DIABESITY

WORKING GROUP

RENAL DISEASE
IN OBESITY AND DIABETES
ADVANCES IN PATHOGENESIS AND THERAPEUTICS

CME course of DIABESITY
LISBON,
NOVEMBER 24 and 25
2017

EUROPEAN RENAL ASSOCIATION · EUROPEAN DIALYSIS AND TRANSPLANT ASSOCIATION
ERA EDTA

PROGRAMME

November 24

8.30 Welcome-Introduction. *Ivo Laranjinha, Portugal*

LECTURE "Kidney Disease in Diabetes and Obesity: Common pathways ... similar treatments?"
Piero Ruggenenti, Bergamo.
Chair: Ivo Laranjinha, Portugal; Esteban Porrini, Tenerife.

Lipotoxicity, inflammation and insulin resistance
9.10 Renal lipotoxicity in diabetes and obesity. *Gema Medina, Madrid.*
9.40 Inflammation in renal disease in Diabetes. *Juan Navarro, Tenerife.*

Discussion.

10.15 Coffee Break

Lessons from experimental models
Chair: Antonio Bulnes, Madrid
10.45 Animal models of renal disease in obesity and diabetes. *Antonio Bulnes, Madrid*
11.15 New insights in the pathogenesis of Renal Disease in Experimental Diabetes.
Josep Cruzado, Barcelona.

Discussion.

12.00 Lunch

Hyperfiltration in renal disease.
Chair: Enrique Morales, Madrid
14.00 Glomerular Hyperfiltration: Pathogenesis and Consequences.
Avry Chagnac, Israel
14.30 The ENBiBA project: Renal histology in patients with T2DM, metabolic syndrome and obesity.
Esteban Porrini, Tenerife
15.00 Metabolic Syndrome, obesity and beta-cell dysfunction.
Andraž Stožer, Slovenia.

Discussion

15.30 Coffee break

16.00 ABSTRACT SESSION (oral). *Chair: Mads Hornum, Denmark).*
1 / "Comparison of a marker of kidney disease progression between two animal models of pre-diabetes" *Clara Dias et al, Portugal.*
2 / "CB1 receptor modulates renal proximal tubule GLUT2 expression and dynamics" *Liad Hinden et al, Israel.*
3 / Moderate salt restriction with or without paricalcitol in overweight/obese and hypertensive patients with T2DM and losartan-resistant macroalbuminuria: The PROCEED randomized, placebo-controlled trial. *Matias Trillini et al, Italy.*
4 / Diabetes and Cardiovascular disease in Chronic Kidney Disease stage I-V in a cohort study. *Rie Louise Dyhr, Denmark*
5 / The Iberian Pig Fed with High Fat Diet: A Model of Obesity-Related Glomerulopathy and Diabetoid Changes. *Rosa Rodriguez-Rodriguez, Spain.*
6 / Chronic Kidney Disease Classification: is the correct method to define renal damage or is it just an illusion? *F. Trevisani, Italy*

17.30 Coffee break and Poster Presentation

PROGRAMME

November 25

9.00 **LECTURE "Kidney pancreas transplantation - the solution?"**
(Anibal Ferreira -Lisboa) (chair: Ivo Laranjinha, Esteban Porrini)

The impact of weight reduction in renal disease.
Chair: F Trevisani, Milan

9.30 Weight reduction to prevent renal disease in diabetes? CRESO I and II
Piero Ruggenenti, Bergamo

10.00 Bariatric surgery to prevent renal disease? *Enrique Morales, Madrid*

10.30 Childhood obesity and its impacts on the kidney.
Liane Correia-Costa (Porto, Portugal)

Discussion

11.00 Coffee break

Treatment of Renal Disease in Diabetes
Chairman: Piero Ruggenenti

11.30 Dual RAS blockade in renal disease in diabetes and obesity. (Frederik Persson-Denmark)

12.00 SGLT2 for renoprotection in T2DM? (Christoph Wanner –Germany)

12.30 Diabetic nephropathy - role of incretin based medication?" Mads Hornum (Denmark)

13.00 The future: Experimental treatments for renal disease in diabetes (Luigi Gnudi, UK)
Discussion.
Concluding remarks: Piero Ruggenenti

13.30 Lunch

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ABSTRACTS

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CB_1 RECEPTOR MODULATES RENAL PROXIMAL TUBULE GLUT2 EXPRESSION AND DYNAMICS

Liad Hinden[1], Shiran Udi[1], Adi Drori[1], Asaad Gammal[1], Alina Nemirovski[1], Rivka Hadar[1], Saja Baraghithy[1], Anna Permyakova[1], Matan Geron[2], Merav Cohen[3,4], Sabina Tsytkin-Kirschenzweig[3,4], Yael Riahi[5], Gil Leibowitz[5], Yaakov Nahmias[3,4], Avi Priel[2], and Joseph Tam[1].

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Background and aims: Overactivation of the renal endocannabinoid system via the cannabinoid-1 receptor (CB_1R) is well known to enhance the development of diabetic nephropathy (DN). In fact, its activation increases proteinuria, inflammation, and renal dysfunction by affecting several compartments in the kidney. Chronic treatment with globally acting CB_1R antagonists has been shown to improve renal function in different murine models for diabetes. However, their clinical use is halted due to centrally-mediated neuropsychiatric side effects. Recently, the development of peripherally restricted CB_1R antagonists have revised the clinical potential of CB_1R blockade for the treatment of DN.

Similarly to CB_1R, the expression of the facilitative glucose transporter GLUT2, localized in the renal proximal tubule cells (RPTCs), is also upregulated during diabetic conditions. Moreover, it is recruited to the apical/brush border membrane (BBM) of the RPTCs to increase glucose reabsorption. This, in turn, may contribute to renal injury, inflammation, and tubulointerstitial fibrosis.

Here, we investigated the link between CB_1R and GLUT2 in the development of DN, and examined the therapeutic efficacy of peripherally restricted CB_1R blockade on diabetes-induced renal injury, inflammation and fibrosis.

Materials and methods: The therapeutic potential of peripheral CB_1R blockade was assessed in two animal models for type-1 DN (streptozotocin (STZ)-induced diabetes, and Akita mice) treated with JD5037 (3 mg/kg, po). The specific role of CB_1R in RPTCs was deciphered in a novel mouse strain that lacks CB_1R in these cells. Primary human RPTCs, and MDCK II cells expressing a

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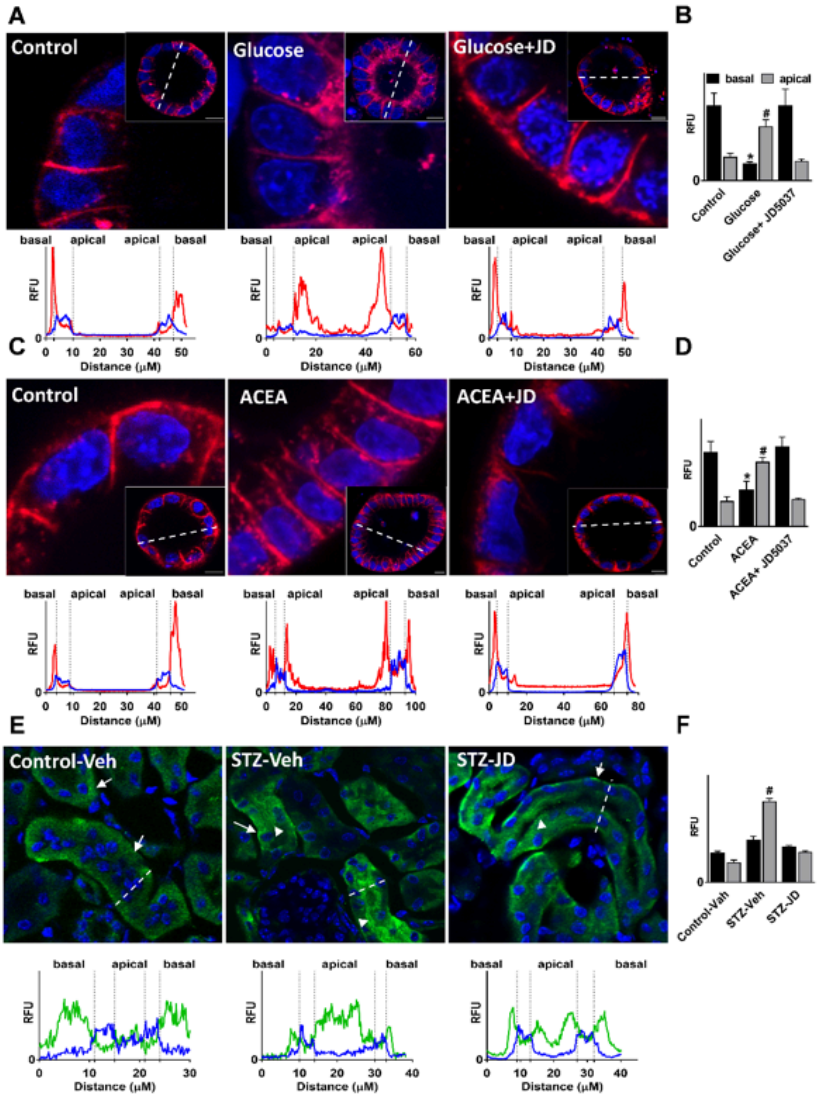
C-terminal GLUT2–mCherry fusion protein were used to delineate the underlying molecular linking CB_1R and GLUT2.

Results: The diabetes-induced structural and functional changes in the kidney, together with increased inflammation and fibrosis were completely attenuated by a selective blockade of CB_1Rs in periphery in both diabetic mouse strains. These effects were associated with a significant reduction in GLUT2 expression in the RPTC's BBM. Moreover, genetic inactivation of CB_1R in RPTCs attenuated the development of DN in mice, and reduced glucose transport across the RPTCs. Furthermore, CB_1R antagonism ameliorated the high-glucose- or CB_1R-induced translocation of GLUT2 to the BBM in RPTCs. These effects were linked to decreased Ca2+ influx and downregulation of PKC-β1 expression in RPTCs.



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Conclusion: Altogether, targeting peripheral CB_1R or inhibiting GLUT2 dynamics in RPTCs has the potential to ameliorate DN. These findings may support the rationale for clinical testing of peripherally restricted CB_1R antagonists or pre-clinical developing novel renal-specific GLUT2 inhibitors for the treatment of DN.

