CLINICAL EPIDEMIOLOGY AND CKD

FO039 BIRTHWEIGHT PREDICTS GLOMERULAR FILTRATION RATE
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Introduction and Aims: To examine the relationship of birthweight, and prematurity, to risk factors and markers for chronic kidney disease (CKD) in postnatal life.

Methods: The AusDiab study is a longitudinal study where baseline data on 11,247 participants, aged = 25 years, were collected in 1999-2000. During the 2004-05 follow-up AusDiab survey, questions about birthweight were included. Also, we approached four hundred and twelve CKD patients, and 339 agreed to participate in the study. The study population included all those who participated in the AusDiab study. Medical records were reviewed to check the diagnoses, causes of kidney disease and SCR levels. Two control subjects, matched for gender and age, were selected for each CKD patient from participants in the AusDiab study who reported their birthweight. Also, we studied children and teenage subjects of a cohort, of VLBW due to prematurity. This cohort and a control group were enrolled in our study. Data were collected from participants, their medical records and clinical examination and laboratory investigations.

Results: eGFR was strongly and positively associated with birthweight, with a predicted increase of 2.6 ml/min/(CI 2.1, 3.2) and 3.8 (3.0, 4.5) for each kg of birthweight for females and males, respectively. The OR (CI) for low eGFR (<61.0 ml/min for females and < 87.4 males) in people of LBW compared with those of NBW was 2.04 (1.45, 2.88) for females and 3.4 (2.11, 5.36) for males. 189 chronic kidney disease (CKD) patients reported their birthweight; 106 were male. Their age was 60.3(15) years. Their mean birthweight was 3.27 (0.62) kg, vs 3.46 (0.6) kg for their AusDiab controls, p=0.001 and the proportions with birthweight=2.5 kg were 18% and 4.4%; p=0.001. Among CKD patients, 22.8%, 21.7%, 18% and 37.6% were in CKD stages 2, 3, 4 and 5 respectively. Birthweights by CKD stage and their AusDiab controls were as follows: 3.38 (0.52) vs 3.49 (0.52), p=0.251 for CKD2; 3.28 (0.54) vs 3.44 (0.54), p=0.121 for CKD3; 3.19 (0.72) vs 3.43 (0.56), p= 0.112 for CKD4 and 3.09 (0.65) vs 3.47 (0.67), p=0.001 for CKD5. 37 premature children (17 girls) of premature cohort children and 23 full term children (9 girls) were consented for clinical examination, urine, blood and ultrasound examinations of their children. Kidney volume was calculated using the ellipsoid formula: volume (ml) = [length x width x (depth1+depth2)/2] × 0.523. The gestational age for preterm cohort was 26.7 (2.6) and ranged from 23 to 35 weeks. Their birthweight was 867 (248) grams vs. 3433 (285) for full term babies. The age of premature children was 12(3.8) years vs. 11.5 (3.5) years for full term children. Children born prematurely had lower lower kidney volumes (99.7 ml (89.3, 110) vs. 131 (111, 151), P<0.01 and lower eGFR (87.0 (78.5, 113) vs. 113 (99.1, 128), p<0.001. Kidney volume correlated well with eGFR (0.83).

Conclusions: In an affluent Western country with a good adult health profile, LBW people were predisposed to higher rates of lower eGFR in later life. In all instances it would be prudent to adopt policies of intensiﬁed whole of life surveillance of lower birthweight people, anticipating this risk. The general public awareness of the effect of LBW on development of chronic diseases in later life is of vital importance. The general public, in addition to the awareness of people in medical practice of the role of LBW, will set a trend towards a better management of this group of our population that is increasingly surviving into adulthood.

FO040 SERUM URIC ACID AND RISK OF CHRONIC KIDNEY DISEASE: THE ROTTERDAM STUDY AND META-ANALYSIS
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Introduction and Aims: Serum uric acid has been associated with risk factors of chronic kidney disease (CKD) such as hypertension and diabetes. However, the role of serum uric acid as an independent risk factor in the pathogenesis of CKD remains unclear.

