONS

We found that MS and DM induce an increase in the total urinary lipid, with higher levels of saturated fatty acids resulting in a relative depletion of polyunsaturated fatty acids (PUFA).

THE MULAGUA STUDY: A SPANISH COHORT RENAL ON RENAL HEALTH: preliminary results

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INTRODUCTION

Chronic kidney disease (CKD) is a common and serious disease. It significantly increases morbidity and mortality, and the risk of cardiovascular events (CVEs) up to 3.4 times in the final stage of CKD (eGFR <15 ml/min) in people who suffer from it. The prevalence of CKD in Spain is unclear, although it is estimated to be between 9% and 15%. This is because the current figures obtained are calculated using formulas that estimate Glomerular Filtration Rate (eGFR) based on serum creatinine and cystatin C, with an average margin of error of ± 30%. It is therefore essential to analyze the real prevalence using measured Glomerular Filtration Rate (mGFR). Consequently, the Mulagua study has been designed to analyze the real prevalence of CKD and its risk factors in the Spanish population using iohexol-DBS plasma clearance.

OBJECTIVES

The main objective of this study is to analyze the actual prevalence of CKD using measured mGFR. Secondary outcomes include: (a) the impact of the error of formulas in the prevalence of CKD; (b) the prevalence of occult CKD (mGFR <60 ml/min with estimated GFR > 60 ml/min); (c) the prevalence of risk factors for CKD like hypertension, diabetes, overweight/obesity, dyslipidemia, prediabetes, insulin resistance, etc; (d) the prevalence of albuminuria. All of these analyses will be presented stratified by age and sex.

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Finally, another outcome is to establish a Spanish baseline cohort of renal health that will serve as a reference for future prospective studies and allow for the evaluation of the progression of renal function, the factors associated with its deterioration, and the occurrence of related cardiovascular events.

METHODOLOGY

This is a cross-sectional study.
Inclusion criteria: 1. Age over 18 years; 2. Ambulatory status; 3. People who sign written informed consent; 4. Clinical stability.
Exclusion criteria: 1. History of allergy to iodinated contrasts; 2. Inability to understand the protocol; 3. Pregnancy; 4. Active cancer.
Measured GFR: All patients will undergo plasma clearance of iohexol by dried blood spot analysis (iohexol-DBS).
Estimated GFR: by formulas in the baseline serum sample, creatinine and cystatin-C based formulas.
Clinical variables: biochemistry analysis, albumin/creatinine ratio, demographic data (date of birth, sex, race), anthropometric data (weight, height, abdominal circumference, BMI, blood pressure), tobacco and alcohol consumption, underlying disease (if any), treatments received (if any).
Surveys: dietary adherence, exercise and sedentary lifestyle and socio-economic status.
Serum/plasma/urine/DNA banks.

RESULTS

The results obtained are shown in Table 1.

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Table 1. Baseline characteristics for subjects.

N=500		
Male (n, %)		205 (41%)
Female (n, %)		295 (59%)
Age, yr	Mean ± SD	57 ± 16
	Median, IQR	58; 46 - 68
	Min	18
	Max	93
Height (cm)		1.63 ± 9
Body Weight (kg)		79 ± 17
BMI (kg/m^2)	Mean ± SD	30 ± 5
	Median, IQR	29; 26 - 33
Diabetes (n, %)		105 (21%)
Impaired fasting glucose (n,%)		124 (25%)
Dyslipidemia (n, %)		310 (62%)
Hypertension (n, %)		238 (48%)
Known CKD (n, %)		21 (4,2%)
Unknown CKD? (n, %) **GFR<60ml/min**		37 (7,4%)
Unknown CKD with CKD-EPI (n, %)		17 (46%)

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SEXUAL DIMORPHISM IN EARLY POST-TRANSPLANT METABOLIC ADAPTATION: THE IMPACT OF PTDM ON MUSCLE PERFORMANCE. A LONGITUDINAL COHORT STUDY

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INTRODUCTION

Kidney transplantation is the gold-standard treatment for End-Stage Kidney Disease (ESKD). However, the initiation of immunosuppressive therapy – primarily corticosteroids and calcineurin inhibitors – during the early post-transplant months induces significant metabolic adaptations. Key complications include weight gain and Post-Transplant Diabetes Mellitus (PTDM). PTDM also accelerates sarcopenia, compromising muscle quality through mechanisms involving insulin resistance and inflammation. Although sarcopenia is a known risk factor for mortality, the specific impact of PTDM on locomotor performance during the early post-transplant phase remains under-investigated, particularly regarding sex differences.

This study aims to evaluate the incidence of PTDM, associated metabolic alterations, and their impact on body composition and muscle function during the first six months post- transplant, with a specific focus on sexual dimorphism.