CB_1R regulates the basal-to-apical translocation of GLUT2 in RPTCs. Fluorescent images of MDCK II cell cysts, expressing GLUT2–mCherry fusion protein and cultured in Matrigel®, show that both high-glucose levels (75 mM) (A, B) and CB_1R stimulation by ACEA (10 μM) (C, D) induced basal-to-apical translocation of GLUT2, which were inhibited by pre-exposing the cysts to JD5037 (100nM). Scale bar, 20 μm. Data represent the mean±SEM from 5-10 cells in each cyst, 3-4 cysts per treatment. Fluorescent images of kidney sections from high-STZ (185 mg/kg, ip)-induced diabetic mice treated with JD5037 (3 mg/kg, po) or Veh, in comparison with their Veh-treated non-diabetic controls indicate that hyperglycemia induced the apical translocation of GLUT2, which was inhibited by JD5037 treatment (E, F). ACEA- arachidonyl-2'-chloroethylamide (CB_1R agonist), JD5037- peripherally restricted CB_1R antagonist. Data represent the mean±SEM from 8-10 tubules per treatment. *P<0.05 relative to the corresponding basal group from all treatments, #P<0.05 relative to the corresponding apical group from all treatments. Legend: Arrow- BLM, arrow head- BBM.

Adopted from Hinden et al., J AM Soc Nephrol, 2017, in press.

Acknowledgments: Funded by the ERC-2015-StG grant (#676841) to Joseph Tam.

THE IBERIAN PIG FED WITH HIGH FAT DIET: A MODEL OF OBESITY-RELATED GLOMERULOPATHY AND DIABETOID CHANGES

Rosa Rodríguez[1], Consolación García-Contreras[2], Marta Vázquez-Gómez[3], Laura Torres-Rovira[2], José Luis Pesantez[2], M. Victoria Sanz-Fernández[2], Jorge González[4], Beatriz Isabel[3], Susana Astiz[2], Sergio Luis Lima[1], Antonio González-Bulnes[2,3] and Esteban Porrini[1].

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Introduction: Obesity, particularly in the context of metabolic syndrome is a risk factor for chronic kidney disease (CKD). Obese patients may develop obesity-related glomerulopathy (ORG) which is characterized by focal and segmental glomerulosclerosis and/or glomerulomegaly. Importantly, about 50% of individuals with ORG may also have "diabetoid changes" in the kidney, even without clinical evidence of diabetes. However, the pathogenesis of ORG is still poorly understood, in spite of a plethora of interventional studies in rodent models. The fact is that rodent models do not completely resemble ORG features, which may be due to pivotal differences in renal anatomy and function. In this sense, large animals (specifically swine) show structure, function and physiology of the kidney more similar to humans. Concomitantly, swine is the most amenable large animal model for the study of obesity-related pathologies, with some breeds, like the Iberian pig, showing a background of insulin resistance.

Material and methods: We evaluated the suitability of the Iberian pig for the study of obesity-related renal disorders. Twenty-eight Iberian sows were fed with either a standard diet fulfilling their maintenance requirements (group CON: n=17; 2.5kg/animal/day with 2.8% of polyunsaturated fat) or an obesogenic diet (group OB; n=11; 4-5kg/animal/day with 6.8% of saturated fat) for 100 days. In the group OB, changes in body-weight and subcutaneous fat-depth were measured every 15 days whilst no obesity-related changes were expected in the group CON and, following ethic principles of animal welfare, samplings were only performed at Day 0 and 100. In both groups, changes in glucose and lipids metabolism were evaluated at Days 0 and 100 and, concomitantly, oral glucose tolerance tests (OGTTs) were performed at Days 0 and 90. At Day 95, glomerular filtration rate (GFR) was measured in a subgroup of animals (xx in the group and xx in the group CON) by evaluating plasma

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clearance of iohexol after intravenous injection of 10 ml of Omnipaque. At the end of the study, all the animals were euthanized and the macroscopic appearance of the kidneys was assessed. Immediately, one portion of renal tissue was collected in 2-mL cryotubes and biobanked at -80˚C for assessment of fatty acids, whereas another was fixed in 10% neutral-buffered-formalin for its histological study.

Results: All the animals in the OB group almost doubled their body-weight and tripled their subcutaneous fat-depth, whilst the values in the group CON remained stable. The macroscopic findings during necropsy indicated a severe intra-abdominal fattening in obese sows, with large amounts of mesenteric fat covering all viscerae and mesenteric tissues. The total fat content inside the renal tissue was higher in the obese group than in the controls (15.4±0.5 vs. 12.7±0.7%; P<0.01).

The groups OB and CON showed similar values for lipids and glucose metabolism at the beginning of the study, which remained stable in the group CON. Conversely, in the OB group, triglycerides and cholesterol (P<0.05) and LDL-c (P<0.01) but not HDL-c, increased compared with animals in the CON group; hence, total cholesterol/HDL-c and LDL-c/HDL-c increased with time (P<0.05). Similarly, HOMA-IR increased in the group OB throughout the study (P<0.05); evidencing insulin resistance.

Renal histology: the number of glomeruli was high (~90) and comparable between groups. Very few glomeruli (<2%) were sclerotic (Table 3) and in ~50% of the animals in each group, no diffuse sclerosis was observed. However, the percentage of glomeruli with nodular glomerular sclerosis was significantly higher in the group OB than in the group CON [7.4% ± 7.75 vs 2.4% ± 4.70, respectively (Table 1)]. In addition, the percentage of glomeruli with mesangial expansion was more prominent in the OB group: 24.33% ± 6.5 vs 15.10% ± 6.0 in the CON group; Table 1; figure 1). Tubular atrophy, interstitial fibrosis and inflammation were mild and similar between groups. Finally, no changes in arteriolar hyalinosis or fibrointimal thickening were observed.

Lipids: There were scarce significant differences at the neutral fraction of fat (triglycerides acting as energy depot), but there were major effects at the polar lipid fraction (constitutive of cell membranes). These changes mainly constituted an increase in the content of monounsaturated fatty acids (MUFA; P<0.005) and a decrease in saturated (SFA) and polyunsaturated (PUFA) fatty acids (P<0.005 and P<0.05, respectively), with increase in the ratios of MUFA/SFA and C18:1/C18:0 (i.e.: increase in desaturation index and SCD1 activity; P<0.005 and P<0.0005, respectively), which are indicative of alterations in lipogenesis and insulin regulation and lipotoxicity.

At the end of follow-up, measured GFR was higher in animals fed with obesogenic diet compared with animals on standard diet.

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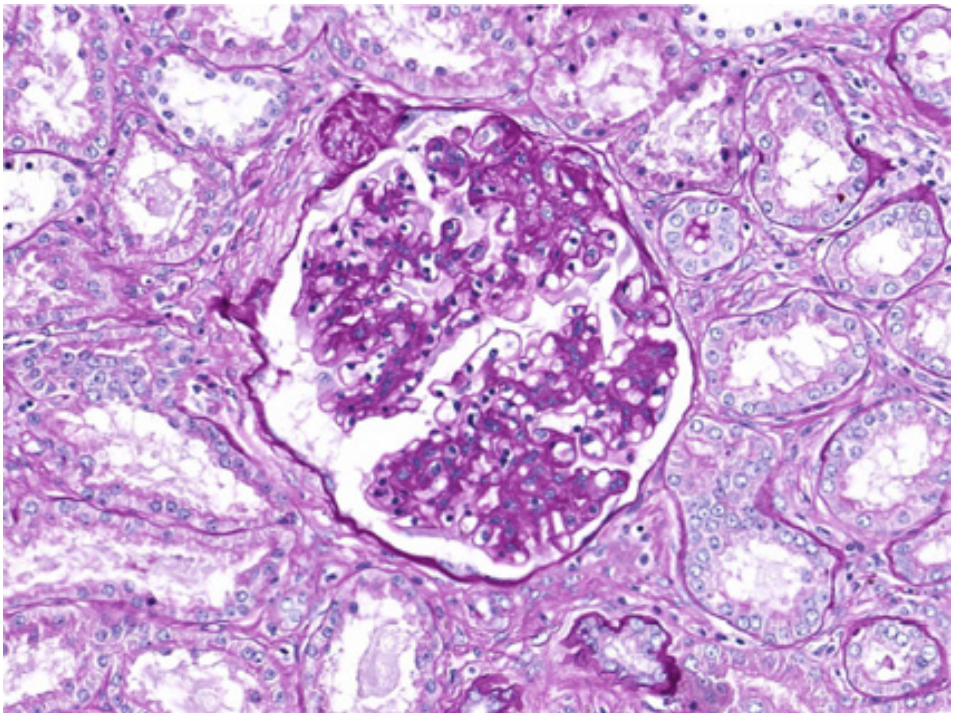
	Standard Diet	High Fat Diet	P
N	17	11	
Glomeruli			
Number	96 ±31	91 ± 22	0.61
N of glomeruli with diffuse sclerosis	1.6 ± 4	1± 1	0.98
% of glomeruli with diffuse sclerosis	1.94 ± 5.6	0.87 ± 1.15	
Animals without diffuse sclerosis (%)	9 (53)	5 (50)	
N of glomeruli with nodular sclerosis	2 ± 4	6 ± 5.5	0.025
% of glomeruli with nodular sclerosis	2.4 ± 4.70	7.4 ± 7.75	0.020
N of glomeruli with mesangial expansion	13.20 ± 4.0	21.40 ± 4.6	<0.0001
% of glomeruli with mesangial expansion	15.10 ± 6.0	24.33 ± 6.5	0.001
Tubuli			
Tubular Atrophy (%)	2 [2-2.5]	2 [2-2]	0.78
Interstitial Fibrosis (%)	2 [1-5]	2 [2-5]	0.55
Interstitial Inflammation (%)	2 [2-2]	2 [2-2]	0.82
Vascular			
Arteriolar hyalinosis	0	1	0.19
Fibrointimal thickening in vessels	0	3	0.28

Figure 1: Glomeruli of a pig fed with high fat diet, mesangial expansion and areas of focal and segmental sclerosis (PAS?).