Methods: In this study, 5139 subjects aged 55 years and over from the Rotterdam Study were included. Renal function was evaluated by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease Study Equation. Outcomes were: natal decline in eGFR between two visits and incident CKD (decline in eGFR to < than 60 mL/min/1.73m2 during follow-up). Additionally, we performed a meta-analysis of previous studies to provide a reliable estimate of the risk of CKD associated with high serum uric acid.

Results: For each unit increase in serum uric acid (mg/dL) we found a 0.22 (95%CI: 0.16, 0.29) increase in eGFR decline and a 1.34 times (95%CI: 1.17, 1.46) increase in the incidence of CKD. The association was significantly stronger in hypertensive compared to normotensive participants (P-value for interaction= 0.807). Combining our findings with the other studies in a meta-analysis, we found an overall relative risk of 1.15 (95%CI: 1.11, 1.19) for incidence of CKD per 1 mg/dL increase in serum uric acid.

Conclusions: High levels of serum uric acid are associated with an increased risk of CKD independently from traditional risk factors. Adequately monitoring and managing abnormal levels of serum uric acid, seems primordial in preventing the development of CKD in hypertensive individuals.

FO041 RELATIVE ENERGY BALANCE, CHRONIC KIDNEY DISEASE AND RISK OF CARDIOVASCULAR AND ALL-CAUSE MORTALITY
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Introduction and Aims: Obesity and excess energy intake relative to output are risk factors for cardiovascular and all-cause mortality in the general population. However, previous studies have reported an inverse relationship between obesity and mortality risk in people on dialysis. The association between relative energy intake and mortality risk among those with mild-moderately reduced kidney function is unclear. We aimed to determine the association between the relative energy intake, and the risk of all-cause and cardiovascular mortality in people with early to moderate stage CKD.

Methods: Analysis included men and women aged ≥49 years from a population-based cohort in the Blue Mountains, Sydney, Australia, undergoing detailed interview, food frequency questionnaire, and physical examination including body weight, height, blood pressure and laboratory tests. We assessed the relationship between relative energy balance and the risk of all-cause and cardiovascular mortality in people with and without reduced kidney function using unadjusted and adjusted Cox proportional regression models, with results expressed as hazard ratios (HR) and their respective 95% confidence intervals (95%CI).

Results: Overall, 1245 men and 1490 women were included in the study. The median follow up period was 14.5 years, IQR ranging from 9.4 to 15.2 years, resulting in 44192.15 person-years of follow up. The total cumulative incidence of all-cause mortality in the non-CKD and CKD populations were 242 per 1000 person-years and 40.1 per 1000 person-years, respectively (HR: 1.70, 95% CI: 1.52 to 1.90, p<0.001). There was an increased risk of all-cause (adjusted HR 1.48, 95% CI 1.05 to 2.06).

Methods: In this study, 5139 subjects aged 55 years and over from the Rotterdam Study were included. Renal function was evaluated by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease Study Equation. Outcomes were: natal decline in eGFR between two visits and incident CKD (decline in eGFR to < than 60 mL/min/1.73m2 during follow-up). Additionally, we performed a meta-analysis of previous studies to provide a reliable estimate of the risk of CKD associated with high serum uric acid.

Results: For each unit increase in serum uric acid (mg/dL) we found a 0.22 (95%CI: 0.16, 0.29) increase in eGFR decline and a 1.34 times (95%CI: 1.17, 1.46) increase in the incidence of CKD. The association was significantly stronger in hypertensive compared to normotensive participants (P-value for interaction= 0.807). Combining our findings with the other studies in a meta-analysis, we found an overall relative risk of 1.15 (95%CI: 1.11, 1.19) for incidence of CKD per 1 mg/dL increase in serum uric acid.