MATERIALS AND METHODS

A retrospective longitudinal cohort study was conducted on 133 kidney transplant recipients (85 males, 48 females; mean age 50.5 ± 10.9 years) followed at the Multidisciplinary Outpatient Clinic of the Policlinico San Matteo in Pavia between December 2015 and February 2020. Clinical and functional evaluations were performed at 1 (T1), 3 (T3), and 6 (T6) months post-transplant. Analyzed parameters included: Metabolic Profile (fasting glucose, HbA1c, lipid profile, and insulin resistance via HOMA- IR index); Body Composition (Bioelectrical Impedance Analysis [BIA] and anthropometric measurements [BMI, waist and thigh circumferences]) ; and Locomotor Performance (muscle strength assessed using the Medical Research Council [MRC] scale for the

rectus abdominis, and lower limb endurance evaluated via the Wall Squat test and Six-Minute Walking Test). Variables were analyzed using Student's t-test, Mann-Whitney U test, and Chi-square test, with statistical significance set at $p < 0.05$.

RESULTS

The study population was predominantly male (64%) and Caucasian (90%). The prevalence of PTDM increased significantly from a pre-transplant baseline of 6% to a peak of 37% at T6 ($p < 0.0001$). Males exhibited a less favorable metabolic profile. While females showed stable visceral adiposity, males experienced a significant increase in abdominal circumference (T1: 90.6 cm vs. T6: 93.2 cm; $p < 0.05$). Insulin resistance (HOMA-IR > 2.5) was significantly higher in males at T6 (51%) compared to females (33%) ($p = 0.01$). Diabetic status significantly compromised muscle function, predominantly in males. Diabetic males showed a significant reduction in thigh circumference at T6 compared to T1 ($p < 0.05$), a trend not observed in females or non- diabetic males. In the Wall Squat test at T6, diabetic males demonstrated significantly reduced endurance compared to non-diabetic males ($p < 0.05$). Furthermore, abdominal muscle strength recovered linearly in females, whereas males showed a transient loss of strength at T3 before recovering.

DISCUSSION

The study highlights pronounced sexual dimorphism in the early post- transplant phase. Male recipients exhibit a greater predisposition to a "sarcopenic obesity" phenotype, characterised by visceral fat accumulation, insulin resistance, and impaired muscle recovery. In particular, PTDM emerges as a significant negative predictor of physical performance in men, being associated with reduced muscle mass and lower limb strength. In contrast, females appear more protected, likely due to oestrogenic effects and higher daily activity levels, which promote better glycaemic control and muscle preservation.

These findings have important clinical implications: male patients, especially those who develop diabetes, should be referred to intensive nutritional and physical rehabilitation programmes. Importantly, training programmes must be specifically designed to counteract lower limb strength loss and prevent metabolic decline.

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IMPACT OF IRISIN, AN EXERCISE MIMETIC, IN RENAL LIPOTOXICITY.

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The growing increase of obesity intensifies incidence of chronic kidney disease (CKD) across the world. Our group previously demonstrated that mice fed a high-fat diet (HFD) accumulate lipid droplets within proximal tubular epithelial cells (PTEC), a phenomenon associated with albuminuria and dysregulation of AMP-activated protein kinase (AMPK) in the renal cortex. Moreover, we showed that endurance exercise training (EET) mediates improvements in renal function in obese mice though the restoration of AMPK activity. Based on these findings, we hypothesize that myokines produced during exercise are involved in the beneficial effects of EET on renal impairments. Among these myokines, irisin has been recently highlighted to have beneficial effect on kidney. Therefore, in the present study, the impact of irisin on the AMPK activity and renal metabolic adaptation to lipotoxicity was investigated in primary PTEC to identify its benefit in CKD.

To do so, PTEC were isolated from mouse kidneys (mPTEC), the functional characteristics of mPTEC was validated using the BSA-uptake assay, highlighting the absorptive ability of these cells. To mimic the obesity setting, cultured cells were treated with palmitic acid (PA) or its vehicle in presence or not of irisin (I), during 24 h.

We first confirmed that lipid overload in mPTEC disrupts tubular functions and induces significant lipid droplet accumulation (Figure 1.1). These changes were associated to an increased expression in PPAR-gamma transcription factor and its targeted gene, CD36 (Figures 1.2 and 1.3). Interestingly, irisin prevents the lipid accumulation along to prevent increased PPAR-gamma and CD36 gene expressions. In addition, mRNA expressions of key players in lipogenesis and beta oxidation were investigated. While PA treatment induces an increase in beta oxidation gene expression and a reduction of lipogenesis gene expression, irisin did not counteract these changes.

