BOOK OF ABSTRACTS

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Diabetes and Obesity

Diabesity CME course 2022 Maribor

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Introduction

DIABESITY CME Course 2022 in Maribor, Slovenia, is a two-day event that will bring together researchers of the ERA Community, especially of the DIABESITY Working Group of the ERA, and other basic and clinical researchers, Ph.D. and medical students, industry trial planners and directors, industry technical staff working within fields of diabetes, nephrology, obesity and end organ damage research, to address and discuss the latest developments in the mentioned fields.

The programme of the event covers **basic research, epidemiology, evaluation, diagnostic and therapy of obesity, diabetes and chronic kidney disease (CKD**).

The emphasis of **basic research** presentations will be on development of different animal and human models focused on obesity, renal lipotoxicity and diabetic nephropathy.

The **epidemiology** part of the course will present recent data referring to renal disease and comorbidities (obesity, cardiovascular disease, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis).

In the **evaluation** session participants will go through new renal pathohistology findings of diabetic patients.

The **diagnostic and therapy** sessions will follow and cover new markers and new methods to measure kidney function in diabetic patients, presents non-invasive methods to evaluate CKD and different comorbidities and discuss results of recently published studies regarding the SGLT2i, MRA and combination therapy for CKD patients with different comorbidities.

At the event also the **future prospective** and miscellaneous topic of obesity, diabetes and CKD will be present.

Renowned international speakers, ERA members and young speakers, clinical and preclinical researchers, and residents will actively participate with their lectures and provide a high-quality event.

The general aim is to evaluate and share the current knowledge in the field of diabetes, nephrology, obesity and end organ damage research. Each session will be followed by an interactive constructive discussion between all participants. Arrangements are also expected for possible new projects in the future.

On behalf of the Scientific committee

Sebastjan Bevc

BASIC RESEARCH

Renal lipotoxicity, from animal models to humans

Covadonga Rodríguez (Spain)[1]
[1] *Instituto de Tecnologías Biomédicas, University of La Laguna, Tenerife, Spain*

The analysis of lipid species, their abundance and localization, and their metabolism within cells, tissues, and biofluids allows to elucidate their biologic function and specific actions in health and disease conditions. Particularly, small molecular weight lipids such as fatty acids, including essential fatty acids (EFA) and their eicosanoids and docosanoids derivatives, as well as glycerophospholipids, serve diverse and highly complex functions whatever the animal model studied, which can be related with many different biological markers. Obesity can affect the development of chronic kidney disease, and, in addition, there is certain evidence that menopause can contribute to and worsen dyslipidemia condition associated with obesity in the kidney pathology. Scientific knowledge acquired in a long term career by NUTRAHLIPIDS-ULL group members, based on investigations focused on the metabolism and physiology of lipids and their derivatives in animal and human nutrition, has very recently joined to the efforts made by Dr. Porrini and colleagues from the "Chronic kidney disease and transplant group", by studying the potential renal lipotoxicity in induced obese female (ovariectomized or not), and male mice as an animal model. The most relevant findings after an exhaustive mapping (lipid classes and fatty acid profiles of major lipid classes), carried out in kidney and liver tissues, as well as in urine samples of all groups assayed will be presented and discussed. The pending tasks and potential use of other animal models will be also evaluated.

Main research activities focused on lipid physiology and metabolism in marine organisms, farmed animals, and animal models related to the importance of lipids in nutrition, health and well-being.. Full professor at the University of La Laguna (ULL; Tenerife, Spain) since 2016. Positive evaluation by the I3 Research Excellence Program of Spanish Ministry of Education and Science (MEC); various figures as hired researcher funded by the Spanish Government, including a Ramón y Cajal Excellence Program (1997-2006), and a 2-years Postdoctoral scholarship at the Unit of Aquatic Biochemistry (Stirling University, Scotland, UK) (1994-1996). Coordinator of the research groups NUTRAHLIPIDS and AQUAFISMAR, and head of the Lipidomics Unit at ITB (Instituto de Tecnologías Biomédicas, ULL).

Animal model of extreme obesity and renal disease

Maru Navarro[1,2,3]

[1]*Nephrology department, Moisès Broggi's Hospital, Sant Joan Despí, Barcelona, Spain*
[2]*Germans Trias i Pujol's Research Institute, Badalona, Barcelona, Spain*
[3]*Autonomous University of Barcelona, Bellaterra, Barcelona, Spain*

Limited access to renal tissue in obesity is an important limitation for the study of obesity-related glomerulopathy (ORG), particularly after bariatric surgery (BS). For this reason, preclinical studies of BS in experimental ORG may offer a unique opportunity to investigate the renal structural and molecular changes after BS. This work aimed to compare in diet-induced ORG animal model (Wistar rats), the effect of high fat diet (HFD) and the effect of both sleeve gastrectomy and low-fat diet (LFD).

METHODOLOGY: Thirty-six Wistar rats were divided into control rats (n=8) and obese rats fed with HFD (n=28). After 10 weeks, obese rats were subdivided into 3 groups. HFD (n=8), rats submitted to BS (n=12) and rats that switched diet to LFD (n=8). Samples of kidney tissue were processed to evaluate obesity-related kidney lesions and both kidney tissue and urine were processed to perform transcriptomic analysis.

RESULTS: After HFD, all rats become obese increasing >61% of the baseline weight. Obese rats developed renal lesions with early-stages of ORG features. After LFD, an improvement in kidney lesions was observed. After BS, glomerular lesions completely disappeared. Transcriptomic study showed that total RNA and small-RNA in renal tissue were differentially expressed in the different groups studied.

CONCLUSIONS: Our study suggests that bariatric surgery can revert renal lesions of obesity not only by losing weight but also by changing RNA expression.

Maru Navarro MD PhD is a clinical nephrologist, clinical researcher, and assistant professor. In 2002 he started working on the study of morbid obesity and its comorbidities, supported by numerous works that study clinical, biochemical and histological aspects of humoral and renal involvement. Based on his work he developed his doctoral thesis in 2011 entitled: »Renal involvement in morbid obesity«, which he passed with the qualification Cum Laude. Following this line of research, in 2018 the Carlos III Institute granted to finance the research project PI18/01951 »Definition of the gene expression profile in renal biopsies of patients with morbid obesity and early-stages of obesity-related glomerulopathy«. Since 2018 he has been an active member of the Diabesity Working group, becoming vice-president of the group in 2020. He actively participates in the ENBIBA Project (European Nephrectomy Bio-Bank).

BASIC RESEARCH

Preclinical models of DKD

William Martin[1]
[1]*Diabetes Complications Research Centre, Conway Institute of Biomolecular and Biomedical Research, School of Medicine, University College Dublin, Dublin, Ireland*

Liam's talk will contextualise the role of preclinical modelling of diabetic kidney disease in translational nephrology research. Strengths and limitations of preclinical models of DKD will be highlighted. An overview of rodent and non-rodent models of DKD will be provided, with pros and cons of individual models discussed. Means of augmenting kidney injury in preclinical models of DKD will also be highlighted.

Liam will present some original research findings from his PhD, outlining the impact of a non-invasive weight loss intervention designed to mimic the effects of metabolic surgery on kidney injury outcomes in the Zucker Diabetic Fatty and Zucker Diabetic Sprague Dawley rat models of DKD. The findings underscore the renoprotective effects of PPAR-alpha mediated restoration of fatty acid oxidation in the proximal tubule, with several potential avenues for clinical translation.

The final part of Liam's talk will focus on how we can attempt to overcome inherent limitations in experimental design in preclinical models of DKD in an effort to bridge the translational gap to patients with DKD.

William (Liam) is an Irish clinical nephrology trainee. Liam conducted a PhD at University College Dublin from 2018 to 2022 focusing on kidney responses to intentional weight loss interventions in preclinical models of diabetic kidney disease. Specifically, renal transcriptomic and urinary metabolomic responses to surgical and non-surgical weight loss interventions were profiled and integrated. Liam intends to work as a clinician scientist and to leverage skills in statistical analysis, data visualisation, and bioinformatics to improve prognostication of adverse outcomes in people with DKD and to build a case for addressing obesity as a modifiable risk factor for renal functional decline.

Endothelial glycocalyx damage in nephropathy - a path to injury and/or a therapeutic target?

Ivo Laranjinha[1]
[1]*Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal*

Glomerular endothelial cells (as all the endothelial cells in the body) are lined with the glycocalyx, a multilayer, negative-charged, hydrated gel-like structure, which serves as a barrier between blood flow and vessel wall. Their functions are several, such as regulation of vascular permeability; prevention of vascular inflammation (precluding leukocyte adhesion); control of vessel perfusion and shear stress; regulation of cell signaling; etc. Acute and chronic hyperglycemia significantly reduces the glycocalyx size, mediated by reactive oxygen species, advanced glycation end products and activation of glycocalyxdegrading enzymes (sheddases). After these pathways trigger the inicial glycocalyx damage, the heparan sulfate, hyaluronic acid and syndecan fragments promote further inflammation and upregulation of sheddases, forming a vicious circle of glycocalyx destruction.

Damage to the endothelial cell glycocalyx occurs early in the pathogenesis of diabetic nephropathy (before GBM and podocytes lesions are evident) and can be reversible. These observations have also suggested that endothelial glycocalyx dysfunction may be the link between cardiovascular disease and albuminuria, contributing to the pathophysiology of atherosclerosis in systemic vessels as well as to the glomerular filtration barrier dysfunction.

Glycocalyx dysfunction in diabetics appears to be a key factor to endothelial dysfunction - the understanding of its mechanisms can have diagnostic and therapeutic implications.

Ivo Laranjinha, MD, is a nephrologist at a tertiary referral center, Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal. Board member of the ERA-EDTA Diabesity Working Group since 2017 and board member of the Immunonephrology Working Group of the Portuguese Society of Nephrology since 2022. Clinical Scholars Research Training Certificate Program in 2016 by Harvard Medical School. Dr. Laranjinha has received several awards for best abstract in clinical science for works presented in international meetings. Main topics of interest and focus of study are diabetic kidney disease, glomerular diseases, nephrolithiasis and sustainability in nephrology.

EPIDEMIOLOGY

Obesity and CKD

Radovan Hojs[1,2]
[1]*Department of Nephrology, University Medical Centre Maribor, Maribor, Slovenia*
[2]*Faculty of Medicine, University of Maribor, Maribor, Slovenia*

There is a pandemic of obesity worldwide and in Europe up to 30% of the adult population is obese. There is compelling evidence that obesity is associated with chronic kidney disease (CKD). Studies have shown that high body mass index is strongly related to the risk of CKD and end-stage renal disease, also after adjustment for age, sex, race, smoking status, comorbidities, and laboratory tests. The global increase in CKD parallels the obesity and diabetes pandemics, but it is important that obesity is a risk factor for CKD independent of diabetes. The mechanisms by which obesity induces or progresses CKD are still unclear. There are possible direct (glomerular hyperfiltration, lipotoxicity, inflammation, oxidative stress, hormones, etc.), and indirect (metabolic syndrome, diabetes, and hypertension) effects of obesity on the kidney.

Obesity is a major risk factor for all-cause and cardiovascular mortality in the general population. However, in end-stage renal disease patient's obesity is paradoxically associated with better survival. In non-dialysis-dependent chronic kidney disease patients the association between body-mass index or weight with mortality is controversial.

Radovan Hojs is an internal medicine and nephrology specialist, working at the University Clinical Centre Maribor. He is the head of the Clinic of Internal Medicine, full professor of internal medicine and vice-dean for education at the Medical Faculty, University of Maribor. He is co-author of numerous publications. He was associate editor of the European Journal of Internal Medicine, and is section editor of the European Journal of Medical Research, and editorial board member of the World Journal of Diabetes. From 2013 to 2018 he was a board member of the ERA Diabesity working group. Currently he is a member of the Professional Issues and Quality of Care working group by EFIM.