MODERATE SALT RESTRICTION WITH OR WITHOUT PARICALCITOL IN OVERWEIGHT/ OBESE AND HYPERTENSIVE PATIENTS WITH T2DM AND LOSARTAN-RESISTANT MACROALBUMINURIA: THE PROCEED RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Matias Trillini[1], Aneliya Parvanova[1], Manuel A Podestà1[2], Ilian Petrov Iliev[1], Barbara Ruggiero[1], Manuela Abbate[1], Annalisa Perna[1], Francesco Peraro[1], Olimpia Diadei[1], Nadia Rubis[1], Flavio Gaspari[1], Fabiola Carrara[1], Nadia Stucchi[1], Antonio Belviso[4], Antonio C Bossi[5], Roberto Trevisan[6], Giuseppe Remuzzi1,[2,3,] Martin de Borst[7], Piero Ruggenenti[1,2], on behalf of the PROCEED Study Organization and the Scientific Writing Academy (SWA) 2016.

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Background: Albuminuria is an early marker and major determinant of progression of the diabetic kidney disease1 and has become an important treatment target for nephroprotection and cardioprotection in patients with diabetes2. The angiotensin receptor blocker (ARB) losartan is standard therapy for hypertensive type 2 diabetes mellitus (T2DM) patients with macroalbuminuria3 and its effects are strengthened by salt restriction4. Paricalcitol, a vitamin D receptor activator, reduced albuminuria in experimental diabetes and in patients with type 1 diabetes5,6. The VITAL trial7 found that 2 µg per day of paricalcitol significantly reduced albuminuria versus placebo in T2DM patients with micro- and macroalbuminuria despite losartan. Post-hoc analyses found that this effect was almost fully driven by 29 patients with natriuresis exceeding 178 mEq per day (equivalent to a daily salt intake exceeding approximately 4.5 g), whereas no treatment effect was observed in patients with sodium excretion lower than this level.

Aim: We aimed to assess the albuminuria-lowering effects of salt restriction or paricalcitol therapy (or both) in hypertensive T2DM patients with macroalbuminuria.

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Methods: In this randomised, double-blind, placebo-controlled, crossover trial, we recruited hypertensive T2DM adults with albuminuria >300 mg/24h despite 100 mg/day losartan therapy and stable renal function with a serum creatinine concentration of less than 2 mg/dL. We randomized patients to an open label 3 month high-sodium (>200 mEq [4·8 g] per day) or low-sodium (<100 mEq [2·4 g] per day) diet and, within each diet group, to a 1 month double-blind treatment period of oral paricalcitol (2 μg per day) or placebo, followed by 1 month of placebo washout and then a further 1 month double-blind treatment period of paricalcitol or placebo in which patients crossed over to the opposite group. The primary outcome was 24 h albuminuria (median of three consecutive measurements). All analyses were modified intention-to-treat. Outcome assessors were masked to diet group, and patients and investigators were masked to paricalcitol or placebo. This study is registered with ClinicalTrials.gov, number NCT01393808, and the European Union Clinical Trials Register, number 2011-001713-14.

Results: Patient characteristics at baseline were similar between diet groups and treatment sequences. All patients were overweight or frankly obese and their mean (SD) BMI was 30.8 ± 4.8 Kg/m2. Daily sodium intake with diet averaged 190.4 [152.3 to 227.0] mEq, equivalent to 11 grams of salt. In the low sodium diet group sodium intake decreased from 202 [159 to 227] mEq to 166 [130 to 198] mEq at three month, by an average of 30.8 [1 to 65] mEq, equivalent to 1.8 grams of salt per day. Sodium intake did not significantly change in the high sodium diet group. Salt restriction decreased 24 h albuminuria by 36.6% (95% CI 28.5–44.9) from 724 mg (441–1233) at baseline to 481 mg (289–837) at month 3 (p<0.0001), but no significant difference occurred when salt was not restricted (from 730 mg [416–1227] to 801 mg [441–1365]; 2.9% [–16.8 to 16.4] increase; p=0.50). Changes between diet groups differed by 32.4% (17.2–48.8; p<0.0001) and correlated with changes in natriuresis (r= 0.43, p<0.0001). On the high-sodium diet, paricalcitol reduced the salt-induced albuminuria increase by 17.8% (3.9–32.3) versus placebo (p=0.02), whereas on the low-sodium diet, paricalcitol did not have a significant effect versus placebo (increase of 4·1% [–9·3 to 21·6]; p=0·59. During placebo treatment, albuminuria decreased with the low-sodium diet (p=0.0002) and did no significantly change with the high-sodium diet, but changes were significantly different between diet groups (p<0·0004). During paricalcitol therapy there were 14 cases of hypercalciuria, six of hypercalcemia and five of hyperphosphatemia that were possibly treatment-related. However, treatment was well tolerated and no patients withdrew from the study because of treatment-related effects. One stroke and one coronary event occurred during paricalcitol therapy.

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Table 1. Changes in 24 urinary albumin excretion according to sodium diet and treatment group.

	Pre (mg/24h) Median [IQR]	Post (mg/24h) Median [IQR]	Absolute change (mg/24h) Median (95% CI)	P	% change Median (95% CI)	P
Low/high sodium diet						
Baseline to mo.1						
· Low	724 [441, 1233]	519 [325, 1080]	-144.0 (-217.4, -102.2)	<.0001	-31.5% (-37.6%, -15.7%)	<.0001
· High	730 [416, 1227]	672 [403, 1290]	-49.0 (-201.6, 21.6)	0.3839	-10.0% (-20.9%, 3.2%)	0.5347
· Low vs. High	·	·	121.0 (1.4, 259.2)	0.0484	19.6 (6.7, 34.3)	0.0051
Baseline to mo.2						
· Low	724 [441, 1233]	626 [292, 1127]	-106.6 (-181.4, -69.1)	0.0002	-19.4% (-27.4%, -11.6%)	<.0001
· High	730 [416, 1227]	783 [468, 1295]	-13.0 (-115.2, 116.6)	0.8460	-0.7% (-17.9%, 23.9%)	0.4118
· Low vs. High	·	·	152.6 (18.0, 279.4)	0.0234	21.3 (6.2, 38.7)	0.0056
Baseline to mo.3						
· Low	724 [441, 1233]	481 [289, 837]	-237.6 (-385.9, -151.2)	<.0001	-36.6% (-44.9%, -28.5%)	<.0001
· High	730 [416, 1227]	801 [441, 1365]	20.2 (-128.2, 93.6)	0.6343	2.9% (-16.8%, 16.4%)	0.4762
· Low vs. High	·	·	288.0 (138.2, 463.7)	0.0005	32.4 (17.2, 48.8)	<.0001
Paricalcitol/Placebo						
Overall						
· Paricalcitol	711 [413, 1225]	589 [338, 1077]	-108.0 (-145.4, -63.4)	<.0001	-16.5% (-26.9%, -9.2%)	0.0018
· Placebo	760 [415, 1227]	667 [364, 1243]	-40.3 (-97.9, 10.1)	0.1150	-4.9% (-14.9%, 3.0%)	0.2692
· Paricalcitol vs. Placebo	·	·	74.9 (15.8, 125.3)	0.0899	12.5 (3.0, 20.3)	0.0380
Low Sodium						
· Paricalcitol	689 [356, 1225]	540 [289, 981]	-108.0 (-145.4, -60.5)	0.0005	-17.7% (-34.2%, -4.4%)	0.0055
· Placebo	724 [415, 1198]	481 [315, 1084]	-102.2 (-198.7, 46.1)	0.0010	-20.1% (-31.7%, -4.5%)	0.0002
· Paricalcitol vs. Placebo	·	·	33.1 (-56.2, 128.2)	0.5493	4.1 (-9.3, 21.6)	0.5910
High Sodium						
· Paricalcitol	750 [505, 1316]	651 [403, 1120]	-108.0 (-201.6, -41.8)	0.0490	-14.7% (-23.9%, -4.7%)	0.0975
· Placebo	789 [408, 1287]	831 [487, 1365]	23.0 (-66.2, 66.2)	0.4284	3.7% (-9.0%, 12.7%)	0.0978
· Paricalcitol vs. Placebo	·	·	108.0 (24.5, 273.6)	0.0859	17.8 (3.9, 32.3)	0.0228

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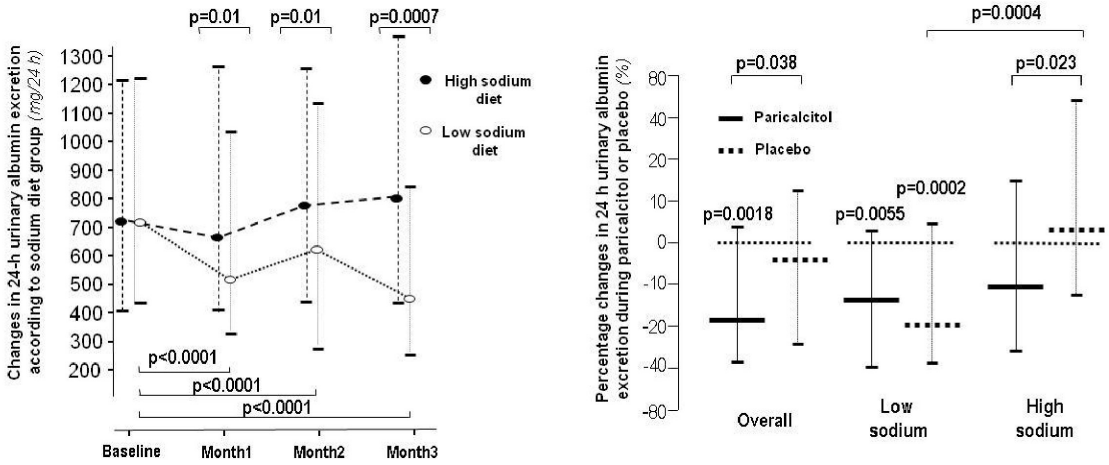

Conclusions: In hypertensive patients with macroalbuminuria and T2DM, moderate salt restriction enhances the antialbuminuric effect of losartan, an effect that could be nephroprotective and cardioprotective in the long-term. The finding that paricalcitol prevents a sodium-induced increase in albuminuria provides background for trials to test the long-term risk-benefit profile of paricalcitol add-on therapy in patients with type 2 diabetes and macroalbuminuria refractory to even moderate salt restriction.

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COMPARISON OF A MARKER OF KIDNEY DISEASE PROGRESSION BETWEEN TWO ANIMAL MODELS OF PRE-DIABETES

C.G. Dias[1], N.R. Coelho[1], M.J. Correia[1], M.J. Meneses[1], I. Sousa-Lima[1], M.P. Macedo[1,2,3], E.C. Monteiro[1], S.A. Pereira[1].