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Overall, our data demonstrate a protective role of irisin against renal lipotoxicity. However, the molecular mechanisms linking irisin to PPAR-γ/CD36 transcriptional regulation remain to be elucidated. Future work will focus on exploring potential signaling pathways, particularly those involving AMPK activation and mitochondrial function.

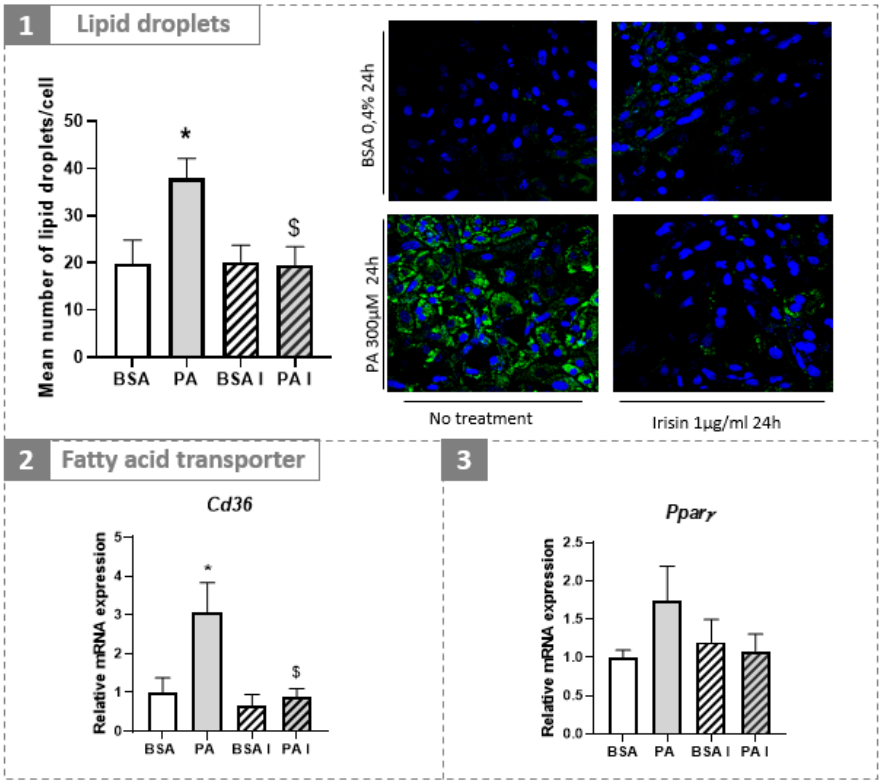

FIGURE 1. Irisin impact on lipid droplets and fatty acid transporter in proximal tubular cell (PTEC) in a lipotoxicity context. (1) Representative micrographs of PTEC treated with 300µM PA/BSA with or without irisin 1µg/ml during 24h. Neutral lipid droplets are staining with BODIPY in green and nucleus with Hoescht in blue. (2) Relative gene expression of CD36, fatty acid transporter in PTEC treated with 300µM PA/BSA with or without irisin 1µg/ml during 24h. (3) Relative gene expression of PPAR gamma, CD36 transcription factor, in PTEC treated with 300µM PA/BSA with or without irisin 1µg/ml during 24h. Statistical analyses were performed by one-way ANOVA followed by Tukey post hoc test. * p≤0.05 vs BSA, $ p≤0.05 vs PA. Data are presented as means ± SEM. n≥4 in each group.

RENAL AMPK PHOSPHORYLATION IS MODULATED BY METABOLIC COMORBIDITIES AND SEX IN OBESE ANIMAL MODELS

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ABSTRACT

Obesity and type 2 *diabetes mellitus* (T2DM) are rising public health issues and established risk factors for chronic kidney disease (CKD). However, obesity alone may not be sufficient to alter renal function and additional metabolic stressors could be required. Moreover, obesity is frequently associated with other comorbidities, notably T2DM, and participates in the metabolic syndrome. At the systemic level, these pathologies lead to various damages. At the cellular level, obesity and T2DM have been shown to induce impairments in bioenergetic and lipid metabolism, notably in the kidney. This context may contribute to CKD pathogenesis and progression.

In recent years, activity of AMP-activated protein kinase (AMPK), a central metabolic regulator, have been found to vary in obesity-induced CKD. To explore this hypothesis, we investigated the activation of AMPK in two animal models under various metabolic conditions.

AMPK-alpha phosphorylation (Thr172/Thr183) was assessed by Western blot in renal tissues from: (i) a C57Bl/6J mouse model of obesity and menopause and (ii) a Sprague Dawley rat model of obesity and T2DM. Obesity was induced by exposing animals to a high-fat diet (HFD) composed of 60% kcal from fat. Animal studies were conducted during twelve or nine months respectively. Menopause was induced in female mice by performing an ovariectomy. In rats, the development of T2DM was catalysed by performing regular Tacrolimus injections.