Link between NAFLD-NASH and CKD

Enrique Morales[1,2]
[1]*Nephrology Department, Hospital Universitario 12 de Octubre. Madrid, Spain*
[2] *Complutense University of Madrid, Madrid, Spain*

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, involving approximately 25% of the general population and increasing in prevalence in patient populations afflicted with metabolic syndrome and type 2 diabetes (T2DM). Due to the variety of metabolic comorbidities, it accompanies, such as hypertension, insulin resistance, DM, dislipemia and central obesity, international experts decided to change its name to metabolic dysfunction-associated fatty liver disease (MAFLD). NAFLD and chronic kidney disease (CKD) are both chronic conditions with rapidly increasing prevalence and incidence worldwide that have led to a significant burden on health-care systems. The association between NAFLD and CKD has recently attracted the attention of many experts. An increasing number of different pathogenic mechanisms are influencing the progression of chronic kidney disease. It is known that NAFLD not only increases the risk of T2DM and cardiovascular disease, but also the incidence of CKD in patients with and without DM. However, the pathological mechanisms leading to the relation between NAFLD and CKD are yet unclear. In recent years, there has been many scientific publications trying to find a link between the two entities. Identification of high-risk individuals with coexisting CKD and NAFLD may empower beneficial pharmacologic interventions such as GLP-1 agonists and SGLT2 inhibitors and amelioration of cardiometabolic disease burden. For this reason, it is of great scientific importance to address this pathogenic mechanism in the genesis of CKD.

Head of Nephrology Department from Hospital Universitario 12 de Octubre. Madrid, Spain. Medical Doctor, Cum Laude, 2005 Complutense University Highest Distinction (PhD). Associate Professor of Medicine, Complutense University. Tutor of Nephrology Trainee from 2005 until 2013. Main investigator or co-investigator in more than 30 clinical trials. A number of presentations at national and international meetings. Author of numerous national and international publications (International Journals >150 and National Journal >50). Member of different scientific societies (Spanish Society of Nephrology, European Society of Nephrology, American Society of Nephrology). Board Member of Diabesity Working Group (ERA-EDTA). Coordinator of the CSUR for complex adult glomerular pathology at the Hospital Universitario 12 de Octubre. Coordinator of ERK-net. Different areas of research: Hyperkaliemia, Obesity and renal diseases, Glomerular pathology, Lupus Nephritis, Malignant hypertension and Thrombotic microangiopathy acute.

EPIDEMIOLOGY

The impact of diabetes on cardiovascular mortality among persons with advanced CKD

Mads Hornum[1]
[1]*Department of Nephrology and University of Copenhagen, Rigshospitalet, Copenhagen, Denmark*

In the presentation the risk of cardiovascular mortality among patients with advanced CKD with and without diabetes is discussed and data from a nationwide registry-based cohort study, where we identified all Danish persons aged ≥ 18 years with an estimated glomerular filtration rate < 30 mL/min/1.73m^2 between 2002 and 2018 is presented. As reference group, every patient with advanced CKD were matched with four individuals from the Danish general population on year of birth and sex. In total, 138,583 patients with advanced CKD were included, of whom 32,698 had diabetes. Mean age was 76.2 (SD 12.9) years and 51.9% were women. The standardized 1-year risk of cardiovascular mortality was 9.4% (95% CI 9.2-9.6) for patients with diabetes and 7.6% (95% CI 7.5-7.7) for patients without diabetes. Compared with age- and sex-matched individuals, cardiovascular mortality hazard ratio in those aged 18-49 years was 43.6 (95% CI 34.1-55.8) and 15.2 (95% CI 12.1-19.0) for patients with and without diabetes, respectively, declining to 2.5 (95% CI 2.4-2.6) and 2.4 (95% CI 2.3-2.4), respectively, in those aged ≥ 80 years. In conclusion patients with advanced CKD, with and without diabetes, had increased risk of cardiovascular mortality compared with the background population with a 2- to 40-fold increased risk depending on age and diabetes status. These results highlight the importance of early cardiovascular risk assessment and demonstrate that these patients pose a special challenge to the clinician.

Mads Hornum is a Professor of Nephrology at University of Copenhagen and Head of Research Laboratory for Medical Kidney Diseases at Copenhagen University Hospital Rigshospitalet. His research group has been focusing on clinical research in chronic kidney diseases (CKD), acute kidney injury (AKI) and solid organ transplantation, epidemiology, pathophysiological mechanisms, prediction, prevention, diagnostics and biomarkers. Monitoring and treatment of CKD and AKI has our special interest with special attention to diabetes and cardiovascular complications. Another focus is gastrointestinal hormones, bile acids and liver metabolism in persons with CKD and diabetes, and glucose/arrythmia/blood volume monitoring of diabetic and non-diabetic persons with CKD stage 3-5 or receiving dialysis treatment.

Adiposity and the risk of glomerular decline

Trond G. Jenssen[1]
[1]*Department of Organ Transplantation, Oslo University Hospital, Rikshospitalet, Norway*

Development of obesity-related glomerulopathy is a clinical entity which is at least partly caused by hyperfiltration. The histological picture is glomerular enlargement and focal glomerulosclerosis. Single nephron hyperfiltration occurs with hyperglycemia or when there is a mismatch between total filtration surface and body mass. Large epidemiological series have shown that BMI may be associated with development of chronic kidney disease (CKD) and also end-stage kidney disease (ESKD), but the results are not consistent. In the Framingham study BMI was no longer assoicated with CKD stage 3 when data were corrected for metabolic risk factors. Some studies show that central obesity is a better predictor for CKD and ESKD than general obesity itself. Central obesity is frequently associated with the metabolic syndrome. European data collected 25 years ago show that only a subset of overweight or obese persons suffer from insulin resistance as assessed by the hyperinsulinemic euglycemic clamp technique. It is of interest to note that many of the metabolic risk factors that outperfrom obesity as a risk factor also are associated with the metabolic syndrome. Thus, more recent epidemiological studies point to that not only blood presserue, but also suttle increases in triglycerides, glucose and uric acid my contribute to kidney damage rather than obesity itself. The relative importance of these metabolic risk factors is, however, not known.

MD University of Tromso 1980, PhD University of Tromsø 1986. Appointed Consultant and Adjunct Professor in Nephrology at the University Hospital of Tromsø 1992. Consultant in Nephrology, University Hospital of Oslo (UHO), Rikshospitalet, Norway (1997-). Adjunct Professor in Nephrology, Institute of Clinical Medicine , University of Oslo (2018-). Leader of the Kidney Medicine and Transplantation Research Group, UHO (2018-). Medical advisor of the Norwegian Diabetes Association (2003-). Research Award of the Norwegian Diabetes Association (2020). Author/ co-author of 330 peer-reviewed publications. Research interests over the last 20 years: Kidney transplantation, posttransplant metabolic disorders including diabetes mellitus, pancreas transplantation, islet transplantation.

EVALUATION

Vascular stiffness in obese patients with CKD and diabetes

Robert Ekart[1,2]
[1]Department of Dialysis, University Medical Centre Maribor, Maribor, Slovenia
[2]Faculty of Medicine, University of Maribor, Maribor, Slovenia

Type 2 diabetes mellitus and obesity are associated with a markedly increased prevalence of vascular fibrosis and stiffness, resulting in an increased risk of cardiovascular and chronic kidney disease (CKD). Arterial stiffness is the result of structural and functional changes in the vessel wall that occur in response to cardiorenal metabolic syndrome, injury, or aging. Measures of arterial stiffness include central pulse pressure/stroke volume index, pulse wave velocity (PWV), and augmentation index (AIx), and it has been positively associated with the rate of decline in renal function.

Increased arterial stiffness is an independent predictor of death from cardiovascular disease, and aortic stiffness is more predictive than stiffness of other arterial regions.

Arterial stiffness has long been considered a complication of hypertension. However, there is a bidirectional interaction between arterial stiffness and hypertension. The pathophysiology of obesity-related hypertension is particularly relevant for premenopausal women with obesity and type 2 diabetes mellitus, who are at high risk for developing arterial stiffness and endothelial dysfunction. Women are more affected by obesity, but the risk of cardiovascular disease due to increased body mass index is generally lower compared with men. Recently, studies have shown that cardiovascular disease morbidity and mortality are greatly increased in patients with CKD compared with patients without kidney disease.

The purpose of this presentation is to discuss some published work in this area and to present our own findings in different groups of CKD patients.

Prof. Robert Ekart, MD, PhD, is a nephrologist and full professor of Internal medicine at the Faculty of Medicine, University of Maribor. He is a head of the Department of Dialysis at the Clinic of Internal Medicine at the University Clinical Centre Maribor. He is a clinician, consultant in internal medicine, nephrology and dialysis, main mentor in training medical students, young doctors and residents in internal medicine and nephrology. She is the leader of the international projects at Department of Dialysis UKC Maribor: LUST, LUST2, SUB LUST, PROG-IMT and PROOF-ATHERO, ABPM feasibility study. He is author/co-author of 87 original scientific articles, according to Google Scholar his h-index is 25, the number of all citations is 2535. He is author/co-author of 122 articles in Pubmed. Since 2017, he is a board member of the ERA working group EURECA-m (EUropean REnal and CArdiovascular Medicine). As the main supervisor, his students have received many awards: 2 Perlach Awards from the University of Maribor for the best student research paper, 8 awards (gold, silver and bronze). He is also a reviewer for more than 50 international medical journals.

Vascular damage in Diabetic Nephropathy The ENBiBA project

Esteban Porrini[1,2]
[1]*Research Unit of the University Hospital of the Canary Islands, La Laguna, Tenerife, Spain*
[2]*Institute of Biomedical Technology, University of La Laguna, Spain*

I will discuss the evidence of intra-renal ischemic damage in patients with diabetes and its consequences in renal dysfunction. Recent evidence of the ENBiBA group showed that arterial hyalinosis and arteriosclerosis are very frequent in patients with diabetes. This may have consequences, leading to ischemia, fibrosis and loss of renal function. This is an unknown topic since vessels are not frequently observed in standard biopsies. This topic deserves more attention in clinical research in future studies.

Esteban Porrini, Nephrologist, Ramón y Cajal researcher, professor of Medicine at the Faculty of Medicine, University of La Laguna, Tenerife, Spain.
Main areas of interest, post-transplant diabetes mellitus, renal disease in diabetes and obesity, the error of estimated GFR by formulas and its consequences.
Founder and former President of the Diabesity Working Group. Leading researcher of the ENBiBa (European Nephrectomy Bio-Bank) project.

EVALUATION

Crosstalk between bone and the vasculature in diabetes and CKD

Maria L Mace[1,2]
[1]*Department of Nephrology, Rigshospitalet, Copenhagen, Denmark*
[2]*Department of Nephrology, University Hospital Zealand, Køge, Denmark*

Vascular calcification and disturbed bone metabolism are common findings in diabetes mellitus and in chronic kidney disease (CKD) patients. Over several decades, numerous studies have reported an association between the presence of vascular calcification and lower BMD in diabetes and CKD. Still, how the complex pathological mechanisms are linked is only sparsely understood. The presentation will discuss the current understanding of development of vascular calcification and its relation to bone metabolism, including the latest experimental research showing a direct link from the vasculature to bone. These findings support the hypothesis of an active role of the calcified vasculature in the systemic CKD - mineral and bone disorder, resulting in a pathological vascular – bone tissue crosstalk.

Doctor of medicine, University of Copenhagen 2009. PhD thesis: Fibroblast growth factor 23 and the kidney-bone-parathyroid axis, University of Copenhagen 2018. Post doc project: The Vascular – Bone Axis, Department of Nephrology, Rigshospitalet 2019-2021. Research area: Experimental and translational research on the mineral and bone disorder in chronic kidney disease, focusing on the fibroblast growth factor 23, vascular calcification and renal osteodystrophy. 22 publications (18 original studies and 4 invited reviews). Several oral and poster presentations at national and international meetings.

Diet intervention in patients with CKD, obesity, metabolic syndrome or diabetes: effect on renal outcomes

Manuela Abbate[1]
[1]*Research Group on Global Health, University of the Balearic Islands, Palma, Spain*

Type 2 diabetes, obesity and metabolic syndrome are associated with increased risk of decline in glomerular filtration and increased albuminuria. With the prevalence of obesity and type 2 diabetes in young adults dramatically increasing, the natural history of the association with their comorbidities, including CKD, may begin early in life.