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Endogenous electrophilic toxic compounds are mainly detoxified through the mercapturate pathway which happens mostly in kidney tubular cells (1). This detoxification pathway begins with the conjugation of these toxic metabolites with glutathione. The end-products of this pathway are mercapturates generated upon cysteine-S-conjugates acetylation by N-acetyltransferase 8 (NAT8) activity (1). This enzyme has been described as a protector factor for kidney function (2). Recently we have described the mercapturate of cysteine-S-disulfides as a marker of kidney disease progression in HIV-infected patients (3). Both HIV-infection and diabetes mellitus share a decreased availability of glutathione, which might impact the mercapturate pathway (4-6).

We investigated the temporal variation of mercapturates of cysteine-S-disulfides in urine (uNAC) using two animal models of pre-diabetes, namely hyper-caloric (HFat) and high fructose (HFruct) diets.

Male C57BL/6 mice (6 weeks of age, n=6 per group) were exposed to three different types of diets. The mice were given ad libitum access to a normal (Chow), HFat or HFruct, for 15 weeks. Urine samples were collected at 0, 1, 2, 4, 8 and 15 weeks of diet. uNAC was used as a urinary surrogate of mercapturates of cysteine-S-disulfides and was quantified by HPLC with fluorescence detection (3). uNAC was normalized by total body weight and % of baseline values, presented as the ratio of HFat or HFruct diet by Chow diet.

At 15 weeks of diet, the HFat group had an increase in weight compared with Chow diet (One-way ANOVA with Dunnett's multiple comparison test, $p<0.001$) (Table 1). Absolute weight values of both kidneys were higher in HFat diet (One-way ANOVA with Dunnett's multiple comparison test, $p<0.001$) **(Table 1)**. During the first two weeks, uNAC levels from HFat and HFruct groups were similar to Chow diet **(Figure 1)**. However, by the fourth week of diet, there was a decrease in 60% in uNAC levels in both diets (One-way ANOVA with

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Dunnett's multiple comparison test, p<0.001 versus week 1). This tendency was maintained until the end of study time for HFat group. At 15 weeks of diet, HFat group had lower uNAC levels than HFruct group (Two-way ANOVA with Bonferroni post-test, p<0.001).

Both models of pre-diabetes show an impairment in the mercapturate pathway. This effect is evident right after 4 weeks of diet, is maintained with the chronicity of diet exposure and might be more pronounced in the model associated with body weight gain. Together, these preliminary results indicate the participation of the mercapturate pathway in the mechanism of diabetic nephropathy.

Table 1 – **Total body weight and kidney weights at the end of the study.**

	Chow	HFat	HFruct
Total body weight (g)	25.56 ± 1.39	44.52 ± 5.87***	25.89 ± 1.60
Left kidney weight (g)	0.12 ± 0.01	0.17 ± 0.02***	0.13 ± 0.01
Right kidney weight (g)	0.13 ± 0.01	0.19 ± 0.02***	0.14 ± 0.02
Left kidney weight (g/100 g body weight)	0.48 ± 0.04	0.39 ± 0.04***	0.48 ± 0.05
Right kidney weight (g/100 g body weight)	0.51 ± 0.04	0.42 ± 0.02***	0.53 ± 0.05

Data presented as Mean ± Standard Deviation; * One-way ANOVA with Dunnett's multiple comparison test

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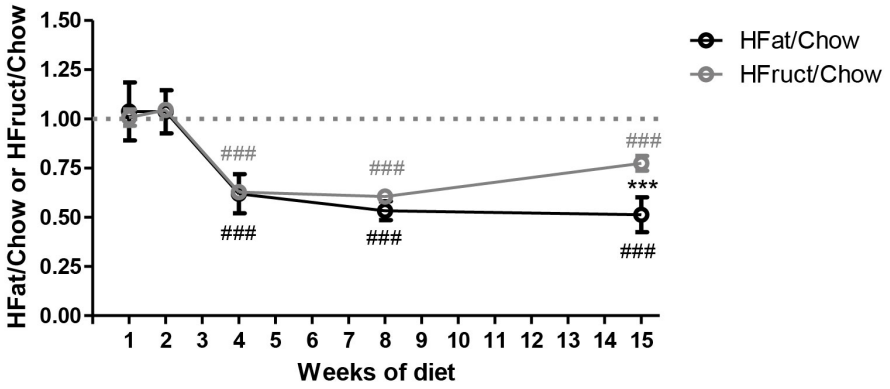

Figure 1 – Temporal uNAC variation. uNAC levels decreased throughout time in both HFat (⊖) and HFruct (⊖) diets. At 15 weeks of diet, HFat group had lower levels of uNAC in comparison with HFruct group)
(uNAC levels were normalized by body weight and % of week 0 values; Data is presented as the ratio of HFat or HFruct by Chow conditions; # One-way ANOVA with Dunnett's Multiple Comparison test, $p<0.001$, vs week 1; * Two-way ANOVA with Bonferroni post-test, $p<0.001$).

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DIABETES AND CARDIOVASCULAR DISEASE IN THE COPENHAGEN CHRONIC KIDNEY DISEASE COHORT

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Abstract

Background: Diabetes and chronic kidney disease (CKD) are two major public health problems. Both have independently been associated with an elevated risk of cardiovascular events and cardiovascular mortality. We investigated the prevalence of cardiovascular disease (CVD) in patients with CKD stage 1 to 5 nd (not on dialysis) without diabetes, pre-diabetes, known- and unknown type 2 diabetes mellitus (T2DM). Furthermore, we investigated the association between CVD and known CVD risk factors such as hypertension, dyslipidaemia and obesity.

Methods: A total of 496 nd, non-transplanted CKD patients were included in the study. Participation comprised an interview and a medical examination at the clinic together with fasting blood samples and a 24-hour urine sample. The diagnosis of T2DM was based on hospital records and/or prescription of antidiabetics. Unknown T2DM and prediabetes was defined as lack of the above-mentioned factors together with a fasting plasma glucose level ≥7 mmol/L or 6.0-6.9 mmol/L, respectively. CVD history, diabetes and medication was assessed from electronic patient journals and from an electronic prescription system.

Results: Approx. one third of the entire cohort had a history of CVD. Age was associated with CVD, OR 1.07 (95% CI: 1.05-1.09), in both univariate and multivariate logistic regression analyses. Female sex was negatively associated with CVD, OR 0.63 (95% CI: 0.40-0.99). The prevalence of CVD was significantly higher ($p<0.001$) in patients with CKD stage 4-5 compared with CKD stage 1-2. Among the 496 subjects, 78 (15.7%) had T2DM, 28 (5.7%) had unknown T2DM and 87 (17.5%) had pre-diabetes. The prevalence of CVD was lowest in the group of patients with no-diabetes (23.1%) and highest in the group with known T2DM (51.3%). The OR of CVD in the T2DM group was 1.9 (95% CI: 1.13-3.27). In the group with normal fasting blood glucose and no history of diabetes the OR of CVD was 0.67 (95% CI: 0.44-1.02). The prevalence of CVD in both unknown T2DM and pre-diabetes was 32.1% and 29.9% ($p = 0.54$ and $p = 0.69$) respectively, compared with 23.1% in patients with no diabetes. The mean BMI was significantly higher ($p<0.001$) in the known T2DM group compared with the no-diabetes group. The former also had a significantly lower activity level compared with the no diabetes group. There was no difference

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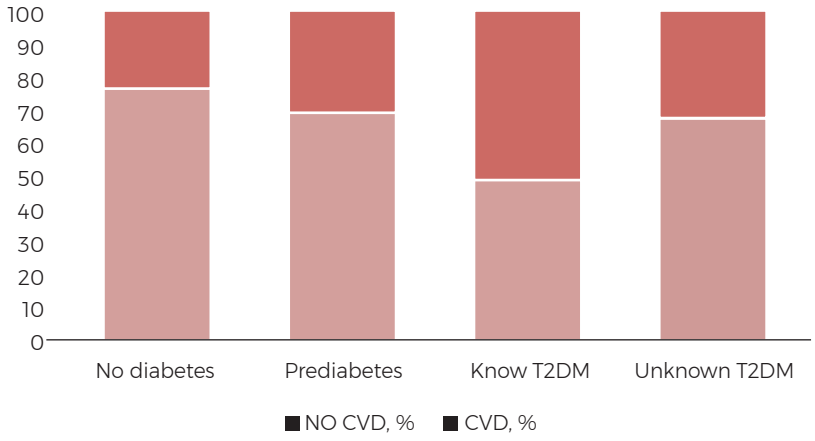
in systolic or diastolic blood pressure between the four groups. Neither did we find any significant difference in LDL- or HDL-levels. Finally, a majority of the patients with known T2DM received antidiabetic treatment (80.1%) and compared with the other groups, a significantly higher amount was treated with statins and antithrombotic agents ($p<0.001$).

Conclusion: In a large CKD population the risk of CVD is associated with age, high CKD-stage (>4) and male sex. After adjusting for these risk factors we found that concomitant T2DM compared to no diabetes more than doubled the risk of CVD. Furthermore, based on fasting blood glucose levels, a considerable amount of the cohort showed to be either pre-diabetic or had unknown T2DM. The prevalence of CVD in these two groups was numerically higher than in the no-diabetes group. Compared with the no-diabetes group, the subjects with known T2DM were significantly more obese and had a significantly more sedentary lifestyle. However, no group had a BMI<25, categorizing the average patient in our cohort as obese. Furthermore, dyslipidaemia was seen in all of the four groups. The known T2DM group received more statins and anticoagulatives when compared with the other groups.
Identifying patients with unknown diabetes or prediabetes may lead to more patients receiving multifactorial intervention in terms of statin and antiplatelet therapy.