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In kidneys from male mice, the HFD induced an increase in AMPK phosphorylation compared to lean controls while this effect was not detected in females, thus suggesting a protective impact of female hormones. We therefore performed experiments on ovariectomised females to investigate the influence of menopause, which did not significantly alter AMPK phosphorylation. Similarly, AMPK was more phosphorylated in kidneys of HFD fed male rats than in control tissues. Combination of obesity with T2DM led to further AMPK activation when compared to obese animals.

Our data suggests that AMPK activity is influenced not only by obesity but also by sex differences and metabolic comorbidities such as T2DM. Interestingly, menopause does not appear sufficient to modulate AMPK phosphorylation, thus suggesting that the decline in oestrogen levels may not directly impact AMPK activity in this model. Our research group has recently highlighted that AMPK and mTOR pathways are similarly affected in kidneys of an Iberian swine model of low-birth weight and obesity. Since AMPK is involved in mitochondrial homeostasis and lipid metabolism, future work will examine these aspects as well as AMPK downstream targets.

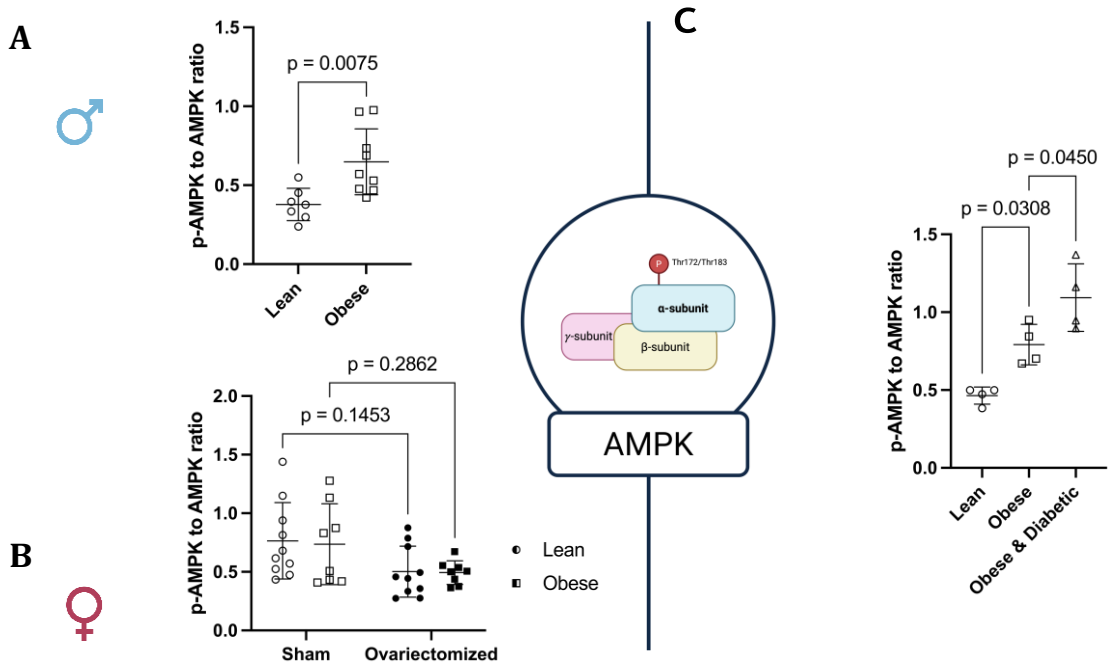

Figure 1: AMPK phosphorylation is upregulated in kidneys of animals with metabolic impairments.

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(**A**) Relative densitometry of Western blot analyses revealed AMPK activation is increased in kidneys samples from male mice exposed to a high-fat diet (HFD) for twelve months. Statistical analyses were performed by an unpaired t-test, two-tailed. (**B**) Relative densitometry of Western blot analyses for female mice kidneys. AMPK phosphorylation is not influenced by diet but could be decreased by menopause. Statistical analyses were performed by a two-way ANOVA followed by Tukey post-hoc test. (**C**) In male rats, the relative densitometry of Western blot analyses indicates that AMPK activation is increased in kidneys of obese animals when compared to lean controls. Induction of diabetes on top of obesity leads to further AMPK phosphorylation when compared to obese individuals.
Statistical analyses were performed by a one-way ANOVA followed by Tukey post-hoc test. All data are presented as: Mean ± SD. n ≥ 4 in each group; experiment was performed twice for each sample.

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CLINICAL-HISTOLOGICAL DISSOCIATION ACROSS STAGES OF CHRONIC KIDNEY DISEASE.