Before loss of renal function in CKD, there might be a phase of glomerular hyperfiltration, which is strongly associated with obesity, hyperinsulinemia, and insulin resistance in both diabetics and non--diabetics. Glomerular hyperfiltration has been recently defined as the first stage of impaired function loss and, most importantly, is a reversible hemodynamic alteration. Hyperfiltration in severe obesity is reduced following bariatric surgery, and amelioration of hyperfiltration through pharmacologically improved blood pressure and metabolic control in type 2 diabetes has been proven to slow down GFR decline in the long term.

Diet intervention such as 6-mo caloric restriction with adequate nutrition (CR) in type 2 diabetic patients with abdominal obesity and normal kidney function achieved a significant reduction in GFR, alongside weight loss and improved cardiometabolic health, when compared to standard diet (SD). Moreover, short-term amelioration of hyperfiltration with 6-mo CR, stabilized the GFR in the long--term whilst in the SD group the GFR continued to decline.

Increased energy expenditure coupled with a caloric restricted Mediterranean Diet for 6 months in patients with metabolic syndrome and fatty liver, significantly reduced GFR in those with hyper-filtration, and reduced mean UACR in those with increased albuminuria, alongside achieving weight loss and improved blood pressure, glucose control, blood lipid profile, and insulin sensitivity. Taken together, such evidence suggests that improving lifestyle habits can produce important cardiometa-bolic changes which could counteract the classical scenario of the evolution of renal function loss and obese/diabetic nephropathy.

Dr. Manuela Abbate is associate professor of nutrition at the University of the Balearic Islands and at the ADEMA University School, and a research member of the Global Health and Lifestyle Research Group of the Health Research Institute of the Balearic Islands. Her research focuses on the effects of lifestyle changes on the prevention of chronic disease. She is particularly interested in the hemodynamic changes associated with hyperfiltration as a risk factor for accelerated renal function loss, and their amelioration through diet and exercise interventions in type 2 diabetes and obesity. She has also recently been exploring the possible association between non-alcoholic fatty liver disease (NAFLD) and metabolic associated fatty liver disease (MAFLD) with hyperfiltration in patients with metabolic syndrome as well as in the general population.

DIAGNOSTICS

The non-invasive CV risk assessment of obese diabetic patients with CKD

Sebastjan Bevc[1,2]
[1]*Department of Nephrology, University Medical Centre Maribor, Maribor, Slovenia*
[2]*Faculty of Medicine, University of Maribor, Maribor, Slovenia*

Diabetes mellitus (DM) is the number one cause of chronic kidney disease (CKD) worldwide and is linked with increased mortality mostly due to cardiovascular causes. Today we are also facing an obesity pandemic worldwide and in Europe up to 30% of the adult population is already obese. Due to the increasing burden of DM, CKD and obesity, prevalence of the cardiovascular disease attributed to advanced and fulminant atherosclerosis will continue to rise. This complex process of atherosclerosis involving the interplay between traditional (male gender, smoking, advanced age, obesity, arterial hypertension, dyslipidemia) and non-traditional, CKD-specific risk factors (anemia, inflammation, proteinuria, volume overload, mineral metabolism abnormalities, oxidative stress, etc.) culminating in endothelial dysfunction, inflammation, plaque formation, and ultimately, target organ ischemia and damage. To reduce morbidity, mortality of these patients, immediate cardiovascular risk assessment is crucial and it appears that a multimarker approach should be used to recognize patients with the highest risk for cardiovascular events.

In the lecture different non-invasive methods of assessing cardiovascular risk in patients with DM and CKD will be discussed and presented some recently published data concerning also obese patients with DM and CKD.

Dr. Sebastjan Bevc is a professor of Internal medicine, head of Department of Nephrology at the University Medical centre Maribor and the head of the Department of Pharmacology of the Faculty of Medicine at University of Maribor, holder of research and participating in national and international projects, he contributed to the knowledge in the field of asymptomatic atherosclerosis, markers of kidney function, hyperuricaemia, metabolic-bone disease, dialysis procedures, development of »in vitro nephron«, pharmacotherapy, bioimpedance, simulations and medical education. He is the associate editor of BMC nephrology, London, section editor of Acta dermatovenerologica Alpina, Panonica et Adriatica, Ljubljana, Slovene Welding Society and Frontiers in Medicine, Lausanne, member of the editorial boards of other domestic and foreign journals, a board member of the Diabesity Working group at the ERA and a board member of the international working group Critical Appraisal of Guidelines at the European Federation of Internal Medicine (EFIM). Dr. Bevc is an active member of the European Kidney Function Consortium (EKFC). He is a reviewer for many international journals covering the field of nephrology, dialysis, internal medicine, pharmacology and medical education.

The error of estimated GFR in Diabetes

Sergio Luis Lima[1], Esteban Porrini[2,3]
[1]*Laboratory, Hospital Universitario de Canarias, Tenerife, Spain*
[2]*Research Unit of the University Hospital of the Canary Islands, La Laguna, Tenerife, Spain*
[3]*Institute of Biomedical Technology, University of La Laguna, Spain*

Renal function can be evaluated by standard methods like creatinine, 24 h creatinine clearance and formulas that estimate GFR. However, the problem is that the reliability of these equations -and there are more than 70 equations in 2022 - is very poor. The average error of any available formula is about 30% of real - measured GFR. I will discuss the problem and consequences of this error in patients with diabetes.

NAFLD and CKD and challenges in diagnostic methods

Therese Adrian[1]
[1]*Department of Nephrology, Copenhagen University Hospital, Copenhagen, Denmark*

Emerging evidence has suggested non-alcoholic fatty liver disease (NAFLD) as being a risk factor for development of chronic kidney disease. NAFLD has become the most common liver disease worldwide affecting around one in four of the general global population. The disease covers a spectrum that ranges from simple steatosis to non-alcoholic steatohepatitis (NASH) with and without fibrosis. To date, most of the published studies are on patients with NAFLD with normal kidney function. Studies in patients with established CKD are few, showing conflicting results. This might be due to 1) differences in study population 2) definition of NAFLD, and 3) choice of method for evaluation of NAFLD.

The focus of this lecture will be on different methodologies used in the evaluation of NAFLD. A liver biopsy is the gold standard method for diagnosing and grading the whole spectrum of NAFLD. Non-invasive methods are used in the evaluation of fibrosis and steatosis. Ultrasound is often used as a first-line imaging technique for steatosis due to its availability, though magnetic resonance spectroscopy and magnetic resonance imaging proton density fat fraction (MRI-PDFF) are considered more accurate. The FibroScan® is used for the evaluation of fibrosis and has potential to be used as screening tool in high-risk individuals in combination with blood tests to evaluate fibrosis such as the Fib-4 score and NAFLD fibrosis score. Future studies evaluating NAFLD in patients with CKD should focus on the severe stages of the spectrum including those with NASH and different stages of fibrosis.

I graduated as a medical doctor in 2016. After a year of internship, I returned to the Department of Nephrology at Copenhagen University Hospital—Rigshospitalet for research. My focus has, during the five last years, been on non-alcoholic fatty liver disease (NAFLD) in patients with chronic kidney disease (CKD) where I have investigated NAFLD in patients with established CKD in two different cohorts. The outcome of the studies is just about to be gathered in a Ph.D. thesis which I am about to submit October 2022.

Role of biomarkers in the early detection of kidney damage

Alberto Ortiz[1,2]

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[2]*Autonomous University of Madrid, Madrid, Spain*

Chronic kidney disease (CKD) is one of the fastest growing global causes of death. This trend has several causes. One of them is the delayed diagnosis of CKD. The thresholds for the most widely used current diagnostic criteria for CKD, estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio (UACR), contribute to this delayed diagnosis, as they imply that over 50% of kidney function has been lost and albuminuria has increased over 6-fold from physiological levels. Moreover, although albuminuria was introduced as a means for earlier diagnosis of CKD, the current epidemiology data, in which the most prevalent CKD category is G3a, suggest that most patients lose over 50% of kidney function before UACR levels are diagnostic of CKD. Thus, earlier biomarkers that meet criteria to be used in the early diagnosis of CKD are needed. These criteria include predicting CKD progression, in this case predicting either rapid eGFR loss or CKD category G3-G5 or category A2-A3, and predicting an increased risk of premature all-cause and cardiovascular death. Currently, the best characterized biomarkers that meet at least part of those criteria are albuminuria itself (the 30 mg/g UACR threshold is arbitrary as the risk of adverse outcomes is linear from values of around 2 mg/g) and urinary peptidomics and, more specifically, the urine peptide panel CKD273 and its variants. Eventually, these novel biomarkers should be incorporated into the KDIGO definition of CKD and standardized techniques should be developed that allow worldwide assessment by validated methods in a cost-effective manner.

Prof. Alberto Ortiz is Chief of Nephrology and Hypertension at the Health Research Institute of the Jiménez Díaz Foundation and University Hospital (IIS-FJD-UAM), Madrid, Spain and Professor of Medicine at the Autonomous University of Madrid (UAM). He was a post-doctoral research fellow at the Renal-Electrolyte Section of the University of Pennsylvania. He is European Renal Association (ERA) Clinical Nephrology Governance Chair/Chair of the Registry, member of European Renal Best Practice (ERBP), coordinator of the Spanish Renal Research Network (REDINREN), RICORS2040 and SPACKDc (ISCIII Precision Medicine initiative), Distinguished Fellow of the ERA (FERA), Board member of SOMANE. He received the 2020 ERA-EDTA Award for Research Excellence.

Mineralocorticoid receptor antagonists in DKD

Nina Vodošek Hojs[1,2]
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Diabetes mellitus and diabetic kidney disease (DKD) represent an important worldwide health issue. Therefore, prevention and treatment of DKD are crucial. DKD is mostly driven by renal and vascular inflammation, matrix formation, and fibrosis. Relative aldosterone excess stimulates the inflammatory and proliferative response in DKD. Therefore, mineralocorticoid receptor antagonists (MRA) have long been of interest in the treatment of DKD. Steroidal MRA reduce proteinuria in CKD, but its use has been limited by side effects, especially hyperkalemia. With the advancement of non-steroidal MRA, who cause fewer side effects, broader use was possible. Till recently hard outcomes such as kidney disease progression, cardiovascular events, and mortality data were missing for all MRA, except finerenone. Finerenone is a non-steroidal MRA and has recently been approved by the FDA and EMA and is recommended in guidelines for management of DKD. In my lecture I will review the mostly studied MRA with a special emphasis on finerenone.

Nina Vodošek Hojs is a nephrologist currently working at the University Medical Centre Maribor. She is also an assistant professor of internal medicine at the Medical Faculty, University of Maribor. During 2016 and 2017 she was an ERA-EDTA research fellow at the St. George's University Hospital NHS Foundation Trust in London. In 2018 she received a Fulbright scholarship during which she joined The Kidney Project at Schools of Pharmacy and Medicine, University of California, San Francisco.

SGLT2 inhibitors: a focus on CKD

Draženka Pongrac Barlovič[1,2]

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[2] *Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia*

During the recent years, SGLT-2 inhibitors have climbed up to the top of diabetes algorithms. They have proven to reduce blood glucose, blood pressure, and body mass index. Within the past few years, large-scale trials have demonstrated that SGLT-2 inhibitors can reduce cardiovascular outcomes and even mortality in high-risk individuals with type 2 diabetes. Moreover, they can be used also in people without diabetes in cases of heart failure or chronic kidney disease (CKD).

Over the last years, two large studies were published that focused on patients with CKD and demonstrated the renal benefits of SGLT-2 inhibitors in these patients. In the CREDENCE trial, canagliflozin demonstrated substantial benefits for renal outcomes in individuals with type 2 diabetes. In the DAPA-CKD trial, individuals with CKD who received dapagliflozin had a significantly lower risk of a composite of renal outcomes compared with those who received placebo, independently of diabetes presence. Similar results have been announced for empagliflozin in EMPA-KIDNEY trial, however, results have not been published yet.

Importantly, post-hoc analyses of large cardiovascular trials have reported similar relative benefits of SGLT-2 inhibitors across all subgroups of participants with type 2 diabetes, regardless of baseline estimated GFR or urinary albumin excretion. In addition, post-hoc analyses revealed that SGLT-2 inhibitors reduce the risk of anaemia and hyperkalaemia in patients with CKD.