Prevalence of CVD



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Cardiovascular disease, cardiovascular risk factors and treatment. N = 496				
	No diabetes N = 303	**Prediabetes N = 87**	**Known T2DM N = 78**	**Unknown T2DM N = 28**
Cardiovascular disease Lipids	70 (23.1%)	26 (29.9%)	40 (51.3%)*	9 (32.1%)
Total cholesterol, mmol/L	5.4 [1.1]	5.2 [1.4]	4.3 [1.0]	5.3 [1.4]
HDL-cholesterol, mmol/L	1.6 [0.6]	1.5 [0.6]	1.2 [0.4]	1.5 [0.7]
LDL-cholesterol, mmol/L	3.3 [1.0]	3.2 [1.1]	2.3 [0.8]	3.2 [1.2]
Triglycerid, mmol/L	1.6 [1.0]	1.7 [0.8]	2.3 [1.7]*	2.0 [0.9]
Systolic blood pressure	132 [17]	134 [18]	135 [18]	134 [11]
Diastolic blood pressure	83 [11]	83 [12]	76 [11]	84 [10]
Receiving antidiabetics	·	·	63 (80.8%)	·
Only oral treatment	·	·	26 (33.3%)	·
Only insulin treatment	·	·	22 (28.2%)	·
Both tablet and insulin	·	·	15 (19.2%)	·
Receiving statins	83 (27.4%)	38 (43.7%)*	67 (85.9%)*	11 (39.3%)
Receiving antihypertensiva	229 (75.6%)	74 (85.1%)	71 (91.0%)*	22 (78.6%)
Receiving anticoagulatives	48 (15.8%)	23 (26.4%)	44 (56.4%)*	6 (21.4%)
BMI, kg/m2	26.5 [4.3]	29.5 [5.7]*	32.6 [6.7]*	30.5 [5.4]*
Waist circumference, cm	97 [13]	106 [15]*	113 [16]*	106 [14]*
Smoking				
Previous	124 (40.9%)	36 (46.2%)	36 (41.4%)	18 (64.3%)
Active	53 (17.5%)	12 (15.4%)	19 (21.8%)	4 (14.3%)
Pack years	13.3 [20.4]	18.2 [24.3]	23.7 [28.3]*	14.9 [14.7]
Units of alcohol, weekly	5.5 [8.3]	7.6 [11.1]	5.1 [8.5]	6.1 [8.9]
Physical activity				
Inactive	27 (8.9%)	11 (12.6%)	27 (34.6%)*	4 (14.3%)
Low	59 (19.5%)	26 (29.9%)	23 (29.5%)	3 (10.7%)
Moderate	177 (58.4%)	40 (46.0%)	27 (34.6%)*	19 (67,9 %)
High	40 (13.2%)	10 (11.5%)	1 (1.3%)*	2 (7.1%)

Values are mean [SD] or n (%).
Comparison was made between the No Diabetes group and prediabetes/known T2DM/unknown T2DM.
* = p<0.05
Cardiovascular disease: history of stroke, myocardial infarction, angina pectoris, percutaneous coronary intervention and/or bypass surgery, percutaneous transluminal angioplasty, peripheral bypass surgery, amputations, atrial flutter or fibrillation, deep-vein thrombosis, chronic cardiac failure, cardiac valve disease, pacemaker or endarterectomy.
1 smoking pack year = 20 cigarettes/day in a year
1 standard unit of alcohol = 12g or 15 ml alcohol
Inactive: < 2 hours light physical activity/week
Low activity: 2-4 hours light physical activity/week
Moderate activity: >4 light physical hours/week OR 2-4 hours hard physical activity/week
High activity: >4 hours hard physical activity/week

CHANGES IN RENAL HEMODYNAMICS OF UNDERNOURISHED FETUSES APPEAR EARLIER THAN EVIDENCES OF INTRAUTERINE GROWTH RETARDATION (IUGR)

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Intrauterine growth restriction (IUGR) is the failure of the fetus to reach its genetically established growth rate, mainly due to an inadequate supply of nutrients and oxygen, usually caused by maternal malnutrition and/or placental insufficiency. IUGR is a concerning health issue because of its implications in perinatal mortality and morbidity and its long-term consequences on health and disease risk of the individuals; mainly on neurological, metabolic, immune, cardiovascular and renal features. Hence, there is a strong necessity of preclinical and clinical research since better antenatal surveillance with improved detection methods and biomarkers are essential tools for alleviating long-term effects of IUGR. The present study used a sheep model of IUGR by maternal undernutrition to determine a possible marker of early damage to the fetal kidney. Our hypothesis was based on the "brain-sparing" effect occurring during IUGR processes, which consists of a redistribution of the blood circulation to maximize the supply of oxygen and nutrients to the brain. In consequence, the growth of the brain is increased to the expenses of the growth of other organs, like the kidneys.

The experiment involved 24 multiparous pregnant Sarda ewes. At Day 24 of gestation (around 15% of the total length of ovine pregnancy, estimated in a mean of 150 days), pregnancy diagnosis was performed by transrectal ultrasonography, with a real-time B-mode scanner (Aloka SSD 500, Aloka Co., Tokyo, Japan) fitted with a 7.5 MHz linear-array probe. At once, the ewes were pair matched in two equal groups; all the sheep were fed with the same standard grain-based diet but fulfilling either their daily maintenance requirements for pregnancy (control group; n=12) or only the 50% of such quantity (food-restricted group; n=12). All the fetuses were assessed by ultrasonography at Day 115 of pregnancy (around 75% of the total length of ovine pregnancy), just prior the overt growth arrest which becomes apparent between 120 and 130

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days of pregnancy in case of IUGR. Ultrasonographic scans were performed with a Voluson-i ultrasound machine (GE, Tiefenbach, Austria) equipped with an automatic 2-5MHz 4D convex probe. Measurements included the thoracic diameter (TD), the biparietal diameter (BPD) and the length and volume of the left kidney (KL and KV; Fig. 1). At once, blood flow parameters (resistance index, RI, pulsatility index, PI, and systolic-to-diastolic peak velocity ratio, SD-ratio) from umbilical cord (UA), middle cerebral (MCA) and renal arteries (RA) were determined in all the fetuses. Assessment of brain-sparing was performed by determining the cerebro-umbilical ratios (i.e. the ratios between MCA and UA values) for RI, PI and SD-ratio.

The results showed that both biparietal and thoracic diameters of the fetuses at Day 115 of gestation were numerically larger in control than in food-restricted pregnancies, but differences did not reach statistical significance. The same was found for the length and volume of the kidneys although assessment of fetal hemodynamics (Table 1) at the umbilical cord artery (UA) showed that maternal food-restriction was related to a higher systolic-to-diastolic ratio (SD-ratio: 3.37±0.09 vs 2.86±0.20 in the control group; $P<0.05$), without effects on indexes of resistance (RI) and pulsatility (PI). There were no effects when evaluating these parameters at the middle cerebral artery (MCA) or when evaluating the cerebro-umbilical (MCA/UA) ratios. The assessment of the kidney showed that maternal food-restriction, despite the lack of significant effects on size of the organ, induced a significant decrease in all the hemodynamic parameters at the renal artery ($P<0.05$ for all) and, in consequence, in the corresponding reno-umbilical ratios (SD-ratio: $P<0.005$; RI: $P<0.05$; PI: $P<0.01$).

In conclusion, fetal blood supply is affected by maternal undernutrition and, even prior to appearance of brain-sparing, there are early changes in the blood supply to the kidneys of underfed fetuses.

Fig. 1. Three-dimensional ultrasound assessment of renal volume in a sheep fetus (left image) and color-Doppler identification (middle image) and assessment of the renal artery waveform in the portion proximal to kidney insertion (right image).

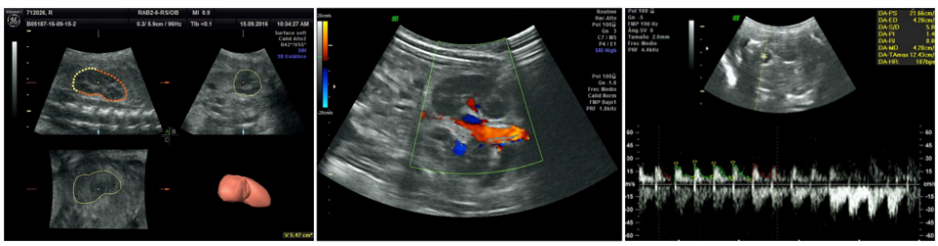

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Table 1. Mean values (± S.E.M.) for fetal hemodynamics assessment [systolic-to-diastolic peak velocity ratio (SD), resistance index (RI) and pulsatility index (PI)] performed at the umbilical cord artery (UA), middle cerebral artery (MCA) and renal artery (RA) of singleton and twin control and food-restricted fetuses at Day 115 of pregnancy.

	CONTROL			FOOD RESTRICTED			P
	SINGLETON	TWINS	P	SINGLETON	TWINS	P	
SD_UA	2.87±0.09			3.38±0.20			0.043
	2.86±0.27	2.87±0.09	0.935	3.75±0.59	3.29±0.22	0.385	
IP_UA	1.05±0.04			1.18±0.06			0.115
	1.02±0.12	1.06±0.03	0.622	1.28±0.19	1.16±0.07	0.503	
IR_UA	0.65±0.01			0.68±0.02			0.154
	0.64±0.03	0.65±0.01	0.703	0.72±0.04	0.67±0.02	0.416	
SD_MCA	2.69±0.31			2.34±0.15			0.271
	2.39±0.03	2.84±0.47	0.555	2.13±0.08	2.44±0.20	0.342	
IP_MCA	1.04±0.11			0.92±0.07			0.334
	0.91±0.06	1.11±0.15	0.461	0.84±0.06	0.96±0.09	0.447	
IR_MCA	0.61±0.03			0.56±0.02			0.223
	0.58±0.01	0.63±0.05	0.618	0.53±0.15	0.58±0.03	0.431	
SD_RA	4.11±0.50			2.97±0.14			0.033
	5.56±1.49	3.51±0,28	0.061	2.59±0.23	3.08±0.17	0.174	
IP_RA	1.30±0.07			1.09±0.05			0.017
	1.41±0.11	1.26±0.08	0.305	0.96±0.11	1.13±0.06	0.212	
IR_RA	0.72±0.02			0.65±0.02			0.015
	0.78±0.05	0.69±0.02	0.092	0.60±0.04	0.66±0.02	0.205	

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OBESITY AND CHRONIC KIDNEY DISEASE

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Introduction. Obesity, the epidemic of the 21st century, carries a markedly increased risk for comorbid complications, such as type 2 diabetes, cancer, hypertension, dyslipidemia, cardiovascular disease, and sleep apnea. In addition, obesity increases the risk for CKD and its progression to ESRD. Paradoxically, even morbid obesity associates with better outcomes in studies of ESRD patients on maintenance dialysis. Because the number of obese CKD and maintenance dialysis patients is projected to increase markedly in developed as well as low- and middle-income countries, obesity is a rapidly emerging problem for the international renal community. Targeting the obesity epidemic represents an unprecedented opportunity for health officials to ameliorate the current worldwide increase in CKD prevalence. Nephrologists need more information about assessing and managing obesity in the setting of CKD. Specifically, more precise estimation of regional fat distribution and the amount of muscle mass should be introduced into regular clinical practice to complement more commonly used practical markers, such as body mass index.