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INTRODUCTION

The KDIGO classification of chronic kidney disease (CKD) is a widely used tool to facilitate the stratification of patients according to their risk of progression to end-stage CKD. However, this classification is not supported by histological findings that corroborate a correct correlation between the degree of actual chronicity and the stages of the disease. Therefore, the objective of this study was to evaluate whether the current classification of CKD corresponds to histological findings of chronicity.

MATERIALS AND METHODS

This was a retrospective multicenter study of a cohort of patients who underwent nephrectomy (partial or radical) for renal carcinoma between January 2015 and December 2022, in which the healthy renal parenchyma was analyzed and the correlation between the chronic damage observed and the degree of CKD was assessed. To this end, patients were divided into two groups (based on estimated glomerular filtration rate [eGFR] before surgery: <60 thousand/min/1.73m2 and >60 thousand/min/1.73m2) and the percentage of sclerotic glomeruli, fibrosis and tubular atrophy, and

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vascular damage was estimated. The correlation coefficient was estimated using Kendall's Tau-b. A multivariate regression analysis was performed, adjusting for age, hypertension, diabetes, degree of proteinuria, dyslipidemia, and obesity.

RESULTS

A total of 357 patients had histological samples analyzed. The median age was 65 years (IQR: 55-74). Sixty-eight percent were male. A total of 229 patients (64%) were hypertensive, while 102 (28%) were diabetic. One hundred seventeen (32%) were obese and 152 (42%) had dyslipidemia. One hundred and one patients (28.3%) had eGFR <60 thousand/min/1.73m2, while 249 (69.7%) had eGFR >60 thousand/min/1.73m2. Within the group with eGFR <60, 24% had less than 10% sclerotic glomeruli, while 19% and 20% had fibrosis and tubular atrophy <5%, respectively. On the other hand, two-thirds of patients with eGFR >60 had moderate arteriolar hyalinosis. The degree of correlation between eGFR and signs of histological damage was weak (r = -0.21, p: <0.001). After performing the multivariate analysis, only age, degree of proteinuria, and degree of fibrosis influenced eGFR.

CONCLUSIONS

Observable histological damage does not appear to correlate reliably with the currently accepted stages of chronic kidney disease.

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VISCERAL ADIPOSE TISSUE ALTERS PODOMETRICS AND RENAL COMPENSATION AFTER UNINEPHRECTOMY

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BACKGROUND

Obesity is a recognized risk factor for chronic kidney disease (CKD), yet increased visceral adipose tissue (VAT), referred to as visceral obesity (VO), can also occur in individuals who are not obese according to body mass index (BMI <30 kg/m^2). Although VO has been associated with impaired kidney function, its impact on kidney microstructure remain insufficiently understood. Moreover, the VAT thresholds required to define VO may differ between men and women. This study investigated the association of VO with glomerular architecture, podocyte morphometry, and functional renal compensation after uninephrectomy in non-obese individuals.

METHODS

In 52 nonproteinuric patients with BMI <30 kg/m^2 undergoing nephrectomy for nonmetastatic renal tumors, VAT area was quantified on preoperative computed tomography (CT) at the level of the third lumbar spine. VO was defined as VAT ≥100cm^2. Kidney volume was additionally derived from CT imaging. Non-tumorous kidney tissue was analyzed using deep- learning-assisted morphometry to assess glomerular size and podocyte characteristics (count, density, and nuclear volume). Functional renal compensation during the first postoperative year (△eGFR) was evaluated using linear regression.

RESULTS

VO was present in 35 of 52 participants. Individuals with VO were predominantly male (78%), whereas most individuals without VO were female (88%). Compared with non-VO individuals, those with VO exhibited significantly larger glomeruli (2.6±0.7 vs. 2.0±0.5 × 10^6 µm^3; *p=0.004)*

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lower podocyte density (194±50 vs.243±59 per106 μm^3 p=0.003), and greater podocyte nuclear volume (226±27 vs. 195±22 μm^3; p<0.001). These results were confirmed in an analysis of covariance (ANCOVA), adjusted for BMI and age.

Men and women with VO showed comparable degrees of glomerulomegaly (2.6±0.7 &2.6±0.8 × 10^6 μm^3) reduced podocyte density (190±50 & 207±48 per10^6 μm^3), and podocyte nuclear hypertrophy (226±28 & 226±25 μm^3), indicating that the absolute VAT cut-off yields comparable biological phenotypes. In regression models including VO and sex, biological sex was not associated with alterations in glomerular volume (p=0.98), podocyte density (p=0.25), or podocyte nuclear volume (p=0.43). VO was further associated with reduced postoperative renal compensation (△eGFR: −24±15 vs. −12±12 ml/min/1.73 m^2; P=0.03), with similar declines observed in men and women (men: −24±16 mL/min/1.73m^2 vs. women: −24±14 mL/min/1.73m^2).