Altogether, published data strengthen the role of an SGLT-2 inhibitor as a foundational element of care in CKD, but also in primary prevention of CKD in individuals with type 2 diabetes.

Drazenka Pongrac Barlovic completed her medical degree at the University of Ljubljana in 2002. She completed her postdoctoral fellowship at the University of Helsinki, Finland, with Professor Per-Henrik Groop as well as at the Baker Heart and Diabetes Institute, Melbourne, Australia, with Professors Mark Cooper and Karin Jandeleit-Dahm. Dr Pongrac Barlovic is a consultant physician at the Clinical Department of endocrinology, diabetes and metabolic diseases at the University Medical Centre Ljubljana and also works as an Adjunct Professor at the Faculty of Medicine, University of Ljubljana. Her research focus is diabetic nephropathy and treatment of diabetes in pregnancy. Work with her colleagues includes publications in Lancet Diabetes Endocrinology, Diabetes care and Diabetologia. She is a current president of the Diabetology Association of Slovenia and is a member of the Coordinative group of the National Program for Diabetes Control at the Ministry of Health, Slovenia.

Role of combination therapy in preventing DKD

Matias Trillini[1]
[1]*Mario Negri Institute for Pharmacological Research, Bergamo, Italy*

Firstly, my presentation is going to address some of the most important trials and achievements in the field of diabetic kidney disease (DKD) in recent clinical history. Despite the improvements in kidney outcomes in diabetic patients reached by RAS inhibitors (ACEi and ARBs) over the last few decades, the following attempts to reduce the still remaining risk of progression towards end stage renal disease by using higher doses of these drugs or both ACEi and ARBs in combination failed to achieve expected outcomes and, in some cases, worsened kidney conditions or added further risk. Additional treatments with vitamin D, reduced salt intake and mineralocorticoid receptor antagonists (MRA) led to minor improvements. For a period of time, substantial results in renal outcomes in DKD remained elusive and standard of care remained unchanged. Secondly, the talk will focus on the importance of hyperfiltration in DKD and provide some reasons for its reduction. Shortly, our experience with calorie restriction in patients with obesity and diabetes. Then, I will get more in depth on how the course of the DKD seems to have been abruptly changed by the booming irruption of the SGLT2i and how these treatments are dramatically impacting both research and clinical practice. This will be followed by a short comment about the role of non-steroidal MRA in DKD and the combination of the latter with SGLT2i. Finally, I will comment on where we currently stand regarding combination treatment and what the future holds for DKD.

Doctor Matias Trillini was born and raised in Bahia Blanca, Argentina and has currently been living and working in Bergamo Italy since 2009. In his native country he has earned a degree in Internal Medicine and Nephrology from University of Buenos Aires and worked as a physician at the Italian Hospital of the same city. His main focus is the conduct of clinical trials in humans in the Nephrology research field. Doctor Trillini is currently working at Mario Negri Institute for Pharmacological Research, where he follows patients with different kidney-related issues, diabetes complications and obesity. He's currently a board member of the DIABESITY group as well as the author of publications in the above mentioned areas.

Atherosclerosis, epigenetic modifications in CKD

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[2]*Faculty of Medicine, University of Maribor, Maribor, Slovenia*

Atherosclerosis is a chronic inflammatory disease of the vessel wall, which is characterized by progressive plaque build up, changes in blood flow through arterial wall stiffening and consequent end organ damage. The impact of chronic kidney disease (CKD) on the process of atherogenesis is through the combination of traditional atherosclerosis risk factors and CKD-specific factors (chronic inflammation, hyperhomocysteinemia, proteinuria, hyperphosphatemia, hyperparathyroidism, etc). MicroRNAs are epigenetic regulators of several processes in the body and can be detected in blood, saliva and urine. Epigenetic dysregulation is common in several pathological states, which is why microRNAs can serve as important biomarkers. For example, MicroRNA-92a (miR-92a) is induced by oxidative stress in endothelial cells and is associated with angiogenesis and atherosclerosis in CKD patients. MiR-126 is associated with endothelial dysfunction and both miR-155 and miR-223 are associated with vascular calcifications and bone mineral disease in the CKD population. Decreased circulating levels of miR-125b and miR-145 have been found in patients with CKD and animal studies imply that they are markers of vascular remodelling. Additionally, miRNAs have vast potential in detecting incident acute kidney injury and delayed graft function after transplantation (upregulation of miR-21), detecting CKD (downregulation of miR-126 and miR-223) and assessing the response to treatment (miR-103a-3p in hypertensive nephropathy). Epigenetic studies are still in its beginning stages, especially in CKD patients, and more studies should be done to determine their role in routine clinical practice.

Nejc Piko, MD is a nephrologist, currently employed at the Department of Dialysis, University Medical Centre, Maribor. His research revolves around cardiovascular disease, atherosclerosis and the impact of chronic kidney disease on atherosclerosis and arterial stiffness. He is currently working on his PhD thesis, studying the role of non-invasively determined arterial stiffness in the prediction of coronary artery disease and the role of chronic kidney disease in atherogenesis. Part of his PhD thesis involves epigenetic regulators of atherosclerosis, micro RNA molecules.

FUTURE PROSPECTIVE

Renal proximal tubular epithelial cells: from harvesting to use in studies

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The kidney is a complex organ with several functions, comprised primarily of glomerular, tubular, mesangial, and endothelial cells, as well as podocytes. One of the main difficulties in curing acute kidney injury or chronic kidney disease (CKD) is the fact that kidney cells are terminally differentiated at 34 weeks of gestation and further regeneration after that is minimal. Additionally, CKD prevalence is ever increasing with very limited treatment modalities available, which is why the medical community should aim to improve existing and develop new methods of treatment. On the other hand, polypharmacy is present in the majority of CKD patients and current pharmacologic study designs are far from ideal. A possible way to tackle all these issues is with isolation and culture of renal cells. Several protocols are currently described to isolate the desired cells, of which the most isolated are the proximal tubular epithelial cells. They play a major role in water homeostasis, acid–base control, reabsorption of compounds, and secretion of xenobiotics and endogenous metabolites. When developing a protocol for isolation and culture one has to focus on several individual steps, such as harvesting cells from biopsy specimens or after nephrectomies as well as using different culture mediums to facilitate selective growth of cells. Additionally, several models exist from simple such as 2D in vitro cultures to more complex created with bioengineering methods such as kidney-on-a-chip models. While their creation and use is dependent on the research question at hand, one should not dismiss factors such as equipment and cost.

Tadej Petreski is an Internal Medicine resident at the Department of Nephrology, University Medical Centre Maribor, Slovenia, who has graduated from the Faculty of Medicine, University of Maribor, Slovenia in 2018. Currently he is a PhD student in his final year, where he studies innovative ways of designing human in vitro kidney cell models to be used for pharmacologic and nephrotoxicity research. Additionally, he works part-time at the Faculty of Medicine, University of Maribor, as a Teaching and Research assistant. His interests include chronic kidney disease, hyperuricemia, cardiovascular disease, kidney cell research, clinical reasoning development, and peer tutoring.

Caloric restriction reverses beta cell functional changes and glucose intolerance in a mouse of type 2 diabetes

Maša Skelin Klemen[1], Jan Kopecky[1], Eva Paradiž Leitgeb[1], Jasmina Kerčmar[1], Lidija Križančić Bombek[1], Viljem Pohorec[1], Ismael Valladolid-Acebes[2], Andraž Stožer[1], Jurij Dolenšek[1,3]

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[2]*Karolinska Institutet, Karolinska University Hospital, Solna, Sweden*

[3]*Faculty of Natural Sciences and Mathematics, University of Maribor, Maribor, Slovenia*

Diet-induced obesity (DIO) mouse models are a valuable research tool in studying pathophysiology of type 2 diabetes mellitus (T2DM), although the animal models currently used have some methodological drawbacks. On the other hand, clinical studies by Taylor et al. strongly suggest that caloric restriction results in effective remission of T2DM in humans, however limited mechanistical explanation is available at the level of beta cell function. We therefore constructed a novel mouse model of DIO that more closely reflects T2DM in humans to clarify functional and/or morphological changes following caloric restriction-induced remission of T2DM. C57BL/6J mice were fed a western diet for 12 weeks staring from the age of 12 weeks, after which they exhibited a T2DM phenotype in the form of fasting hyperglycemia, impaired glucose clearance and increased insulin resistance. 7 days of caloric restriction completely reversed the diabetic phenotype, with normalization of body mass, normalization of glucose handling and insulin sensitivity. To provide a mechanistical explanation for both the DIO and remission following caloric restriction at the level of beta cell function, we performed functional multicellular confocal calcium imaging on acutely prepared pancreatic tissue slices. A left shift in the glucose dependence was detected in the DIO group. Short term caloric restriction completely reversed the above compensatory left shift in beta cells and their oscillatory activity at a given glucose concentration decreased to that of the control group. Our findings further elucidate the impact of caloric restriction on T2DM and our animal model provides a novel platform for studying T2DM.

Maša Skelin Klemen, DVM, PhD

After graduating in veterinary medicine, she worked as a young researcher at the Institute of Physiology, Faculty of Medicine University of Maribor, where she obtained her PhD in Biomedical Technology in 2011. Since 2018, she has been an Assistant Professor of Physiology at the University of Maribor. Her research focuses on the physiology and pathophysiology of the pancreas tissue using acute pancreatic tissue slices combined with single-cell electrophysiology and functional multicellular confocal calcium imaging. She has been a member of the National Ethical Committee for Animal Testing since 2013. She is an animal welfare expert at the Faculty of Medicine University of Maribor.

FUTURE PROSPECTIVE

Involvement of Pro-Inflammatory IL-1 Cytokines in Tubular Fibrosis in Diabetic Kidney Disease

Vladislav Slobodysky[1], Adi Litmanovich[1], Kamal Hassan[1], Khaled Khazim[1]
[1]*Galille Medical Center, Azrieli Faculty of Medicine, Bar Ilan University, Israel.*

Introduction: Diabetic kidney disease is the leading cause of end stage kidney disease worldwide. Both glomerular injury and tubular fibrosis are involved in the progression of the disease. The pro-inflammatory cytokines are involved in the pathogenesis and progression of the disease. Polymorphism in IL-1 genes are associated with increased risk of DKD and progression of CKD

Methods: In vitro study, HK-2 renal proximal tubular epithelial cell line cells were cultured in RPMI 1640 medium, supplemented with 10% Fetal Bovine Serum. We measured both the gene and protein expression of IL-1 in these cells after exposure to high glucose (30 mM) compared to normal glucose (5.5 mM). Fibronectin expression was used as a marker of tubular injury. In the human study both urine and blood samples were collected from diabetic kidney disease patients and a control group. The levels of IL1 were measured from the serum and urine samples.

Results: The gene and protein expression of IL-1 alpha and IL-1 beta were increased in HK-2 cells after exposure to high glucose. In the human samples, urine IL-1 beta levels were significantly increased in diabetic patients compared to the control group, on the other hand the serum levels of IL-1 were similar to the control group.

Conclusions: Hyperglycemia increased IL 1 expression in human kidney tubular cells. The production of the IL 1 cytokine is most likely in situ due to high glucose exposure and may play a role in the pathogenesis of the tubular injury in diabetic kidney disease.

Khaled khazim, M,D. graduated at the faculty of Medicine Universita' Degli Studi Di Genova – Italy in 1995. Internal medicine residency at Poria Hospital, Tiberia, Israel and Nephrology residency at Galilee Medical Center, Israel. Postdoctoral Fellowship UT Health Center, San Antonio, Texas, USA. Senior physician at the nephrology department at the Galilee Medical Center in the years 2013-2021. Since 2021 regional director and clinical nephrologist at Maccabi Health Care Services, at the North of Israel. From 2015 clinical lecturer at the faculty of Medicine, Bar Ilan University. Board member Diabesity Working Group, ERA-EDTA since 2018. Involved in several clinical and basic studies in diabetic kidney disease.