Background/Aims: The prevalence of obesity among Kazakhstan adults has doubled within the past one decades, and if trends continue, over 20% of Kazakhstan adults have been the year 2017. Concurrent with the rising prevalence of obesity is an epidemic of chronic kidney disease (CKD) with an estimated adults currently affected. This review discusses the strong and consistent association between CKD risk and increasing body mass index noted in several observational studies. Potential mechanisms for obesity's role in the development and progression of CKD discussed.

Materials and Methods.
We conducted a questionnaire in 50 obese patients. Among them there was CKD in 15%, diabetes mellitus 20%, arterial hypertension in 45%

Results: Although obesity is an important risk factor for diabetes and hypertension, the two most common etiologies of kidney failure, obesity itself may increase CKD risk by increasing the metabolic demands on the kidney, which leads to higher glomerular capillary pressures and glomerular hypertrophy. The hyperinsulinemia frequently linked with obesity may also accelerate structural damage by interacting with angiotensin II and increasing collagen production and deposition.
Conclusions: Obesity is an important risk factor for CKD. Treatment plans for obese adults with CKD should include weight loss and exercise because these

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interventions may simultaneously reduce the metabolic demands on the kidney, lower systemic and glomerular pressures, and improve insulin sensitivity. However, more studies are needed to further optimize the treatment and prevention of CKD associated with obesity.

THE ERROR OF ESTIMATED GFR IN TYPE 2 DIABETES. THE NEPHROLOGIST IN THE MIST

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Introduction and aims: Type 2 diabetes (T2DM) is one of the major causes of renal disease worldwide. In clinical practice, GFR is evaluated by estimation formulas (eGFR). In clinical studies, renal function is also frequently assessed by estimation formulas (eGFR). However, formulas have an error of ±30% when compared with measured GFR. This has been observed in diverse populations: CKD, kidney transplantation, ADPKD, and T2DM. However, no study evaluated the performance of all the available formulas to estimate GFR, including those based on creatinine and/or cystatin-C. We aimed to assess the performance of 68 formulas compared with mGFR determined by the plasma clearance of iohexol in patients with T2DM and a wide range of renal function.

Methods: We analyzed 346 patients who underwent the measured GFR (mGFR) by plasma clearance of iohexol. Simulstaneously, creatinine and cystatin-C were determined to calculate eGFR. The agreement between mGFR and eGFR was assessed by total deviation index (TDI) and concordance correlation coefficient (CCC). TDI indicates how wide the limits of the differences between mGFR and eGFR need to be to include the majority of eGFR estimations. Empirical TDI was calculated for a theoretical TDI of 10% and a coverage probability of 90%. The CCC is a statistic that combines meaningful components of accuracy and precision. Patients were also analyzed according with CKD stages.

Results: Patients characteristics included: mean age 62.4 ± 11.0, 251 (69%) were male; mGFR ranged from 9.4 to 173.7 ml/min. Table 1 shows the agreement of 10 representative formulas based on creatinine and/or cystatin-C and mGFR. CCC ranged from 0.87 (0.85) to 0.94 (0.92), for the Rule-cr and CKD-EPI-cr equations, respectively (table 1), showing moderate accuracy and precision. TDI ranged from 78.25 (84.97) to 40.68 (44.69) for the Rule-cr, CKD-EPI-cr and

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Stevens equations, respectively (table 1). TDI averaged about 55%, indicating that 90% of the estimations of GFR showed an error ranging from -55 to +55% when compared with mGFR. Similar results were observed in each CKD stage and with the 58 remaining formulas (data not shown). Clinical examples are shown in table 2, including results of 10 selected formulas.

Conclusions: Both creatinine-based and cystatin-C-based formulas have a wide error in reflecting mGFR. This limits the correct assessment of renal function in diabetics. Caution is needed in the use and interpretation of formulas in patients with T2DM.

	Overall (n=346)		<30 ml/min (n=98)		30-60 ml/min (n=110)		60-90 ml/min (n=71)		>90 ml/min (n=67)	
Creatinine	**CCC**	**TDI**	**CCC**	**TDI**	**CCC**	**TDI**	**CCC**	**TDI**	**CCC**	**TDI**
CG	0.88 (0.86)	71.6 (77.3)	0.41 (0.30)	83.5 (97.0)	0.41 (0.30)	83.5 (97.0)	0.26 (0.16)	64.2 (76.6)	0.45 (0.34)	56.7 (67.3)
CKD-EPI	0.94 (0.92)	40.6 (44.6)	0.52 (0.40)	63.0 (73.3)	0.52 (0.40)	63.0 (73.3)	0.36 (0.26)	55.9 (66.7)	0.48 (0.33)	37.7 (44.6)
MDRD	0.92 (0.90)	56.8 (61.5)	0.49 (0.36)	71.2 (83.3)	0.49 (0.36)	71.2 (83.3)	0.24 (0.15)	71.7 (84.6)	0.49 (0.34)	36.3 (42.9)
Rule	0.87 (0.85)	78.2 (84.9)	0.51 (0.38)	66.4 (77.4)	0.51 (0.38)	66.4 (77.4)	0.39 (0.28)	48.4 (57.4)	0.67 (0.54)	24.1 (28.3)
CYSTATIN										
CKD-EPI	0.91 (0.90)	57.7 (62.4)	0.63 (0.48)	59.2 (73.1)	0.63 (0.48)	59.2 (73.1)	0.55 (0.40)	27.3 (32.9)	0.61 (0.41)	32.4 (41.8)
Hoek	0.92 (0.90)	41.6 (45.6)	0.68 (0.54)	53.2 (66.3)	0.68 (0.54)	53.2 (66.3)	0.33 (0.21)	51.7 (62.0)	0.57 (0.36)	38.2 (49.6)
Rule	0.90 (0.88)	54.3 (59.7)	0.72 (0.58)	47.8 (59.9)	0.72 (0.58)	47.8 (59.9)	0.46 (0.32)	37.0 (45.1)	0.70 (0.52)	25.7 (32.9)
C+C										
CKD-EPI	0.92 (0.91)	44.9 (49.4)	0.74 (0.61)	44.5 (55.1)	0.74 (0.61)	44.5 (55.1)	0.42 (0.31)	44.9 (53.8)	0.34 (0.19)	64.3 (79.3)
Ma	0.90 (0.88)	53.2 (58.2)	0.79 (0.67)	37.2 (46.2)	0.79 (0.67)	37.2 (46.2)	0.56 (0.44)	32.5 (39.4)	0.53 (0.33)	39.9 (51.2)
Stevens	0.93 (0.92)	40.6 (44.6)	0.78 (0.66)	40.1 (49.9)	0.78 (0.66)	40.1 (49.9)	0.57 (0.45)	31.0 (37.5)	0.71 (0.53)	24.7 (31.6)

Table 1: Agreement between measured GFR and GFR estimated with 10 creatinine- or-cystatin-c-based formulas. Patients were classified in CKD stages. TDI: total deviation index, TDI (total deviation index); CCC (concordance correlation coefficient). Results expressed for GFR unadjusted by BSA (ml/min).

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	Iohexol	creatinine-based formulas				cystatin-C-based			Creatinine+cystatin		
Case	**GFR**	**CG**	**MDRD**	**RULE**	**CKD-EPI**	**Hoek**	**RULE**	**CKD-EPI**	**Ma**	**Stevens**	**CKD-EPI**
1	9.4	20.9	20.2	19.7	20.9	11.5	8.0	9.3	16.0	14.9	13.0
2	17.9	32.5	27.4	25.9	27.1	27.8	19.9	22.0	28.7	25.7	23.5
3	24.7	48.8	48.7	52.6	47.6	22.4	15.8	16.7	34.4	31.7	26.9
4	33.7	57.6	50.7	76.2	55.5	37.9	29.3	31.6	46.8	42.2	40.5
5	45.2	94.1	61.4	74.1	67.5	55.3	42.7	52.9	64.9	58.9	58.0
6	58.0	134.9	101.5	142.1	112.6	65.1	52.5	63.4	92.7	84.3	83.0
7	60.3	96.3	70.8	94.9	77.6	59.5	47.7	57.7	73.3	66.1	65.7
8	80.0	129.7	128.0	92.1	102.3	93.3	84.9	88.0	126.1	111.2	98.1
9	83.9	173.6	159.4	114.6	127.2	89.6	76.8	79.0	134.5	120.3	102.4
10	94.9	144.7	125.0	104.7	113.6	123.2	119.7	115.8	149.1	130.6	119.9
11	108.4	260.4	196.6	120.1	144.1	171.1	178.2	146.4	232.0	204.5	159.9
12	141.5	256.8	150.4	151.9	159.0	180.0	181.9	170.2	205.8	181.4	171.5

Table 2: Twelve clinical examples of patients in whom GFR was estimated with 12 formulas and measured with the plasma clearance of iohexol.

PREVALENCE AND METABOLIC IMPACT OF NONALCOHOLIC FATTY LIVER DISEASE AMONG DIABETIC PATIENTS WITH NORMAL KIDNEY FUNCTION OR CHRONIC KIDNEY DISEASE AND THE EFFECT OF KIDNEY TRANSPLANTATION

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Adrian et al._Abstract_ Lisbon2017.

Introduction: Diabetes is the single most important cause of end-stage renal disease (ESRD). Furthermore, more than 25 % of patients with moderate to severe chronic kidney disease (CKD) have prediabetic characteristics such as impaired glucose tolerance or impaired fasting glucose. This may contribute to the high morbidity and mortality seen in CKD and ESRD patients.
Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in developed countries affecting approximately 30 % of the general adult population. It represents an important pathogenic factor in the development of type 2 diabetes and is associated with a high risk of cardiovascular disease.

