Background and aims: The purpose of this study was to investigate a possible association between the use of cilostazol (a phosphodiesterase type 3 inhibitor) and the development of chronic kidney disease (CKD) through a post-hoc analysis of a cohort of patients with type 2 diabetes
Materials and methods: From January 2000 to December 2006, 620 patients with type 2 diabetes without diabetic kidney disease (estimated glomerular filtration rate [eGFR] > 90ml/min/1.73m2 and normoalbuminuria [24-hour urine albumin excretion < 30mg/day by consecutive two or more measurements]) were enrolled. The indications for cilostazol use were patients who were over 40 years of age or who had additional cardiovascular risk factors (a family history of cardiovascular disease, hypertension, smoking, dyslipidemia) or had a symptom with intermittent claudication and peripheral artery disease in one or both limbs. The eGFR was measured more than once every year to check the patients' renal function. New-onset CKD was defined as a decreased eGFR of < 60 ml/min/1.73m^2 using a Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. A logistic regression model was used to estimate the adjusted odds ratio with 95% confidence intervals of incident CKD associated with cilostazol use both overall and by cumulative duration of use.
Results: The mean age and duration of diabetes were 54.5 ± 8.3 years and 6.9 ± 5.6 years, respectively. The baseline eGFR and albumin excretion rate were 101.9 ± 8.1 and 10.1 ± 6.7 mg/day. The median follow-up time was 12.1 years. During the study, 86 patients (13.9%) progressed to CKD. After adjusting for multiple confounding factors, the use of cilostazol was significantly associated with a reduced risk of incident CKD (adjusted OR 0.49, 95% CI 0.26-0.93; P = 0.028). A duration-response relation was also observed. The use of cilostazol for more than 10 years associated with a reduced risk of CKD (adjusted OR 0.50, 95% CI 0.25-0.98; P = 0.044). When the duration-response was considered as a continuous variable, the significant association between cilostazol and the development of CKD remained (adjusted OR 0.94 per one year cilostazol use, 95% CI 0.89-0.99; P = 0.017).
Conclusion: The results of this study showed that the use of cilostazol, a phosphodiesterase inhibitor, was associated with a reduced risk of new-onset CKD. In fact, a longer duration of cilostazol use tended to decrease the risk of new-onset CKD.
Disclosure: **Y. Ahn:** None.

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Resistant starch ameliorates advanced glycation endproduct-induced albuminuria in a mouse model of type 2 diabetes

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Background and aims: Long-term excess intake of dietary advanced glycation endproducts (AGEs) contributes to chronic renal injury. Recent research implicates gut dysbiosis in the progression of diabetic nephropathy, however, the role of dietary AGEs in gut dysbiosis and renal injury in the context of diabetes has not yet been explored. The aim of this study was to investigate whether excess consumption of dietary AGEs cause gut dysbiosis, exacerbating renal injury in a mouse model of type 2 diabetes. A secondary aim was to elucidate whether a high fibre diet (resistant starch), may be protective against diabetic nephropathy via altering gut homeostasis.
Materials and methods: Six week old diabetic mice (db/db) (BKS.Cg-Dock7m+/+Leprdb/J) on a C57BL/KsJ background and age-matched non-diabetic control mice (db/m) were randomised (n=12/group) to receive a low AGE (LAGE, unbaked rodent chow) or a high AGE diet (HAGE, baked at 160°C for 1 hour), with or without 25% resistant starch (RS) for 10 weeks. All diets were isocaloric. 24-hour urine was collected for the assessment of albuminuria. At 15 weeks of age, mice were fasted and an oral glucose tolerance test (2g/kg lean body mass) was performed. At 16 weeks of age, intestinal permeability was assessed in vivo by the clearance of FITC-labelled dextran (500mg/kg body weight). Glycated haemoglobin was assessed using a Roche cobas b101 analyser.
Results: The high AGE diet exacerbated albuminuria in db/db mice (874.4±154.8 vs 536.2±96.5μg/24h, P<0.05, db/db HAGE vs db/db LAGE), and this AGE-induced increase in albuminuria was attenuated by RS (874.4±154.8 vs 515.5±71.9μg/24h, P<0.05, db/db HAGE vs db/db HAGE + RS). Db/db mice had increased gut permeability compared to db/m mice (2.38±0.32 vs 1.05±0.11μg/ml, P<0.01, db/db LAGE vs db/m LAGE). Furthermore, the high AGE diet increased gut permeability of db/db mice (3.43±0.43 vs 2.38±0.32μg/ml, P=0.06, db/db HAGE vs db/db LAGE), an effect not observed in RS-fed db/db mice (2.38±0.32 vs 2.86±0.35μg/ml, P>0.05, db/db LAGE vs db/db LAGE+RS). Following OGTT, db/db mice had a higher glucose AUC (74.08±5.98 vs 17.54±2.32 mmol/L x min, P<0.05, db/db LAGE vs db/m LAGE) and glycated haemoglobin (10.47±1.96 vs 4.06±0.12, P<0.05, db/db LAGE vs db/m LAGE) compared to db/m mice. Neither the high AGE diet nor the resistant starch supplemented diets influenced glycaemic control in db/db or db/m mice, as reflected by OGTT AUC (74.08±5.98 vs 75.29±6.45 vs 75.29±6.45 vs 72.64±7.16 mmol/L x min, P>0.05, db/db LAGE vs db/db LAGE+RS vs db/db HAGE vs db/db HAGE+RS), or glycated haemoglobin (10.61±0.46 vs 9.65±0.55 vs 10.98±0.67 vs 10.58±0.67 % glycated haemoglobin, P>0.05, db/db LAGE vs db/db LAGE+RS vs db/db HAGE vs db/db HAGE+RS).
Conclusion: A high AGE diet led to increased intestinal permeability, which was associated with worsening albuminuria in db/db mice. Resistant starch was protective against high AGE induced albuminuria in db/db mice, effects which are not dependant on changes in glucose homeostasis. These preliminary studies support the notion that dietary AGEs contribute to renal disease via alterations in gut homeostasis and suggest a potential role for resistant starch as a renoprotective agent.
Disclosure: **M. Snelson:** None.

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One-year eGFR decline rate is a good predictor for prognosis of renal failure in patients with type 2 diabetes

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Background and aims: Patients who lose renal function faster than the average age-related decline in eGFR tend to progress to ESRD. Progressive renal decline was defined as an eGFR loss of ≥ 3.3% per year, but the calculation of this annual average renal decline rate requires lifelong observation. In this study, we used a data smoothing technique to analyze eGFR trajectories and successfully identified starting points of meaningful eGFR decline.
Materials and methods: All type 2 diabetes patients seen between June 2001 and October 2014 were candidates for this study. Among these patients, subjects whose eGFR was measured more than twice in a half-year for more than three years were included. Patients with no eGFR examination more than a year during the study period, or a mean eGFR < 60 mL/min/1.73 m^2 at baseline were excluded. We performed a smoothing technique called locally weighted regression method to reduce the fluctuation in eGFR trajectory. Every eGFR value was smoothed ($eGFR_{monthly\ smoothing\ data}$) and average $eGFR_{monthly\ smoothing\ data}$ in every half-year was calculated for each patient ($eGFR_{half\ year}$). We calculated each 1-year eGFR decline rate from the difference between each $eGFR_{half\ year}$ value and that of the previous year. We also used the maximum value of $eGFR_{half\ year}$ for ROC analysis. The endpoint was defined as a decline of $eGFR_{half\ year}$ to less than half of eGFR at baseline.