Conclusions: High levels of serum uric acid are associated with an increased risk of CKD independently from traditional risk factors. Adequately monitoring and managing abnormal levels of serum uric acid, seems primordial in preventing the development of CKD in hypertensive individuals.
change in GFR was categorised as =-50%; -49 to -25%; -24 to -10%; ±10%; 10 to 24%;

eGFR was calculated using the first and last GFR within the one year period. Percent
two serum creatinine estimations over a one year period separated by at least 6
function associated with increased risk. The purpose of this study was to see if we
Canada has shown an independent and graded association between short term
Deaths during follow up. The hazard ratio for death was 3.27 (95% CI: 1.75-6.11) for those with eGFR decline = -50% and 1.83 (95% CI 1.46, 2.29) for -49 to -25% compared to those with stable eGFR (Figure). Participants with the greatest percent increase in eGFR also showed a trend toward increased mortality (HR 1.36, 95% CI 0.92, 2.01). Similar results were observed when results were stratified by CKD

Conclusions: Our data shows an independent and graded association between change in kidney function and mortality similar to that found in Alberta, Canada.

Short term changes in GFR over one year of greater than 25% are associated with an increased risk of death in patients with or without CKD.

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**IS THERE AN ASSOCIATION BETWEEN SHORT TERM CHANGES IN KIDNEY FUNCTION AND MORTALITY?**

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Introduction and Aims: Data from a province-wide laboratory registry from Alberta,
Canada has shown an independent and graded association between short term
change in kidney function and mortality, with both a decline and increase in kidney
function associated with increased risk. The purpose of this study was to see if we
could reproduce these findings in a primary care population in the UK.

Methods: Participants were identified from primary care databases in our area
between 2004 and 2008. We included 29,156 adults aged over 18 years with at least
two serum creatinine estimations over a one year period separated by at least 6
months. Patient demographics, stage of CKD, history of hypertension, diabetes, heart
failure and ischaemic heart disease were extracted. The percent change in CKD-EPI
eGFR was calculated using the first and last GFR within the one year period. Percent
change in GFR was categorised as =-50% to -25%; -24% to -10%; ±10%; 10 to 24%;

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25 to 49% and Δ=50%, to reflect both a decline and increase in eGFR. Patients with established stage 5 CKD were excluded. Adjusted hazard ratios for all cause mortality (with follow up to March 31 2011) were calculated using stable eGFR (percent change ±10%) as the reference.

Results: Mean age of participants was 66.3±15.2 years, 45% were male, 5% had
hypertension and 8% had diabetes. Percent change in GFR was normally distributed
around the reference, 18.1% had an increase and 17.3% a decline in eGFR. There were
1612 deaths during follow up. The hazard ratio for death was 3.27 (95% CI: 1.75-6.11) for those with eGFR decline = -50% and 1.83 (95% CI 1.46, 2.29) for -49 to -25% compared to those with stable eGFR (Figure). Participants with the greatest percent increase in eGFR also showed a trend toward increased mortality (HR 1.36, 95% CI 0.92, 2.01). Similar results were observed when results were stratified by CKD

Conclusions: Our data shows an independent and graded association between change in kidney function and mortality similar to that found in Alberta, Canada.

Short term changes in GFR over one year of greater than 25% are associated with an increased risk of death in patients with or without CKD.

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**Fibroblast Growth Factor 23 (FGF23) and Asymmetrical Dimethylarginine (ADMA) Are Interactive Factors in the High Risk for CKD Progression in Stage 2-5 CKD Patients.**

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Introduction and Aims: FGF-23 is a pleiotropic hormone and high levels of this phosphate -regulating factor have been associated with endothelial dysfunction and raised plasma ADMA levels in stage 3-4 CKD patients (Kidney Int 78:679, 2010). Since both FGF23 and ADMA induce renal damage in experimental models, these associations may be implicated in the risk of CKD progression.

Methods: We investigated a) the cross-sectional association between FGF23 and ADMA with the GFR and their interaction in a large cohort (n=759) of stage 2-5 CKD patients and b) the hypothesis that elevated FGF23 and ADMA levels may be interactive factors in the high risk for renal disease progression in a three-year prospective study in the same cohort.