In patients with CKD, previous studies with less sensitive ultrasonic methods have demonstrated a high prevalence of NAFLD, which also strongly associates with cardiovascular disease. Although ESRD often is attributed to diabetes, gluco-metabolic disturbances are also very common in non-diabetic ESRD patients and NAFLD is also present in non-diabetic patients with ESRD. This co-existence of CKD, NAFLD, gluco-metabolic changes including diabetes and a high risk and incidence of cardiovascular disease have called for

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several interesting hypotheses, but the potential association with gluco-metabolic disturbances in patients with CKD and the ethology, pathogenesis, incidence and treatment options as well as preventive strategies of NAFLD in diabetic CKD patients has not been clarified. There are also clear limitations of the current knowledge of fatty liver disease, bile acids and its potential role in gluco-metabolic changes and new-onset diabetes often seen after kidney transplantation. Delineation of these issues may provide new treatment targets for the benefit of patients and societies.

The aim of this study is to identify the prevalence and etiology of nonalcoholic fatty liver disease among diabetes type 2 patients with chronic kidney disease and also investigate possible effects on kidney transplantation. To our knowledge we will be the first to investigate potential development or progression of NAFLD among kidney transplant patients.

Methods and analysis: The project involves two distinct studies; study 1 is a cross-sectional study while study 2 is a prospective cohort study. In the first study fat accumulation in the liver will be determined by MR Spectroscopy and the prevalence of NAFLD among type 2 diabetes mellitus patients with normal kidney function or CKD 3-5 will be investigated. A continuous glucose monitoring for four days and bile acid analysis, metabolomic and lipidomic analysis will also be performed. This will involve 54 patients with type 2 diabetes mellitus with normal kidney function and 54 patients with type 2 diabetes mellitus and CKD stage 3-5.

In the second study the effect of kidney transplantation compared to healthy controls will be examined regarding development and progression of fat accumulation in the liver. In addition to the examinations included in study 1 an oral glucose tolerance test and a two stage hyperglycemic clamp with estimates of insulin sensitivity and secretion and an incretin clamp (to establish the gluco-metabolic status) will be performed. In this study sixteen kidney transplanted patients will be included and examined before transplantation and after three and twelve months. A healthy age-, sex- and BMI matched control group will be examined once.

For study 1 a sample size of 98 patients in a parallel design is needed to demonstrate a difference in relative fat signal between type 2 diabetes patients with CKD 3-5 and type 2 diabetes patients with normal renal function of 30 %. A total of 108 patients, including 10 extra patients, are therefore planned to be examined. For study 2 a sample size of 16 patients in a paired design is needed to demonstrate a difference in liver fat accumulation between the time points of 50 %.

After completion of the study and data completion the results are analysed according to primary and secondary endpoints. Results are reported as mean

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values with confidence interval or median and range. Data are analysed with parametric (normally distributed data) or non-parametric statistics (non-normal-distributed data). A 95 % confidence interval is accepted as statistically significant (p<0, 05).

Ethics and dissemination

The study will be sent to the Danish Ethical Committee in the end of the year 2017 and we expect it to be accepted. The study is in adherence with the Helsinki declaration. The project is planned to run from the beginning of 2019 to the end of 2021. The protocol will be submitted for publication in BMJ Open or similar protocol source and results and outcomes will be disseminated through publication and will be presented at scientific conferences.

Table 1. Selection criteria, study 1.

Inclusion criteria
· Age 18-90 years AND
· Diagnosed type 2 diabetes mellitus AND
· Outpatient at the department of endocrinology at either Rigshospitalet, Herlev Hospital, Gentofte Hospital or Steno Diabetes Center Copenhagen with normal kidney function OR
· Outpatient at the department of nephrology at Rigshospitalet or Herlev Hospital with eGFR <60 mL/min/1,73 m2
Exclusion criteria
· End stage liver disease as diagnosed by MELD (model for end stage liver disease) criteria OR
· At the waiting list for liver transplantation OR
· Daily alcohol consumption above 20 g and 30 g for women and men respectively OR
· Known hepatitis A, B or C or hepatocellular carcinoma or other known liver disease
· Dialysis therapy OR
· Pregnancy OR
· Body weight > 130 kg OR

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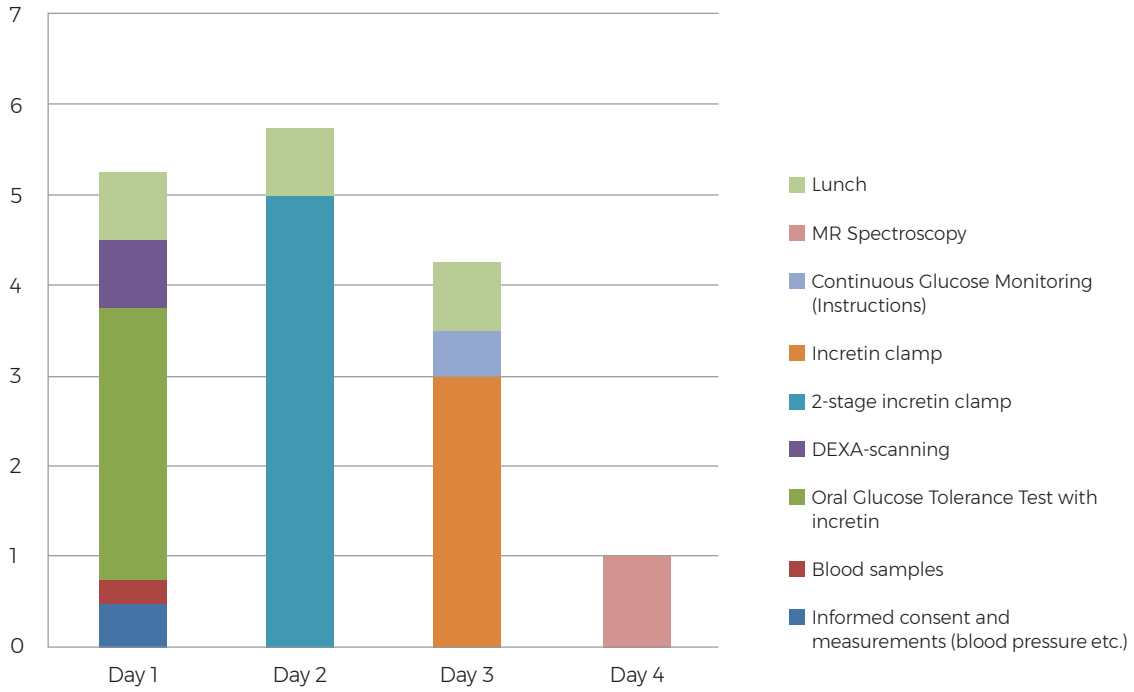

Figure 1. Time schedule for a participant in study 2
Time (days) on the x-axis, Time (hours) for the examinations on the y-axis.

INCREASED PRE-GLOMERULAR RESISTANCE AND KIDNEY HYPOPERFUSION MAY SUSTAIN ACCELERATED GFR DECLINE IN HYPERTENSIVE, OVERWEIGHT/OBESE, TYPE 2 DIABETICS WITH NORMO- OR MICROALBUMINURIA

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Background: Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease worldwide1. Proteinuria plays a central role in the progression of the disease. However, the DEMAND trial2 showed that, despite optimized blood pressure and metabolic control, the glomerular filtration rate (GFR) may progressively decline, by a median of 3 mL/min/1.73m2/year, even in hypertensive, overweight/obese type 2 diabetics with normo- or micro- albuminuria.

Aim: We sought to investigate which and to what extent changes in glomerular hemodynamics, beyond glomerular hyperfiltration3,4, could explain GFR decline in diabetic patients without proteinuria.

Methods: We indirectly estimated glomerular hemodynamic parameters such as afferent (Ra), efferent (Re) arteriolar resistance and glomerular hydrostatic pressure (Pglo) by using the Gomez5 formula in a representative subgroup of 60 type 2 diabetics with normo- and microalbuminuria from the DEMAND trial who had their GFR and renal plasma flow (RPF) measured at baseline by plasmatic clearances of non-radioactive iohexol and ParaAmminoHippurate, respectively6,7 and their GFR prospectively monitored every six months up to three years of follow up. GFR decline was evaluated by regression analysis in the patients who had at least three GFR measurements after the baseline evaluation. Patients with a GFR decline > or < the median cut-off of 3 mL/min/1.73m2/year, were categorized as "progressors" and "non progressors", respectively.

Results: Baseline characteristics of patients considered as a whole (overall) and of progressors and non progressors considered separately are shown in the table.

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Baseline Characteristics of Patiens	Overall (n=60)	Progressors (N=35)	Non Progressors (N=25)
Age, y	59±7	61±6	56±9*
Male sex, n (%)	49 (82)	28 (80)	21 (84)
Body mass index, Kg/m²	29.24±3.97	29.13±3.56	29.40±4.59
Systolic, mmHg	148.48±13.93	148.39±13.96	148.61±14.18
Diastolic, mmHg	87.76±9.56	88.543 ±10.41	86.61±8.26
Mean arterial pressure, mmHg	108.00±10.07	108.49 ±10.92	107.28±8.86
Serum creatinine, mg/dL	0.93±0.14	0.95±0.15	0.91±0.11
Cholesterol, mg/dL	196.59±33.51	198.60±36.81	193.67±28.51
Glycosylated hemoglobin, mmol/mol	54.79±13.09	53.77±11.85	56.26±14.86
Urinary albumin excretion, µg/min	7.06 (4.55 to 15.79)	8.09 (5.17 to 22.02)	5.26 (3.76 to 13.08)
ACE-I n° (%)	37 (62)	22 (63)	15 (60)
Glomerular Filtration rate, mL/min/1.73 m²	110.32±19.24	105.87±18.33	116.60±19.50*
Renal Plasma Flow, mL/min/1.73 m²	687.86±163.40	682.66±182.56	697.43±137.81
Filtration fraction	0.17±0.03	0.16±0.04	0.17±0.03
Renal vascular resistance, mmHg/mL/min/1.73m²	0.096±0.026	0.100±0.030	0.091±0.017
Glomerular hydrostatic pressure (Pglo), mmHg	57.57±5.14	56.51±5.43	59.03±4.50
Afferent arteriolar resistance (Ra), dyne•sec•cm^{-5}	3249.91±1149.13	3487.26±1349.25	2877.00±668.88*
Efferent arteriolar resistance (Re), dyne•sec•cm^{-5}	2633.94±666.82	2575.68±758.36	2708.63±526.13
Ra/Re	1.28±0.45	1.41±0.50	1.10±0.30#

Data are numbers (%), mean±SD or median (interquartile range) * p<0.05, #p<0.01 vs. Progressors. angiotensin-converting enzyme inhibitor (ACE-I)

Median (IQR) GFR decline 4.06 (5.46 - 2.00) mL/min/1.73m2/year in the study group as a whole, and 1.71 (2.14 – 1.33) and 5.35 (6.60 – 4.48) mL/min/1.73m2/year in non progressors and progressors, considered separately. Progressors had a higher baseline Ra (3487.26±1349.25 dyne•sec•cm-5 vs. 2877.00±668.88 dyne•sec•cm-5, p<0.05, Table, Figure Panel A) and higher resistance ratio Ra/Re (1.41±0.50 vs. 1.10±0.30, p<0.01, Table, Figure Panel B) than non-progressors.