Across the entire cohort, glomerular enlargement, reduced podocyte density, and podocyte nuclear hypertrophy each correlated with impaired △eGFR. Fully adjusted regression models remained robust across four sensitivity frameworks: a) VAT and BMI, b) VAT, diabetes, hypertension, age, and sex, c) height-adjusted kidney volume and baseline eGFR, and d) histopathological scores.

CONCLUSIONS

In non-obese individuals, VO is associated with adverse structural alterations in glomerular and podocyte structure, as well as with diminished renal compensatory capacity after nephrectomy. The combination of glomerular enlargement and reduced podocyte density may reflect a reduced potential for further adaptive hyperfiltration in the remaining nephrons. Quantification of VAT may therefore provide clinically meaningful information for individualized preoperative risk stratification.

Given the marked imbalance in sex distribution between the VO and non-VO subgroups, sex-specific VAT thresholds merit consideration. Nevertheless, the application of an absolute VAT cut-off of 100 cm^2 yielded broadly comparable histological alterations in both men and women, suggesting that this threshold may be adequate across sexes. Future studies should clarify the long-term implications of VO in patients undergoing nephrectomy and determine whether VO is best defined using absolute or sex-specific VAT criteria.

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Table 1: Morphometric features of patients with and without visceral obesity (VO), dependent on patients' sex.

	Non-VO (Male) (n=2)		**Non-VO (Female) (n=15)**		**VO (Male) (n=27)**		**VO (Female) (n=8)**	
Morphometric Parameter	**Mean**	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**
Sclerotic glomeruli (%) – median (interquartile range)	1	(0-1)	0	(0-2)	2	(0-3)	1	(0-4)
Non-sclerotic glomerular count	380	(±1)	279	(±128)	305	(±98)	212	(±81)
Glomerular volume ($\times 10^6$ µm³)[#]	**1.9**	**(±0.4)**	**2.0**	**(±0.5)**	**2.6**	**(±0.7)**	**2.5**	**(±0.8)**
Podocyte count per glomerulus	391	(±25)	480	(±135)	477	(±148)	506	(±138)
Podocyte density (per 10^6 µm³)	**210**	**(±27)**	**248**	**(±61)**	**190**	**(±50)**	**207**	**(±48)**
Apparent podocyte nuclear caliper diameter *d* (µm)	5.3	(±0.1)	5.7	(±0.2)	5.9	(±0.2)	5.9	(±0.2)
Estimated true podocyte nuclear caliper diameter *D* (µm)	6.3	(±0.0)	6.7	(±0.2)	7.0	(±0.3)	7.0	(±0.2)
Correction factor for podocyte density estimation	0.417	(±0.002)	0.410	(±0.016)	0.396	(±0.014)	0.396	(±0.014)
Podocyte nuclear volume (µm³)	**165**	**(±5)**	**199**	**(±20)**	**226**	**(±28)**	**226**	**(±25)**
Podocyte nuclear volume per glomerulus ($\times 10^5$ µm³)	0.6	(±0.1)	1.0	(±0.3)	1.1	(±0.4)	1.1	(±0.3)

Legend: Visceral obesity (VO) was defined as visceral adipose tissue area ≥100 cm².
Gaussian-distributed parameters were displayed as means and standard deviations (SD),
non-Gaussian distributed data as medians and interquartile ranges.
[#]Glomerular volume was calculated with non-sclerotic glomeruli.

EARLY CLINICAL OUTCOMES IN THE FIRST 37 RECIPIENTS FOLLOWING SIMULTANEOUS PANCREAS–KIDNEY TRANSPLANTATION IN DENMARK AFTER PROGRAM REINITIATION.

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BACKGROUND

Simultaneous pancreas_kidney transplantation (SPK) is a definitive treatment for patients with type 1 diabetes complicated by end-stage renal disease, providing renal function and sustained independence from insulin treatment. SPK transplantation was re-initiated in 2015 in DK. We report short-term outcomes of the first 37 patients transplanted following the program´s reactivation.

METHODS

This single-center retrospective cohort included 37 consecutive SPK recipients transplanted at Rigshospitalet, Copenhagen, Denmark between 2015 and 2021. Biochemical markers— serum creatinine, plasma glucose, HbA1c, and C-peptide— were recorded preoperatively and at post-operative days 7, 14, 30, 90, and 365. One-year kidney graft, pancreas graft and patient survival were observed in accordance with current data-permission restrictions. All patients underwent standardized daily graft ultrasonography during the first 7 days index admission to explore

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potential sonographic predictors of rejection and thrombosis. Postoperative length of stay (LOS) was documented for each patient from the day of transplantation until discharge.