CO-rebreathing and bioimpendance for measuring volume-changes in patients with CKD and diabetes treated with SGLT2 inhibitors

Tobias Bomholt[1]
[1]*Department of Nephrology, Copenhagen University Hospital, Copenhagen, Denmark*

Sodium-Glucose Cotransport-2 (SGLT-2) inhibitors are a relatively new class of drugs with renal protective effect. Proposed mechanisms include reduced renal energy consumption, improved glycaemic control, and reduced intraglomerular blood pressure. However, the impact on blood volume remains unelucidated. Studies do find that SGLT-2 inhibitors induce a significant loss in body weight and cause an increase in haematocrit that could reflect a reduction in plasma volume and thereby in blood volume. Bioimpedance and carbon monoxide rebreathing test allows for easy and reliable assessments of fluid status, body composition and intravascular blood volume−thus, allowing for measurements of the impact on these parameters of SGLT-2 inhibitors. Identification of changes in blood volume and fluid status, induced by SGLT-2 inhibitors, could contribute to the understanding of their beneficial effects in CKD patients.

Based in Copenhagen where I work as a consultant physician in Nephrology. Research focus is on diabetes and metabolic changes in patients with CKD—ranging from the mild stages to end-stage kidney disease and renal transplant recipients.

FUTURE PROSPECTIVE

New epigenetic insights related to high fat diet; a bridge between obesity and renal cancer. The Re.me.Diet study

Francesco Trevisani[1]
[1]*San Raffaele Scientific Institute, Milan, Italy*

Metabolic diseases are dramatically increasing their prevalence and incidence, becoming one of the most important and costly problems affecting population worldwide and the health care systems. The strongest predictor of such diseases as Diabetes is represented by obesity, which is rapidly increasing worldwide mainly due to an unbalanced and uncontrolled diet together with a reduced physical exercise. However, the onset of obesity as precursor of diabetes is also related to another insidious threat: renal cancer development. Renal cell carcinoma (RCC) is considered the most lethal neoplasm among the common genitourinary cancers, accounting for approximately 4% of all new malignancies worldwide and showing an increasing rate of incidence. The crosslink between obesity and renal cancer could be summarized by the establishment, in obese people, of a chronic inflammation in fat tissue evoked by cytokines and chemokines as well as extracellular matrix enzymes, which in turn damages the genetic information within the cells promoting mutations resulting in carcinogenesis. Therefore, a correct diet regimen could prevent not only the onset of obesity and subsequently diabetes, but also the development of a fatal malignancy such as renal cancer. In the last decade literature has clearly demonstrated that nutrition can modulate gene expression thanks to a precise epigenetic mechanism. In the REMEDIET translational study we demonstrated the epigenetic impact of an high fat diet on an animal model based on Iberian pigs with a clear differential gene expression related to different targets such as insulin resistance, cell fate determination, smooth muscle differentiation and mesenchymal differentiation.

Francesco Trevisani, MD, PhD, is an Associate Professor of Nephrology. Additionally he is on the Board of Diabesity ERA-EDTA working group, with the project of EUROPEAN NEPHRECTOMY BIOBANK (ENBIBA), is a Junior Leader of the Uro-oncological and Uro-nephrological projects inside the Urological Research Institute and the Department of Urology directed by Professor Montorsi, a consultant of Nephrology on staff in the Department of Urology, San Raffaele Scientific Institute, Milan, and founder and CEO of Biorek, an innovative molecular diagnostic startup focuses on liquid biopsies for the detection, diagnosis and monitoring of Kidney Cancer. He is the founder and project leader of REMEDIET project, an European molecular translational research aimed to investigate the epigenetic impact of the Mediterranean Diet on Renal function in Obese patients through a Next Generation Sequencing approach.

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Inflammation, Renal Lipotoxicity And Menopause In Obesity-Related Renal Disease

Afonso-Alí Aaron[1], Porrini Esteban[1], Teixidó Silvia[1], Rodríguez-González, Covadonga[2], Pérez Pérez Jose[2], Acosta González Nieves[2], Rodríguez-Rodríguez Ana[3]

[1]*University of La Laguna, Faculty of Medicine, Santa Cruz de Tenerife, Spain*

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Introduction: Obesity and overweight are risk factors for chronic kidney disease (CKD). Epidemiological studies suggest that patients with obesity in the context of metabolic syndrome are at a high risk of kidney damage. Furthermore, this damage may be exacerbated in women after menopause. However, the pathogenesis of these associations is unknown. We evaluated the interaction between inflammation, lipotoxicity and menopause in a mice animal model of metabolic syndrome: the C57/BL6J fed with fat-enriched diet.

Material and methods: Female mice (ovariectomized or not) and male mice were randomized to standard and a "cafeteria diet« for 6 months. This is a sub-analysis of a previous study (Rodriguez-Rodriguez et al. Menopause 2021) in which we found that obese animals developed albuminuria and glomerular hyperfiltration. For this study, we evaluated inflammation and performed a lipidomic analysis in renal tissue. Four inflammatory markers were analyzed by immunohistochemistry: NF-kβ, IL-1β, TNF-α and MCP-1. Total lipid, lipid classes, total fatty acids and fatty acids in lipid classes were determined by thin-layer chromatography (TLC) and gas chromatograph coupled mass spectrometer.

Results: Obese animals had higher levels TNF-alpha and MPC-1 in renal tissue and this profile was exacerbated after castration in obese females. Only obese males and obese-ovariectomized females had higher IL1β. In the lipidomc analysis we found an unbalance between some pro- and anti--inflammatory fatty acids, both in membrane lipids and triglycerides. Obese mice showed lower 20:2 n-6 and higher 22:6 n-3 in total fatty acids. All obese animals had less 20:3 n-6 in all phospholipids and minor levels of 18:2 n-6 in phosphatidylcholine. In triglycerides, obese animal showed lower 16:0, 16:1 n-7 and more 18:1 n-9. Most of these lipidomic changes were exacerbated in those castrated obese females than the other groups. Only obese and castrated females showed an increased 18:0 DMA in phosphatidylethanolamine and 18:0 in phosphatidylcholine and triglycerides.

Conclusion: Obesity induces an increase in inflammatory markers and an unbalanced lipidomic profile in renal tissue. This damage is exacerbated by obesity and menopause.

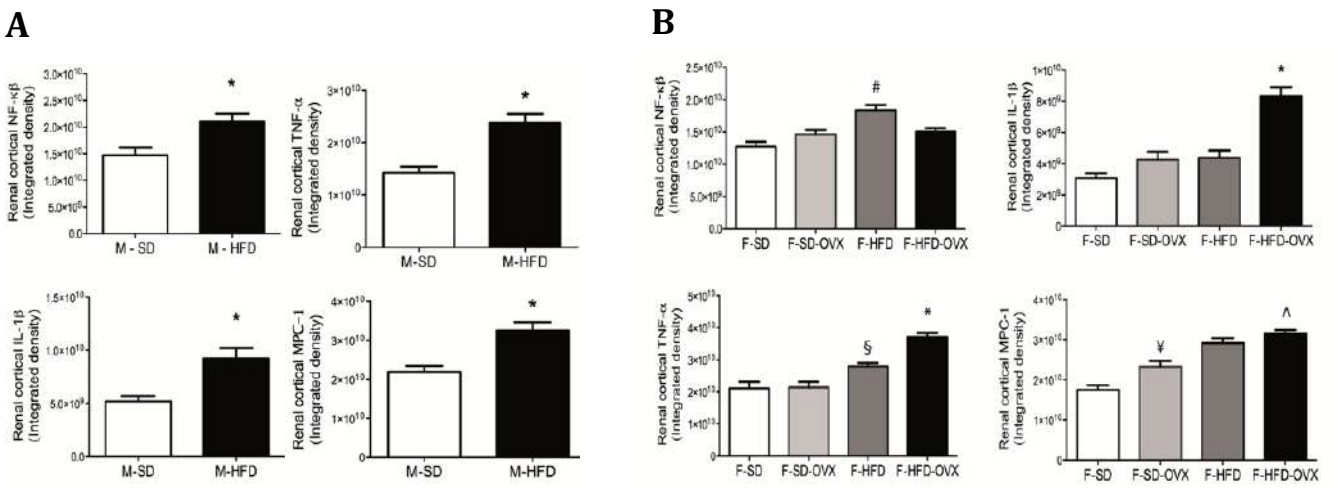

Figure 1. Quantitative analysis of each inflammation marker. Data are represented as mean ± SEM. #, M-SD vs. M-HFD p≤0.0037. **A:** Males: *, M-SD vs. M-HFD p≤0.001. M-SD: male standard diet; M-HFD: male high fat diet. **B**: Females: #, F-SD vs. F-HFD p≤0.0001; *, F-HFD-OVX vs. F-HFD and vs. F-SD-OVX vs. p≤0.0001; §, F-SD vs. F-HFD p≤0.0109; ¥, F-SD vs. F-SD-OVX p≤0.0153; ^, F-SD-OVX vs. F-HFD-OVX p≤0.0001. F-SD: female standard diet; F-HFD: female high fat diet; F-SD-OVX: female standard diet ovariectomized; F-HFD-OVX: female high fat diet ovariectomized.

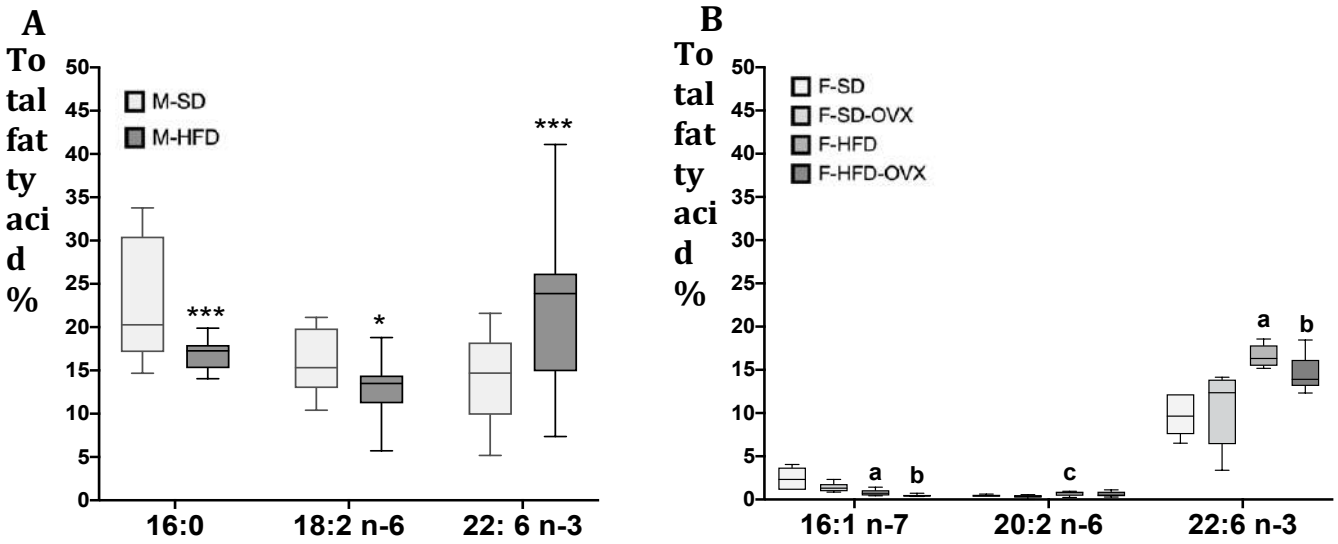

Figure 2. Total fatty acids in renal tissue of male and female animals. Data are represented as mean ± SEM**. A:** Males: M-SD vs. M-HFD, * *p < 0,05,* ** *p < 0,01,* ** *p < 0,001*: M-SD: M-SD: male standard diet; M-HFD: male high fat diet. **B**: Females: ***a,*** F-HFD vs. F-SD and vs. F-SD-OVX. p≤0.05. **b**, F-HFD-OVX vs. F-SD and vs. F-SD-OVX. p≤0.05. **c,** F-HFD vs F-SD-OVX. p≤ 0.05 females on standard diet, F-SD-OVX: females on standard diet + castration, F-HFD: F-SD: female standard diet; F-HFD: female high fat diet; F-SD-OVX: female standard diet ovariectomized; F-HFD-OVX:

Tacrolimus and the pancreatic β-cell: searching for a non-genotypic animal model of Type 2 Diabetes Mellitus

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[2]Institute of Biomedical Technology, University of La Laguna, Spain
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[4]Nephrology Department, University Hospital of the Canary Islands, La Laguna, Tenerife, Spain

Introduction. Type 2 Diabetes Mellitus (T2DM) is one of the most common diseases worldwide. It is associated with a higher risk of cardiovascular events, end stage renal disease, cancer and blindness. To treat and prevent T2DM it is essential to understand the pathophysiology of the disease. This is possible through the use of animal models. Unfortunately, there is no reliable animal model which properly reflects the pathophysiology of T2DM and chronic organ damage associated with the disease. Current models are mostly genotypic and monogenic and they infrequently develop the complications related to diabetes. Thus, a new model of T2DM is needed.