Ra inversely correlated with GFR (p<0.0001), while Re directly correlated with GFR (p<0.001). Both, Ra and Re, inversely correlated with RPF (p<0.001). Re, FF and Pglo were associated significantly with HbA1C (p<0.05). Multivariable logistic analysis showed that Ra/Re, but not Ra, Re or Pglo, was significantly and independently associated with GFR decline: Odds ratio 5.82 [95% CI: 1.44 - 23.49].

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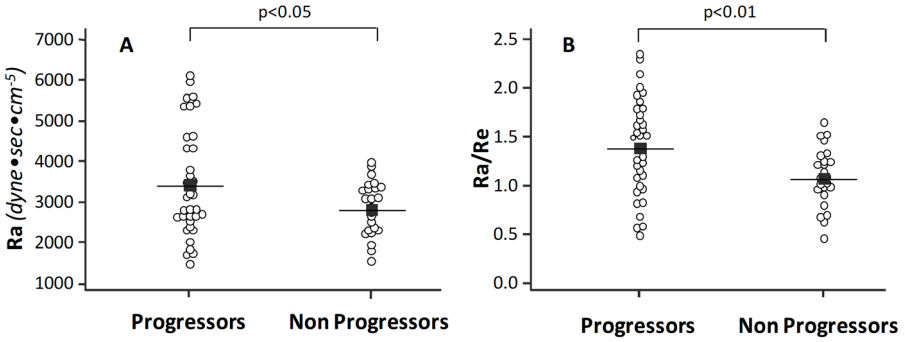

Conclusions: Increased pre-glomerular resistances and in particular increased ratio between pre-and post glomerular resistances are associated with accelerated GFR decline in overweight/obese, hypertensive type 2 diabetics without proteinuria. These changes might be explained by pre glomerular arteriolar narrowing with secondary kidney hypoperfusion and chronic ischemic injury. Evaluation of the Ra/Re ratio might help identifying diabetic patients at increased risk of progressive kidney function loss even without evidence of glomerular hyperfiltration and/or overt proteinuria.

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CHARACTERIZATION OF HOSPITALIZATIONS WITH DIAGNOSIS OF CHRONIC KIDNEY DISEASE AND DIABETES MELLITUS

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Diabetes mellitus (DM) is a disorder of carbohydrate metabolism characterized by hyperglycaemia and resulting from insulin resistance, inadequate insulin secretion and excessive or inappropriate glucagon secretion. DM plays a significant role in the pathophysiology of chronic kidney disease (CKD), being diabetic nephropathy a microvascular complication of diabetes. The aim of this retrospective study is to characterize the hospitalizations with concomitant diagnosis of CKD and type 2 DM and compare them with those with CKD without DM.

The data analysis was performed by consulting the clinical files and codified diagnosis of all hospitalizations in one internal medicine ward of a district hospital for one year. The age, gender, CKD stage, days of hospitalization and main diagnosis, Charlson comorbidity index and antidiabetic therapy were recorded. The statistical analysis was performed with IBM SPSS Statistics 24®.

In total, 2247 hospitalizations were included, 29,9% (n=671) had the diagnosis of DM, 10,8% (n=242) of CKD and 4,1% (n=91) of CKD and DM. Most of hospitalizations with diagnosis of CKD didn't have DM (62,4%, n=151), which points to other possible aetiologies. The group with CKD and DM had a median age of 81,0±10,7 years and was mostly female (60,4%, n=55). The other patients with CKD diagnosis had a median age of 86,0±7,2 years and female gender represents 52,3% (n=79). Both groups appear to have similar CKD staging (table 1). The mortality rates were 12,1% and 20,5% in CKD with and without DM, respectively, and don't seem to have been considerably influenced by CKD stages. The main diagnoses of hospitalization in patients with CKD and DM were congestive heart failure (40,7%, n=37), respiratory tract infections (9,9%, n=9), acute exacerbation of chronic obstructive pulmonary disease (8,8%, n=8) and acute on CKD (7,7%, n=15). In patients with CKD without DM, the principal diagnoses were the same and their prevalence was, respectively, 22,5% (n=34), 20,5% (n=31), 9,3% (n=14) and 9,9% (n=15). The group with CKD without DM had a higher prevalence of respiratory tract infections, while group with CKD and DM had a higher prevalence of congestive heart failure. The length of hospitalization was similar, with a median of 7,0±6,6 and 6,0±8,1 days for CKD with and without DM, respectively. The median Charlson comorbidity index (CCI) was comparable, 10,0±1,8 for CKD with DM and 9,0±1,6 for CKD without DM.

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Table 1 . Chronic kidney disease (CKD) staging of patient hospitalizations with and without diagnosis of diabetes mellitus (DM).

CKD Stages	CKD with DM (n=91)	CKD without DM (n=151)	All CKD (n=242)
1	4,4	1,3	2,5
2	9,9	9,9	9,9
3	41,7	49,7	46,7
4	44,0	39,1	40,9
5	0,0	0,0	0,0

In the hospitalizations with concomitant diagnosis of CKD and DM, patients were predominantly medicated in ambulatory with one antidiabetic drug (79,1%, n=72). In monotherapy, the most prescribed drug was insulin, followed by gliptins and sulfonylureas (figure 1). The association of two and three antidiabetic drugs was also used, being gliptins the most prescribed (81,8%, n=9). Some patients with diagnosis of DM weren't taking any antidiabetic drug.

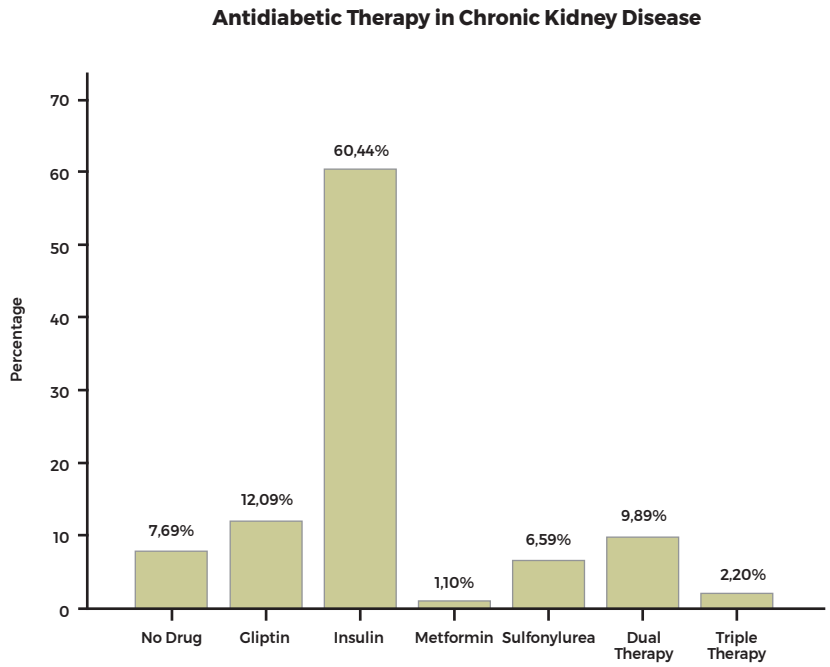

Figure 1. Antidiabetic therapy prescribed in patients with concomitant diagnosis of chronic kidney disease and diabetes mellitus.

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We concluded that, in our study, patients with CKD and DM appear to have the same characteristics as those with CKD with different aetiologies. The staging of CKD is similar with or without DM, which means that the development and progression of CKD seems to be due to other causes. Poor renal function is not related to higher mortality rates and the complexity of these patients is also the same. The higher mortality rate in patients with CKD without DM is possibly explained by higher prevalence of respiratory tract infections in this group. So, although it is not a statistically significant correlation, this main diagnosis has tendency to be related with higher mortality rate. The metabolic control of patients with DM is important to prevent the development and progression of CKD, which explains the preference for insulin. In other hand, the gliptins are a relatively safe drug, explaining their association with insulin.

EFFECT OF BODY WEIGHT VARIATION IN KIDNEY TRANSPLANTATION: A RESTROSPECTIVE COHORTS STUDY

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Kidney allograft recipients have an increased risk of surgical complications, delayed graft function (DGF), prolonged hospital stay and late graft failure. However, there is lack of information regarding the effect of body mass index (BMI) variation after kidney transplantation (KT). In this longitudinal study, we used data from Catalan Renal Registry including first KT recipients within 1990 and 2011 (n= 5,983). The annual change on post-transplantation BMI was calculated all patient follow-up (until December 2015). Main outcome variables were DGF, eGFR (CKD-EPI), patient and graft survival. Statistical analysis was adjusted for variables impacting on outcome. Obesity was observed in 609 patients (10.9%) at the time of transplantation. Obese patients were transplanted more recently, were younger and received kidneys from younger donors. Incidence of DGF was significantly higher in obese (40.38% vs 29.5%, P<0.001). Multivariate logistic regression model showed that baseline obesity was a risk factor for DGF (class I obesity: OR 1.7; 95%CI 1.3-2.1, P<0.001 and class II OR 2.2; 95%CI 1.5-3.2, P<0.001) whereas under-weight was protective (OR 0.5; 95%CI 0.3-0.8, P=0.005). Moreover, baseline obesity was a detrimental factor concerning patient (SHR 1.23; 95%CI 1.01-1.51, P= 0.037) and graft survival (SHR 1.75 95%CI 1.26-2.43, P= 0.001). In obese patients, BMI increase of between 4-7% was associated with increased risk of death and a BMI loss of >7% was associated with worse eGFR and graft survival. Our conclusion is that BMI reduction after KT was not associated with eGFR improvement and did not modify the long-term graft and patient survival.