RESULTS

Rapid and sustained metabolic and renal improvements were observed. Median LOS was 19 days (95% CI 17.5 – 21.0). Creatinine (µmol/L) declined from a baseline mean of 654.8 (95% CI 586.5–723.0) to 129.1 (95% CI 111.1–147.1) at 12 months. This correlates to a mean eGFR at baseline of 8.19 (95% CI 6.85 – 9.53) and a mean eGFR of 56.15 (95% CI 49,72 – 62,58) at 12 months.

C-peptide (pmol/L) increased from 64.3 (95% CI 0–130.2) to 1,097.9 (95% CI 939.6–1,256.2) at 12 months. Plasma glucose (mmol/L) declined from 13.6 (95% CI 11.1–16.1) to 5.45 (95% CI 5.16–5.74). HbA1c (mmol/mol) decreased from 63.2 (95% CI 58.7–67.7) preoperatively to 35.3 (95% CI 33.7– 36.9) at 12 months. One-year patient survival was 94.6%, with two mortalities occurring within the first year (postoperative day 6 and month 4). Death censored kidney graft survival was 100%, and 97.1% of survivors remained insulin independent at 12 months post-transplant.

Routine evening ultrasound scans did not alter management in any cases. Specialized SPK ward rounds benefitted from routine morning ultrasound scans.

CONCLUSIONS

The reinitiated Danish SPK program demonstrates excellent early outcomes with rapid normalization of metabolic parameters and high one-year patient, kidney and pancreas graft survival.

PERSPECTIVES

One-year patient survival (94.6%) and pancreas graft function (97.1% insulin independence) are comparable to UK (96–97% patient survival, 90% insulin independence), Nordic cohorts (Sweden 95.5% and Norway >95% patient survival) and other European centers. These results indicate that the reinitiated Danish program achieves early outcomes equivalent to established international centers. Long-term follow-up is pending to evaluate graft durability, late rejection, and overall survival. The analysis of the predictive value of ultrasound scans in detecting complications leading to surgery early leads to a discussion on whether routine evening ultrasound scans can be safely omitted from the protocol.

Figure 1: Survival in months after Simultaneous Pancreas-Kidney transplant in 37 consecutive patients following the program's reactivation in 2015. 1 year survival was 94.6%. 3-year survival was also 94.6% and 5-year survival was 93.75%

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IMPACT OF MGFR *VERSUS* EGFR ON THE PHARMACOKINETICS OF A RENALLY EXCRETED MODEL DRUG IN OLDER MEDICAL PATIENTS: A PROOF-OF-CONCEPT TRIAL

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INTRODUCTION

The most common equations for estimated glomerular filtration rate (eGFR) are creatinine-based, but the influence of non-renal factors on creatinine levels is considerable and magnified in older adults, especially those affected by malnutrition. This study used population pharmacokinetic modeling to evaluate the accuracy of measured GFR (mGFR) and ten different eGFR equations based on creatinine, cystatin C, β-2 microglobulin, and/or β-trace protein for predicting individual clearance of the renally excreted drug gentamicin in older patients with poor appetite.

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METHODS

In this prospective study in older patients with poor appetite, 5 mg/kg of gentamicin was administered intravenously, and plasma gentamicin levels were followed for 21-29 hours. mGFR was determined by 99m-Tc-DTPA plasma clearance, and eGFR according to each of ten equations was calculated based on plasma filtration marker concentrations. Gentamicin population pharmacokinetics were modeled using non-linear mixed-effects modeling, and the prediction accuracy of mGFR and eGFR equations as covariates on clearance was assessed by comparing objective function values (OFV). Clinical impact was assessed by model-based simulations of gentamicin exposure.

RESULTS

Using gentamicin plasma concentration-time data from 52 medical patients (age ≥65 years, BMI ≤26), a qualified population pharmacokinetic model was developed. The most accurate predictor of model-estimated individual clearance of gentamicin was mGFR in mL/min (-ΔOFV = 115.00). Among eGFR equations, those combining creatinine and cystatin C in mL/min (-ΔOFV = 72.58-77.11) were more accurate than single-biomarker equations. Creatinine-only equations showed the worst performance (-ΔOFV <63.69), and GFR expressed in absolute units was generally more accurate than GFR expressed in body surface area-indexed units.

CONCLUSIONS

Creatinine-only eGFR equations are inaccurate predictors of drug clearance in this patient demographic, which is problematic for both drug development and clinical practice. If measuring GFR is unfeasible, estimating GFR based on a combination of creatinine and cystatin C is the best alternative.