Objectives. We aim to develop a non-genotypic animal model of chronic T2DM. Based on our previous studies (1) we propose a model based on Sprague Dawley rats fed with a high fat diet (HFD) to induce metabolic syndrome in which Tacrolimus will accelerate the appearance of diabetes.

Material and Methods. In the first stage we'll induce metabolic syndrome in male Sprague Dawley with 45 days of a high fat diet. The metabolic syndrome will be confirmed by the performance of glucose tolerance test (IPGTT) and insulin tolerance test (ITT). In the second stage, on top of this metabolic syndrome we'll induce acute diabetes by the administration of Tacrolimus intraperitoneally at doses of 1 mg/kg/daily during 15 days. The induction of acute diabetes will be confirmed by IPGTT and ITT. Levels of blood Tacrolimus will be measured by LC-HRMS. In the third stage, to maintain a model of chronic diabetes during 3 – 6 months, Tacrolimus administration will vary every 2 – 3 days with dose regulation. Chronic organ damage will be evaluated in pancreas, kidneys, liver and vascular system. Chronic diabetes will be controlled by IPGTT, ITT and GFR measurements.

Results. In the first stage, metabolic syndrome has been induced by feeding the rats with a HFD during 45 days. Blood glucose levels were slightly increased in HFD groups compared to controls in a standard diet. In the second stage, short-term Tacrolimus treatment of 1 mg/kg/daily result in severs hyperglycaemias only in HFD fasted rats and at the 120 minutes of the IPGTT. Body weight remained constant throughout the experiment, thus the continuous administration of a high dose of Tacrolimus seems not to be harmful for the animals. With these results we can confirm the induction of acute T2DM in obese Sprague Dawley rats. Basing on this, we will focus in the development of a chronic and non-genotypic T2DM Sprague Dawley model by the long-term administration of Tacrolimus.

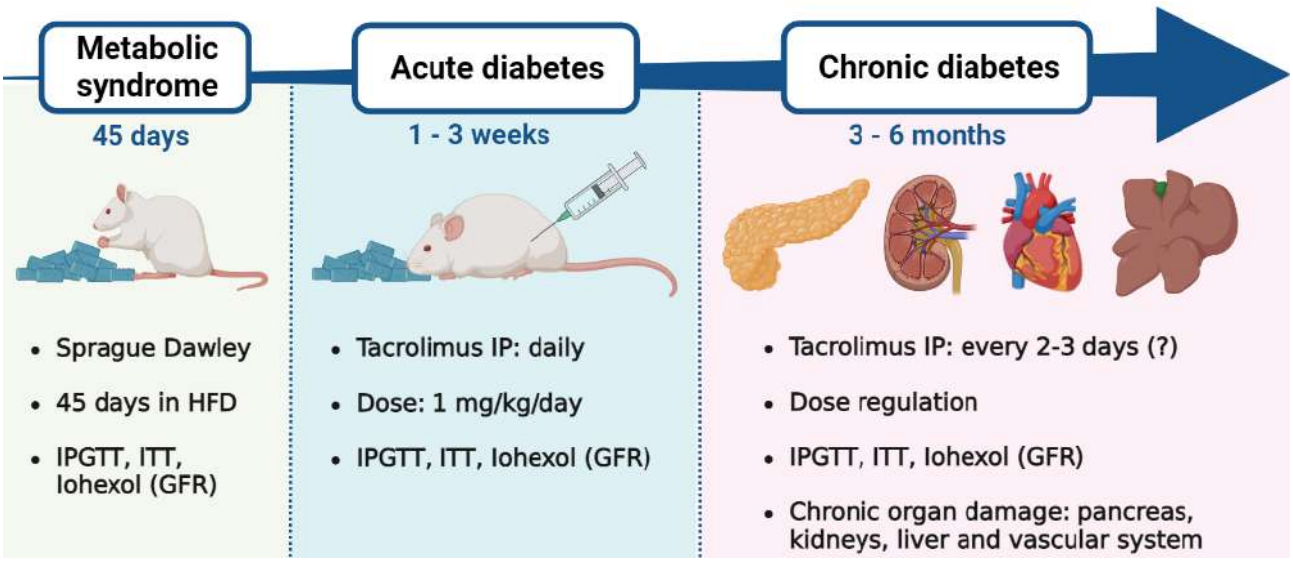

Figure 1: experimental design proposed for the development of a non-genotypic animal model of T2DM. In the first stage we'll induce metabolic syndrome in male Sprague Dawley with 45 days of a high fat diet. In the second stage we'll induce acute diabetes by the administration of Tacrolimus intraperitoneally at doses of 1 mg/kg/daily during 15 days. In the third stage, to maintain a model of chronic diabetes during 3 – 6 months, Tacrolimus administration will vary every 2 – 3 days with dose regulation. Chronic organ damage will be evaluated in pancreas, kidneys, liver and vascular system.

References

1. Rodriguez-Rodriguez AE, Triñanes J, Velazquez-Garcia S, et al. The higher diabetogenic risk of tacrolimus depends on pre-existing insulin resistance. A study in obese and lean Zucker rats. Am J Transplant. 2013;13(7):1665-1675. doi:10.1111/ajt.12236

Exercise and Renal Disease: EX-RED – preliminary results

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Background: obesity and metabolic syndrome (MS) are risk factors for renal disease progression in patients with established chronic kidney disease (CKD). However, the effect of intervention on obesity/MS on major renal outcomes: proteinuria and/or glomerular filtration rate (GFR) decline is scarcely known.

Objective: to evaluate the effect of therapeutic exercise in patients with CKD and MS on renal parameters: GFR and proteinuria and the amelioration of MS traits.

Methods: EX-RED is a 6-month prospective exploratory study. Inclusion criteria: (1) CKD of different causes, (2) age>18 y (3) GFR 30-90 ml/min/kg2, (4) (5) MS, at least 3 traits: obesity (IMC≥ 27 Kg/m2), prediabetes, dyslipidemia, hypertension and (6) capacity to perform exercise. Exercise treatment: incremental protocol based on physical status and individual response on follow-up, using both aerobic and strength exercise. A plan of adherence based on phone calls, an activity tracker and visits to the hospital. Glomerular filtration rate was measured (iohexol) at baseline, at 3 and 6 months. Also, changes in MS traits, analytics and albuminuria/proteinuria were collected. Sample size included 40 cases with an estimated drop-out of 10-15%.

Results: preliminary analysis at 3-month follow-up with 23 cases. Mean age was 58.4 y ± 12, 70% male. All patients were obese-overweight and 70% were diabetic (HbA1c 6.6% ± 1.2). The most frequent kidney diseases were glomerulopathies (39%) and diabetic nephropathy (30%). Most patients were on ACE inhibitors/ARAs (96%), lipid-lowering agents (52%). At 3 months patients were grouped in those who ameliorated MS (n=18) or not (n=5). However, no major changes were observed in GFR and albumin/proteinuria ratio between groups. In a sub-analysis we re-evaluated those patients with changes in MS in 2 subgroups (a) those who lost weight and had a reduction in GFR (N=5) and (b) those who lost weight without changes in GFR (N=13). In first subgroup there was a significant decrease in GFR (65 ml/min ± 22 to 56±19.1) and albuminuria/proteinuria (788ml/min ± 767.9 to 499 ml/min ± 758.7) – see table 1.

Conclusions: exercise is an effective intervention method to lose weight and improve metabolic profile in CKD. Not all patients who lose weight have an effect on renal parameters. The pathogenic background of this different effect needs future attention.

	CHANGES IN GFR AND PROTEINURIA		NO CHANGES IN GFR AND PROTEINURIA	
	BASELINE	3 MONTHS	BASELINE	3 MONTHS
N	5 (28%)		13 (72%)	
Age (years)	60.9 ± 11.9		57.7 ± 12.4	
Sex (♂-%)	2 (40%)		10 (77%)	
Diabetes (%)	3 (60%)		8 (62%)	
Weight (kg)	94.9 ± 21.1	89 ± 22	97.7 ± 17	90.8 ± 15.4
BMI (kg/m²)	34.8 ± 6.6	32.6 ± 7	35.9 ± 3.7	33.4 ± 3.5
SBP (mmHg)	133.8 ± 22.8	138.4 ± 25.8	145.1 ± 24.1	130.6 ± 17.6 [a]
DBP (mmHg)	72.9 ± 6.6	70.5 ± 14.4	76.8 ± 9.9	69.6 ± 7.9 [b]
HbA1c (%)	6.6 ± 1.3	5.9 ± 0.5 [c]	6.3 ± 1.1	6 ± 0.6 [d]
TG (mg/dL)	209.8 ± 88.7	174.6 ± 65.8	191.2 ± 82.1	112 ± 43.1 [e]
Iohexol ml/min	64.7 ± 22.1	56.3 ± 19.1 [f]	51.9 ± 18.6	53.2 ± 18.5
Alb/Cr (mg/g)	787.9 ± 767.9	498.8 ± 758.7 [g]	877.5 ± 1070.8	816.9 ± 894.2

Table 1. Baseline and 3 months characteristics of patients according to the evolution of weight and glomerular filtration rate. The data are represented as mean/percentages ± SD. Abbreviations: BMI (Body Mass Index), SBP (Systolic Blood Pressure), DBP (Diastolic Blood Pressure), HbA1c (Glycated Haemoglobin), TC (Total Cholesterol), TG (Triglycerides) and C. Alb/Cr (Albumin/Creatinine Ratio).

Super index legend: a (p=0.04NS); b (p=0.05); c (p=0.042); d (p=0.018); e (p=0.002) f (p=0.016) and g (p=0.043).

Inflammation On The Waiting List And The Risk For New Onset Prediabetes And Post-Transplant Diabetes Mellitus (Ptdm)

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Background/Objective: Inflammation is a risk factor for T2DM in the general population. The role of inflammation in prediabetes or PTDM is not clear. Our objective was to examine the association between inflammatory markers on the waiting list with prediabetes and PTDM after one-year transplantation.

Methods: Nondiabetic patients on the waiting list for kidney transplantation were enrolled. The patients were monitored up to 12 months for prediabetes or PTDM after transplantation. Oral glucose tolerance test (OGTT) was performed before and after transplantation. Prediabetes patients was defined as impaired fasting glucose (IFG: fasting glucose ≥100 and ≤125 mg/dL) and impaired glucose tolerance (IGT: glucose at 120 min between ≥140 and <200 mg/dL) and PTDM or occult diabetes mellitus (DMo) with fasting glucose ≥126 and/or glucose at 120 min ≥200 mg/dL. Inflammatory cytokines (TNFα, IL6, IL1β, CRP, MCP1) were measured before kidney transplantation. Those markers were selected based on the available evidence as risk factors for T2DM in the general population.