Results: Serum FGF23 (median 60.6 pg/ml, interquartile range 41.3-91.0) and plasma ADMA (0.83±0.18 μmol/L) were directly inter-related (r=0.15, P<0.001) and closely associated with the eGFR (r=0.48 and r=0.21, both P<0.001). These relationships held true (both P<0.001) in analyses adjusting for age, gender, smoking, diabetes, cholesterol, arterial pressure, Hb, albumin, hs-CRP and proteinuria. Of note, the FG23-eGFR relationship varied across ADMA quartiles (P=0.016 for effect modification) because a 100 pg/ml increase in FGF23 signalled a 4.0 ml/min decrease in GFR in the first ADMA quartile but only a 2.0 ml/min decrease in the fourth ADMA quartile. In the cohort study, 244 patients had renal events (>30% decrease in the GFR or dialysis/transplantation). Both FGF23 [HR (100 pg/ml): 1.19, 95% CI: 1.12-1.26, P<0.001] and ADMA [HR (1.00 μmol/L): 1.14, 95% CI: 1.07-1.22, P<0.001] predicted the incidence rate of renal events and these relationships were confirmed in analyses adjusting for eGFR, proteinuria and other potential confounders [FGF23, HR: 1.12, 95% CI: 1.05-1.19, P<0.001; ADMA, HR: 1.08, 95%

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**Fibroblast Growth Factor 23 Levels Predict Incident Cardiovascular Event Before But Not After the Start of Dialysis.**

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Introduction and Aims: Low 25-hydroxyvitamin D (25D), high levels of fibroblast growth factor 23 (FGF23), parathyroid hormone (PTH), and alkaline phosphatase (ALP) were reported to be risk factors for mortality in chronic kidney disease (CKD). However, the independent associations of these factors with cardiovascular disease (CVD), the leading cause of death among CKD patients, remain unclear. Our purpose was to identify which of these factors, serum 25D, FGF23, PTH, and bone-specific ALP (BSAP), predict incident CVD in CKD.

Methods: In this observational study of two nephrology units in Japan, we enrolled 738 CKD outpatients. We measured intact FGF23 using the assay by Kainos Laboratories. We defined the primary endpoint as fatal or non-fatal cardiovascular event requiring hospitalization. The secondary outcome was all-cause death. We employed Cox proportional hazards analyses to elucidate predictors of the endpoints. Multiple imputation method was performed for missing values.

Results: At baseline, mean estimated GFR (eGFR) was 35mL/min/1.73m2. During a median follow-up duration of 4.4 (IQR, 4.0-4.6) years, 86 patients developed the endpoint, of whom 62 patients achieved the endpoint before the initiation of dialysis and 24 patients achieved the endpoint after the initiation of dialysis, and 58 patients died. The crude rate for cardiovascular events and death were 3.0 and 1.9 per 100 person-years, respectively. In the univariate Cox models, PTH and FGF23 were related to cardiovascular events before the initiation of dialysis, while 25D and BSAP were not. Multivariable Cox analyses revealed that high serum intact FGF23 levels predicted the outcome preceding dialysis initiation (hazard ratio (HR) [95% confidence interval (CI)] per lnFGF23 (SD), 1.64 [1.27-2.30]), while 25D, PTH, and bone-specific ALP did not. Interactions between FGF23 and prior CVD or diabetes mellitus (DM) were not significant (P=0.32 for prior CVD and 0.38 for DM) (Figure). Adding FGF23 levels to the base model including age, sex, DM, prior CVD, pulse pressure, eGFR, body mass index, and urinary protein, only 25D was associated with mortality. HR per 10 ng/mL [95%CI] was 0.54 [0.30-0.99]. Additional adjustment for hemoglobin eliminated the significance of 25D, since hemoglobin was a confounder.

Conclusions: Intact FGF23 levels in predialysis CKD predicted incident cardiovascular events requiring hospitalization before the initiation of dialysis, but did not predict events during the entire follow-up period, including post dialysis initiation. Low 25D levels predicted mortality. Figure. Cumulative fatal/non-fatal cardiovascular event rate before the initiation of dialysis.