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INCIDENT CHRONIC KIDNEY DISEASE, DIABETES AND HIGHER ALBUMINURIC LEVELS ARE CONSISTENTLY ASSOCIATED WITH A HIGHER 1-YEAR RISK OF MICROVASCULAR COMPLICATIONS IN A NATIONWIDE DANISH COHORT STUDY

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BACKGROUND AND AIMS

Albuminuria is a hallmark of diabetic nephropathy and a well-established prognostic marker in individuals with diabetes and chronic kidney disease (CKD). However, evidence remains sparse on how different levels of albuminuria relate to the development of microvascular complications. We aimed to investigate the association between urine albumin-creatinine ratio (UACR) and both baseline prevalence and development of microvascular complications in individuals with diabetes and CKD.

METHODS

We identified a nationwide cohort in Danish health care registers from 2010–2023. Eligible individuals were adults with incident non–end-stage CKD, defined as ≥2 estimated glomerular filtration rate (eGFR) measurements <60 ml/min/1.73 m^2 separated by ≥90 days with no intervening eGFR ≥60 ml/min/1.73 m^2, with index defined as the date of the second measurement. Additional criteria included prevalent diabetes (≥2 redeemed prescriptions for glucose-lowering medication

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within 2 years before index, excluding Glucagon-Like Peptide 1 analogs and Sodium-Glucose Cotransporter 2 inhibitors) and ≥1 UACR measurement within 1 year before index. Microvascular outcomes were identified as diabetic retinopathy, CKD progression, and polyneuropathy. Baseline odds were evaluated using logistic regression and cause-specific Cox regression were used to estimate the standardized 1-year risks. Models were adjusted for sex and age and stratified by UACR (<30, 30–299, ≥300 mg/g; normo-, micro-, and macroalbuminuria).

RESULTS

A total of 30,310 individuals were included (median age 73.5 years [SD 9.4], 58.5% male, median eGFR 53 ml/min/1.73 m^2 [IQR 47–56], 6.7% with type 1 diabetes), see Table 1. Normo-, micro-, and macroalbuminuria were present in 52.8%, 34.4%, and 12.8%, respectively. Odds ratios for baseline microvascular complications (normoalbuminuria as reference) were 1.27 (95% CI) and 2.27 (95% CI) for retinopathy and 1.42 (95% CI) and 1.93 (95% CI) for neuropathy in patient with micro- and macroalbuminuria, respectively. Across strata of UACR, standardized 1-year risks were 0.6% (95% CI), 0.8% (95% CI), and 1.4% (95% CI) for retinopathy, 0.4% (95% CI), 0.7% (95% CI), and 2.7% (95% CI) for CKD progression; and 2.9% (95% CI), 3.9% (95% CI), and 5.0% (95% CI) for polyneuropathy.

CONCLUSION

In individuals with incident CKD and diabetes, higher UACR levels were consistently associated with both greater baseline burden and higher 1-year risk of microvascular complications.

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Table 1

	Normoalbuminuria (UACR <30 mg/g) N=16.006	**Microalbuminuria** (UACR 30-299 mg/g) N=10.426	**Macroalbuminuria** (UACR ≥300 mg/g) N=3.878	**Total** N=30.310
Female sex n (%)	7.589 (47.4)	3.865 (37.1)	1.128 (29.1)	12.582 (41.5)
Age, years mean (SD)	74.1 (8.5)	74.4 (9.1)	68.6 (12.1)	73.5 (9.4)
eGFR, ml/min/1.73 m² median [IQR]	53 [48, 57]	52 [46, 56]	51 [44, 55]	53 [47, 56]
HbA1c value (mmol/mol)* median [IQR]	51 [45, 58]	53 [46, 62]	56 [48, 68]	52 [46, 61]
Type 1 DM n (%)	2.019 (12.6)	1.801 (17.3)	1.174 (30.3)	4.994 (16.5)
Comorbidities n (%)				
Ischemic heart disease	3.042 (19.0)	2.131 (20.4)	745 (19.2)	5.918 (19.5)
Stroke	826 (5.2)	619 (5.9)	307 (7.9)	1.752 (5.8)
Peripheral artery disease	731 (4.6)	660 (6.3)	314 (8.1)	1.705 (5.6)
Heart failure	2.061 (12.9)	1.504 (14.4)	470 (12.1)	4.035 (13.3)
Hypertension	13.295 (83.1)	8.883 (85.2)	3.433 (88.5)	25.611 (84.5)

Abbreviations: DM, diabetes mellitus; eGFR, estimated glomerular filtrations rate; UACR, urine albumin-creatinine ratio

Missing values: HbA1c: 42

Definitions:

- Type 1 DM: ICD-10 code E10 + antidiabetic monotherapy with insulin
- Ischemic heart disease: ICD-10 code I20, I21, I23-25
- Stroke: ICD-10 code I63-64
- Peripheral artery disease: ICD-10 code I739
- Heart failure: ICD-10 code I50
- Hypertension: prescription redemption for ≥2 antihypertensive agents