Results: We studied 110 patients on the waiting list of whom 74 did not present alterations in glucose metabolism before transplantation and 36 patients had: 30 (27%) had prediabetes and 6 (5.5%) DMo. The evolution of these patients to one year after transplantation is summarized in figure 1. The variables independently associated with a higher risk of prediabetes or PTDM one year after transplantation were BMI (OR:1.17 95% CI: 1.055-1.304), the cumulative dose of steroids (OR: 1 95% CI: 1-1.001) and the presence of previous prediabetes or DMo (OR: 2.4 95% CI: 0.951-6.048) although with borderline significance. No inflammatory marker was significant in the multivariant model (table, model A). To evaluate possible causes of the lack of association between inflammations and prediabetes and PTDM we tested the concomitant appearance of obesity, alterations in glucose metabolism and inflammation in the waiting list (figure II). In general, 75% of the obese had inflammation and/or alterations in glucose metabolism (prediabetes/DMo). Between 40-70% of the cases with alterations in glucose metabolism also presented obesity and/or inflammation. Finally, 40-60% of the inflamed patients also had prediabetes/DMo and/or obesity. Therefore, in two out of three patients share common metabolic markers: prediabetes, inflammation, obesity. This strongly limits the evaluation of the independent effect of one factor. So, to evaluate the impact of inflammation on new onset prediabetes/PTDM one year after transplantation, we selected in the waiting list the subjects without prediabetes/DMo (n=72). Of these patients, 15 (20%) developed prediabetes and 17 (23%) had PTDM one year after transplantation. In this group, BMI (OR: 1.19 95% CI: 1.02-1.37) and TNFα levels (OR:

1.09 95% CI: 1.01-1.18) were independently associated with a higher risk of prediabetes or PTDM one year after transplantation in the multivariant model (table, model B).

Conclusion: Inflammation in the waiting list precedes the development of prediabetes or PTDM after transplantation. This may indicate a subgroup of patients at higher risk for these complications.

Figure I: Evolution from pre-transplantation to 12 months after kidney transplantation

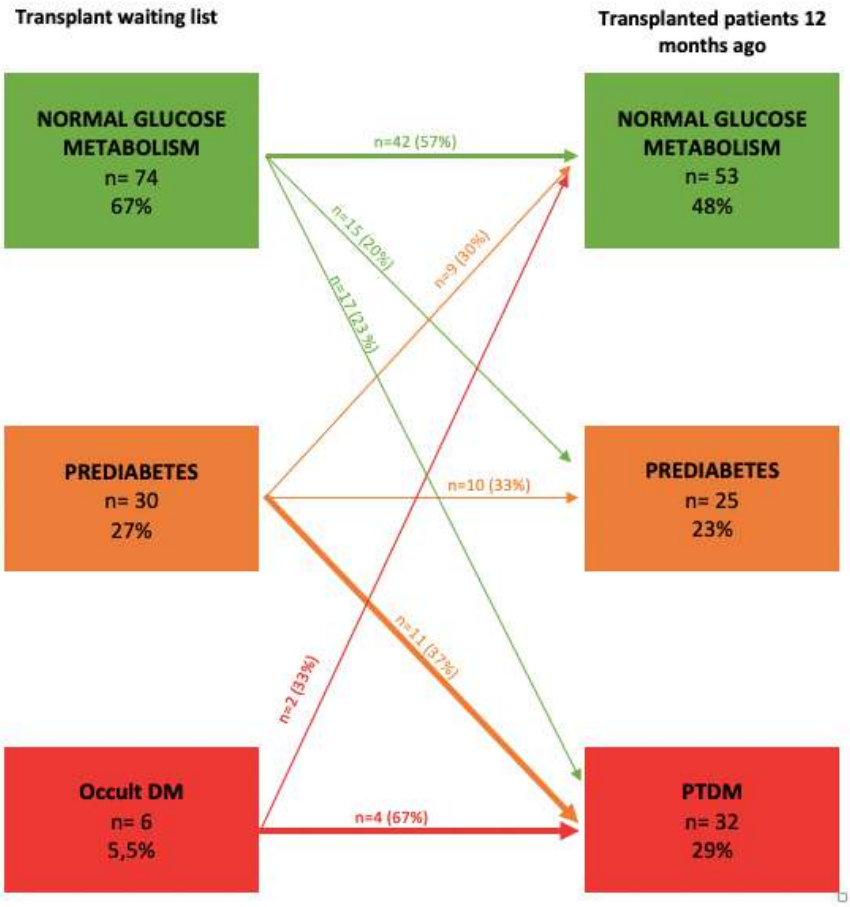
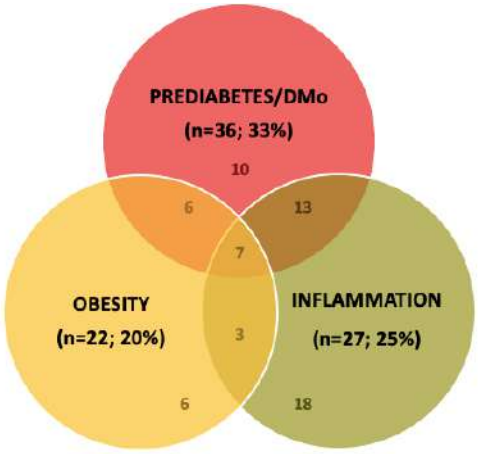


Figure II: Obesity, glucose metabolism alterations and Inflammation defined with TNFα levels

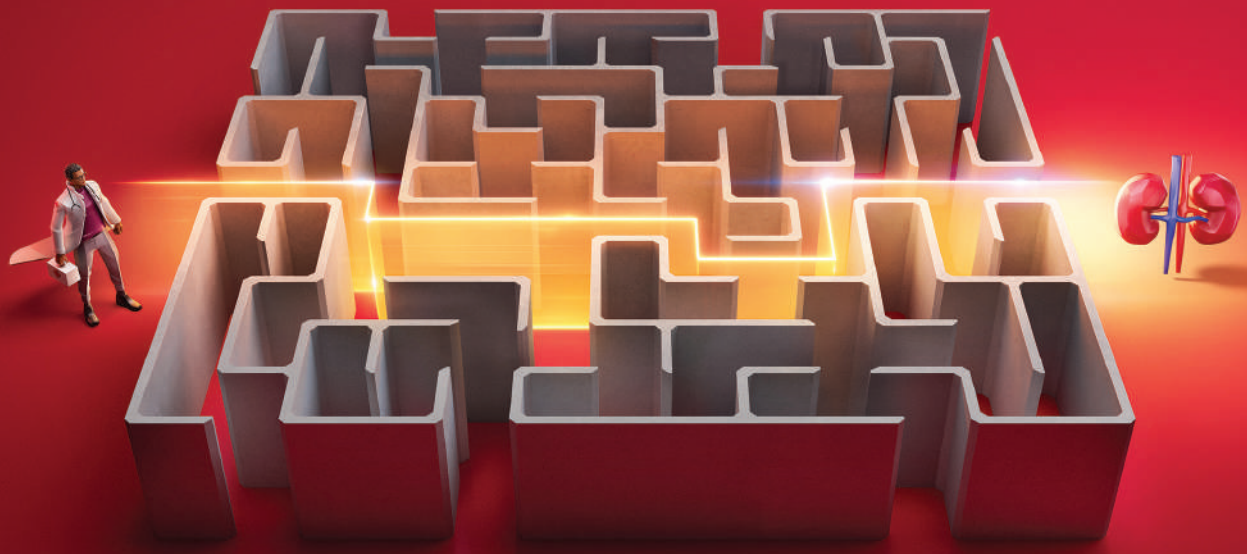


		OR	IC 95%	P-value
Model A	BMI (kg/m^2)	1.17	1.06-1.3	0
	Cumulative dose steroids (mg)	1	1-1.00	0.05
	Prediabetes or Dmo (yes)	2.4	0.95-6.05	0.06
Model B	BMI (kg/m^2)	1.19	1.02-1,37	0.02
	TNFα (pg/mL)	1.09	1.01-1.18	0.03

For adult patients with CKD and T2D*

A different pathway leads to different possibilities

Delay CKD progression with Kerendia[1,2]



The first and only selective mineralocorticoid receptor antagonist (MRA) approved to treat CKD in T2D[1]

- Proven to delay CKD progression and reduce the risk of a CV event[1]
- Simple to combine with existing therapy[1,2*]

Indication: Kerendia is indicated for the treatment of chronic kidney disease (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adult patients.

* Please refer to your local prescribing guidelines for any contraindication before prescribing.[1]
CKD=chronic kidney disease; CV=cardiovascular; T2D=type 2 diabetes
References: 1. Kerendia Summary of Product Characteristics (february 2022). 2. Bakris GL, et al; FIDELIO-DKD Investigators. N Engl J Med.2020;383(23):2219-2229.

▼ This medicinal product is subject to additional monitoring Adverse events should be reported. Please report any suspected adverse reaction to National Pharmacovigilance Centre (JAZMP), Website: (http://www.jazmp.si/humana-zdravila/farmakovigilanca/porocanje-o-nezelenih-ucinkih-zdravil/)

Kerendia 10 mg/ 20mg film-coated tablets
(Refer to full SmPC before prescribing.)
COMPOSITION: ACTIVE INGREDIENT: 10 mg/20 mg finerenone. Excipients[2]: microcrystalline cellulose, croscarmellose sodium, hypromellose 2910, lactose monohydrate, magnesium stearate, sodium laurilsulfate, talc, titanium dioxide, iron oxide red (E 172) (Kerendia 10 mg only), iron oxide yellow (E 172) (Kerendia 20 mg only). **INDICATION:** Kerendia is indicated for the treatment of chronic kidney disease (stage 3 and 4 with albuminuria) associated with type 2 diabetes in adults. **CONTRAINDICATIONS:** Hyperkalaemia has been observed in patients treated with finerenone. Risk factors to develop hyperkalemia include low eGFR, higher serum potassium and previous episodes of hyperkalaemia. In these patients more frequent monitoring has to be considered. Finerenone treatment should not be initiated in patients with serum potassium > 5.0 mmol/L, with eGFR < 25 mL/min/1.73 m^2, or severe hepatic impairment. If serum potassium > 5.5 mmol/L, finerenone treatment has to be withheld, once serum potassium ≤ 5.0 mmol/L, finerenone treatment can be restarted at 10 mg once daily. Serum potassium and eGFR have to be remeasured in all patients 4 weeks after initiation, re-start or increase in dose of finerenone. Finerenone should not be given concomitantly with potassium-sparing diuretics, other mineralocorticoid receptor antagonists (MRA) and with strong or moderate CYP3A4 inducers. Grapefruit or grapefruit juice should not be consumed during finerenone treatment. Finerenone should be used with caution and serum potassium should be monitored when taken concomitantly with potassium supplements, trimethoprim, or trimethoprim/sulfamethoxazole, moderate or weak CYP3A4 inhibitors and in patients with moderate hepatic impairment. Due to limited clinical data, finerenone treatment should be discontinued in patients who have progressed to end-stage renal disease (eGFR < 15 mL/min/1.73 m^2). Finerenone should not be used during pregnancy unless there has been careful consideration of the benefit for the mother and the risk to the foetus. Women should be advised not to breast-feed during treatment with finerenone. This medicinal product contains lactose. **UNDESIRABLE EFFECTS:** *Very common:* hyperkalaemia; *Common:* hyponatraemia, hypotension, pruritus, glomerular filtration rate decreased; *Uncommon:* haemoglobin decreased. **On prescription only. Marketing Authorisation Holder:** Bayer AG, 51368 Leverkusen, Germany. **Date of revision of the underlying Prescribing Information:** February 2022

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PP-KER-SI-0026-1_09.2022

Kerendia® finerenone

forxiga®
(dapagliflozin)

ZAŠČITI ŽIVLJENJE
Eno zdravilo - tri indikacije[1]

PRVI IN EDINI SGLT2i

z indikacijo za zdravljenje **kronične ledvične bolezni** pri odraslih, z ali brez SB2[1-4]

- **39 % RRR** za napredovanje **KLB, KLO ali smrt** zaradi ledvičnih ali srčno-žilnih vzrokov v primerjavi s placebom[1,5*]
- **31 % RRR za smrt** iz kateregakoli vzroka v primerjavi s placebom[1,5**]

Dosledni podatki o učinkovitosti in varnosti pri bolnikih s KLB, z ali brez sočasne SB2[1,5,6]

Slovarček:
* V študiji DAPA-CKD so rezultati primarnega cilja opazovanja pokazali, da FORXIGA kot dodatek standardnemu zdravljenju omogoča 39 % RRR za sestavljen cilj opazovanja, ki vključuje trajno zmanjšano oGF za ≥ 50 %, razvoj končne odpovedi ledvic ali nastop smrti zaradi ledvičnih ali srčno-žilnih vzrokov (ARR 5,3 %) v primerjavi z uporabo samo standardnega zdravljenja pri 4.304 odraslih bolnikih s kronično ledvično boleznijo z oGF od 75 do 25 ml/min/1,73m2 (mediano trajanje spremljanja je bilo 2,4 leta; p < 0,001). Končna ledvična odpoved je bila opredeljena s potrebo po vzdrževalnem dializnem zdravljenju (peritonealni dializi ali hemodializi) najmanj 28 dni in s presaditvijo ledvic ali z dolgotrajno oGF < 15 ml/min/1,73m2 najmanj 28 dni.
** V študiji DAPA-CKD so rezultati sekundarnih ciljev opazovanja pokazali, da FORXIGA kot dodatek standardnemu zdravljenju omogoča 31 % RRR za smrt iz kateregakoli vzroka (ARR 2,1 %) v primerjavi z uporabo samo standardnega zdravljenja in 29 % RRR za sestavljen cilj opazovanja, ki vključuje srčno-žilno smrt ali hospitalizacijo zaradi srčnega popuščanja (ARR 1,8 %). Zaradi nenačrtovane predčasne ustavitve se sekundarni izidi upoštevajo kot nominalni.

ARR: absolutno zmanjšanje tveganja; **DAPA-CKD:** Dapagliflozin in preprečevanje neželenih izidov pri kronični ledvični bolezni (Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease); **KLO:** končna ledvična odpoved; **KLB:** kronična ledvična bolezen; **oGF:** ocenjena hitrost glomerulne filtracije; **RRR:** relativno zmanjšanje tveganja; **SB2:** sladkorna bolezen tipa 2; **SGLT2i:** zaviralec natrij glukoznega soprenašalca 2.

Reference:
1. Povzetek glavnih značilnosti zdravila Forxiga, julij 2022. **2.** Povzetek glavnih značilnosti zdravila Invokana. **3.** Povzetek glavnih značilnosti zdravila Jardiance. **4.** Povzetek glavnih značilnosti zdravila Steglatro. **5.** Heerspink HJL et al. N Engl J Med. 2020;383(15):1436–1446. **6.** Wheeler DC et al. Lancet Diabetes Endocrinol. 2021;9(1):22–31.

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Forxiga 5 mg filmsko obložene tablete
Forxiga 10 mg filmsko obložene tablete

Sestava: Ena tableta vsebuje 5 mg ali 10 mg dapagliflozina. **Farmacevtska oblika:** filmsko obložena tableta.
Indikacije: Zdravilo Forxiga je indicirano pri odraslih in otrocih starih 10 let in več za zdravljenje nezadostno urejene sladkorne bolezni tipa 2 kot dodatek dieti in telesni dejavnosti ali kot samostojno zdravljenje (monoterapija), če metformin zaradi intolerance ni primeren ali kot dodatek drugim zdravilom za zdravljenje sladkorne bolezni tipa 2. Zdravilo Forxiga je indicirano pri odraslih za zdravljenje simptomatskega kroničnega srčnega popuščanja z zmanjšanim iztisnim deležem. Zdravilo Forxiga je indicirano pri odraslih za zdravljenje kronične ledvične bolezni. **Odmerjanje in način uporabe:** Sladkorna bolezen tipa 2: Priporočeni odmerek je 10 mg dapagliflozina enkrat na dan. Kadar se dapagliflozin uporablja v kombinaciji z insulinom ali z zdravili, ki spodbujajo izločanje insulina, kot so sulfonilsečnine, je za zmanjšanje tveganja za pojav hipoglikemije treba razmisliti o manjšem odmerku insulina oziroma zdravila, ki spodbuja izločanje insulina. Srčno popuščanje: Priporočeni odmerek je 10 mg dapagliflozina enkrat na dan. Kronična ledvična bolezen: Priporočeni odmerek je 10 mg dapagliflozina enkrat na dan. Pediatrična populacija: Za zdravljenje sladkorne bolezni tipa 2 pri otrocih, starih 10 let in več, prilagoditev odmerka ni potrebna. Za otroke mlajše od 10 let podatkov ni na voljo. Varnost in učinkovitost dapagliflozina za zdravljenje srčnega popuščanja ali za zdravljenje kronične ledvične bolezni pri otrocih, starih < 18 let še nista bili dokazani. Zdravilo Forxiga se jemlje peroralno, enkrat na dan, kadarkoli tekom dneva, s hrano ali brez nje. Tablete je treba zaužiti cele. **Kontraindikacije:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov.
Posebna opozorila in previdnostni ukrepi: Okvara ledvic: Prilagoditev odmerka glede na delovanje ledvic ni potrebna. Zaradi omejenih izkušenj zdravljenja z dapagliflozinom ni priporočljivo uvesti pri bolnikih z GFR < 25 ml/min. Pri bolnikih s sladkorno boleznijo tipa 2 in hitrostjo glomerulne filtracije (GFR-glomerular filtration rate) < 45 ml/min se učinkovitost dapagliflozina pri zniževanju glukoze zmanjša, pri bolnikih s hudo ledvično okvaro pa verjetno ni učinkovit. Če torej GFR pade pod 45 ml/min in je potreben nadaljnji nadzor glikemije, je treba pri bolnikih s sladkorno boleznijo tipa 2 razmisliti o dodatnem zdravljenju za zniževanje glukoze. Okvara jeter: Izpostavljenost dapagliflozinu je povečana pri bolnikih s hudo okvaro jeter, zato je priporočljiva uporaba začetnega odmerka 5 mg, ki se lahko poveča na 10 mg, če je to indicirano. Uporaba pri bolnikih s tveganjem za zmanjšanje volumna in/ali hipotenzijo: Previdnost je potrebna pri bolnikih, pri katerih bi z dapagliflozinom povzročen padec krvnega tlaka lahko pomenil tveganje, npr. pri bolnikih, ki se zdravijo z antihipertenzivi in imajo hipotenzijo v anamnezi ali pri starejših bolnikih. Diabetična ketoacidoza: Če se pojavijo nespecifični simptomi, npr. navzea, bruhanje, anoreksija, bolečine v trebuhu, prekomerna žeja, težko dihanje, zmedenost, neobičajna utrujenost ali zaspanost, je treba upoštevati možnost, da gre za diabetično ketoacidozo. Če se pojavijo ti simptomi, je treba takoj preveriti, ali gre za ketoacidozo, in sicer ne glede na koncentracijo glukoze v krvi. V primeru suma na DKA ali diagnosticirane DKA je treba zdravljenje z dapagliflozinom takoj prenehati. Zdravljenje je treba prekiniti pri bolnikih, sprejetih v bolnišnico zaradi večjega kirurškega posega ali akutne resne bolezni. Pri teh bolnikih se priporoča spremljanje ketonov. Ravni ketonov je bolj priporočljivo meriti v krvi kot urinu. Zdravljenje z dapagliflozinom je mogoče znova uvesti, ko so vrednosti ketonov normalne in se bolnikovo stanje stabilizira. Pred uvedbo dapagliflozina je treba v bolnikovi anamnezi oceniti dejavnike, ki bi lahko povečevali nagnjenost h ketoacidozi. Med bolniki, ki imajo lahko večje tveganje za DKA, so bolniki z majhno funkcijsko rezervo celic beta (npr. bolniki s sladkorno boleznijo tipa 2 z nizkim C-peptidom ali latentno avtoimunsko sladkorno boleznijo odraslih (LADA latent autoimmune diabetes in adults) ali bolniki po prebolelem pankreatitisu), bolniki z boleznimi, ki zmanjšajo uživanje hrane ali povzročijo hudo dehidracijo, bolniki po zmanjšanju odmerka insulina in bolniki, ki imajo povečano potrebo po insulinu zaradi akutnih internističnih bolezni, operacije ali zlorabe alkohola. Zaviralce SGLT2 je treba pri teh bolnikih previdno uporabljati. Bolnikom, ki so kdaj imeli DKA med zdravljenjem z zaviralcem SGLT2, zaviralca SGLT2 ni priporočljivo znova uvesti, razen če je ugotovljen in odpravljen kakšen drug nedvomen sprožilni dejavnik. V študijah z dapagliflozinom pri sladkorni bolezni tipa 1 so o DKA poročali s pogostnostjo "pogosto". Dapagliflozina se ne sme uporabljati za zdravljenje bolnikov s sladkorno boleznijo tipa 1. Amputacije na spodnjih okončinah: V dolgoročnih kliničnih študijah pri sladkorni bolezni z zaviralci SGLT2, so opazili povečano število primerov amputacij na spodnjih okončinah (predvsem prstov na nogah). Ni znano, ali gre za učinek, ki je značilen za celo skupino zdravil. Pomembno je, da bolnike s sladkorno boleznijo podučimo o rutinski preventivni negi stopal. Laboratorijske preiskave urina: Bolniki, ki jemljejo zdravilo Forxiga, bodo zaradi njegovega mehanizma delovanja pozitivni na preiskavi za prisotnost glukoze v urinu. Nekrotizirajoči fascitis presredka (Fournierjeva gangrena): Po začetku trženja so poročali o primerih nekrotizirajočega fasciitisa presredka (znan tudi kot Fournierjeva gangrena) pri bolnikih in bolnicah, ki so jemali zaviralce SGLT2. Če obstaja sum na Fournierjevo gangreno, je treba zdravilo Forxiga ukiniti in uvesti takojšnje zdravljenje (vključno z antibiotiki in kirurško odstranitvijo prizadetega tkiva). Okužbe sečil: Izločanje glukoze z urinom je lahko povezano s povečanjem tveganja za okužbe sečil, zato je med zdravljenjem pielonefritisa ali urosepse treba razmisliti o začasnem prenehanju uporabe dapagliflozina. Srčno popuščanje: Izkušnj z dapagliflozinom v razredu IV po NYHA je malo. Kronična ledvična bolezen: Izkušenj z uporabo dapagliflozina za zdravljenje kronične ledvične bolezni pri bolnikih brez sladkorne bolezni, ki nimajo albuminurije, ni. Bolniki z albuminurijo bodo morda imeli več koristi od zdravljenja z dapagliflozinom. Laktoza: Tablete vsebujejo laktozo. Bolniki z redko dedno intoleranco za galaktozo, laponsko obliko zmanjšane aktivnosti laktaze ali malabsorbcijo glukoze/galaktoze ne smejo jemati tega zdravila. Nosečnost in dojenje: Ko je ugotovljena nosečnost, je treba zdravljenje z dapagliflozinom prekiniti, prav tako se ga ne sme uporabljati v obdobju dojenja. **Medsebojno delovanje z drugimi zdravili:** Dapagliflozin lahko prispeva k diuretičnemu učinku tiazidnih diuretikov ter diuretikov zanke in lahko poveča tveganje za pojav dehidracije ter hipotenzije. V kombinaciji z dapagliflozinom bo morda potreben manjši odmerek insulina ali zdravila, ki spodbuja izločanje insulina, da bi zmanjšali tveganje za pojav hipoglikemije pri bolnikih s sladkorno boleznijo tipa 2. Dapagliflozin lahko poveča izločanje litija skozi ledvice, zato se lahko koncentracija litija v krvi zmanjša. Po uvedbi dapagliflozina in spremembi njegovega odmerka je treba koncentracijo litija v serumu pogosteje spremljati. **Neželeni učinki:** Kot zelo pogosti neželen učinek se je pojavila hipoglikemija (pri sočasni uporabi s SU ali insulinom). Kot pogosti neželeni učinki so se pojavili: okužba sečil, vulvovaginitis, balanitis in sorodne okužbe spolovil, izpuščaj, omotica, bolečine v hrbtu, disurija, poliurija, dislipidemija, povečan hematokrit in zmanjšan ledvični očistek kreatinina med uvodnim zdravljenjem. **Režim predpisovanja in izdaje zdravila:** Predpisovanje in izdaja zdravila je le na recept. **Datum zadnje revizije besedila:** 15.07.2022(SI-2319) **Imetnik dovoljenja za promet:** AstraZeneca AB, SE-151 85 Södertälje, Švedska **Dodatne informacije so na voljo pri:** AstraZeneca UK Limited, Podružnica v Sloveniji, Verovškova 55, 1000 Ljubljana, telefon: 01/51 35 600. **Prosimo, da pred predpisovanjem preberete celoten povzetek glavnih značilnosti zdravila.**

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