TRANSLATIONAL CKD RESEARCH

TO056 USING HUMAN PLURIPOTENT STEM CELLS TO MODEL KIDNEY DISEASE PATHOPHYSIOLOGY AND THERAPY

Benjamin S. Freedman1,2, Albert Q Lam1,2, Jamie L. Sundsbak3, Rujiy Morizane4, Rossella Iatrino4, Xuefeng Su1, Sarah J. Koon3, Maoqing Wu1, Kaohsiung, Taiwan,2National Institute of Cancer Research, National Health

FGF2, and retinoic acid induced differentiation into cells expressing markers typical of levels. Sequential treatment of ES or iPS cells with CHIR99021 (a GSK3β inhibitor), immunofluorescence. Gene sequencing revealed mutations in PC1, not PC2, epithelial cells from all three ADPKD patients expressed significantly reduced primary cilia and expressed polycystin-1 (PC1), PC2, and fibrocystin/polyductin, the into diverse somatic cell types and tissues. PKD and control iPS cells elaborated differentiation into embryonic and adult kidney lineages. Results: The derived iPS cells demonstrated extensive self-renewal and differentiation into diverse somatic cell types and tissues. PKD and control iPS cells elaborated primary cilia and expressed polycystin-1 (PC1), PC2, and fibrocystin/polyductin, the proteins in which PKD mutations are found. Importantly, iPS and descendant epithelial cells from all three ADPKD patients expressed significantly reduced quantities of PC2 at the primary cilia, as assessed by quantitative immunofluorescence. Gene sequencing revealed mutations in PC1, not PC2, suggesting that PC1 regulates PC2 trafficking to cilia. Consistent with this hypothesis, overexpression of wild-type but not mutant PC1 significantly increased ciliary PC2 levels. Sequential treatment of ES or iPS cells with CHIR99021 (a GSK3β inhibitor), FGFR2, and retinoic acid induced differentiation into cells expressing markers typical of intermediate mesoderm (PA2X2-LHX1+), nephrogenic cap mesenchyme (SIIX2-WT1+ SALL1+), and proximal tubule (KSP-LITL+), indicating potential for renal lineage differentiation.

Conclusions: Ciliary PC2 mislocalization is an early and highly penetrant phenotype in ADPKD-iPS cells, which can be screened in vitro to identify candidate therapeutics. PC1 overexpression rescues PC2 localization, suggesting a possible therapeutic approach. Derivation of embryonic and adult kidney cells from iPS cells provides a potential source of cells for transplant which would be 100% immunocompatible with the original patient. The ability of iPS cells to provide novel mechanistic insights into human cellular pathophysiology, together with their potential as regenerative cell therapies, makes them a powerful new resource for kidney disease research.

TO058 EARLY MORTALITY WAS HIGH AND WAS HIGHLY ASSOCIATED WITH FUNCTIONAL STATUS (FS) IN THE INCIDENT JAPANESE HEMODIALYSIS PATIENTS, ESPECIALLY IN THE ELDERLY

Masahiko Yazawa1, Ryo Kido2, Kenjiro Kimura1, Seiji Chira3, Takeshi Hasegawa4, Norio Hanafusa4, Kuntoishi Iseki4, Yoshitaru Tsukaharah4 and Yugo Shibagaki1
1St. Marianna University School of Medicine, Kanagawa, Japan, 2Inagi Municipal Hospital, Tokyo, Japan, 3Sapporo Kita Clinic, Sapporo, Hokkaido, Japan, 4The Committee of Renal Data Registry, Japanese Society for Dialysis Therapy, Tokyo, Japan

Introduction and Aims: In Japan, the overall survival of patients with hemodialysis (HD) is reported to be superior to the rest of the world, and it is very rare not to start dialysis in patients with end stage kidney disease (ESKD). However, the incidence of early mortality was high because physicians are not exempt from law suits for not to start life prolonging treatment. However, the average age of Japanese incident HD patients is patients still being skyrocketed. Thus, this is a very relevant issue both for patients and physicians since it means the failure of HD in prolonging survival, and therefore affects the judgment whether it is appropriate to start HD in each patient. However, little is known regarding the incidence and the predictive factors of early mortality after starting HD. Moreover, although FS is reported to rapidly and steadily decline rather than improve after starting HD in the elderly, it remains unclear whether FS with early mortality in incident HD patients. Methods: We obtained data from the Japanese Society for Dialysis Therapy (JSDT) registry in which data were collected from 99% of dialysis facilities in Japan. Among 33,281 patients aged 20 years of age who had started HD in 2007 and had subsequently been followed for 12 months, we first examined the prevalence of early mortality defined as death within first 3 months after starting HD, stratified by patient’s age. Among those, we then selected 7,664 patients with records of FS at the start of HD and investigated the association of FS with the early mortality. Levels of functional disability in the patients were categorized in three as follows: Severe, totally bedridden; Moderate, overt difficulties in exerting basic activities of daily living; Mild/None, those who are without severe nor moderate functional disabilities. Categorization into three groups in each patient was based on the careful estimation by experienced nephrologist. Risk ratio (RR) and 95% confidence interval (CI) were computed to estimate the association of FS with early mortality, and further accounting for difference of patient’s age (<60, 60-69, 70-79, >80 years), using modified Poisson regression with robust variance to adjust for characteristics, comorbid conditions, and laboratory data of patient at starting HD.

Results: Among 33,281 incident HD patients, 7.1% died within the first 3 months, accounting for as much as 50% of death within 12 months after starting HD. Older patients showed higher prevalence of early mortality, and as much as 16% of the patients aged 80 years or above died within first 3 months. Among 7,664 patients with records of FS at the start of HD, both the Moderate and the Severe groups had higher risk of early mortality (Moderate, RR 2.4, 95%CI 1.8-3.1; Severe, RR 3.9, 95%CI 3.5-5.1) as compared with the Mild/None group. This association of FS and early mortality was reproduced in any age categories, but was augmented in older patients with higher impaired levels of FS. Especially, 37% of patients aged 80 years or above in Severe group had experienced early mortality, with 15.2-fold (95%CI 7.0-33.4) greater risk as compared with those aged less than 60 years in Mild/None group.

Conclusions: Early mortality was very high even in incident Japanese HD patients and it was highly associated with FS, especially in the elderly. This underscores the importance of considering FS as well as in deciding whether to start dialysis and if decide to dialyze, how to manage in Japanese patients with ESKD.
Higher Mortality in Rural End Stage Kidney Disease Patients in Australia

Srdha Kotwal1, Angela Webster2, Alan Cass3 and Martin Gallagher1,4
1The George Institute for Global Health, Sydney, Australia, 2Sydney School of Public Health, Sydney, Australia, 3Menzies School of Health Research, Darwin, Australia, 4Concord Clinical School, Sydney, Australia

Introduction and Aims: Higher mortality with increasing remoteness from health services has been demonstrated in various clinical conditions. The impact of remoteness upon mortality in treated end stage kidney (ESKD) patients in Australia is not known. Our study compares mortality of ESKD patients in rural versus urban Australia using data linkage, adjusting for differences in baseline characteristics.

Methods: The Australia and New Zealand Dialysis and transplant Registry (ANZDATA) was used to identify all incident ESKD patients living in Australia’s most populous state, New South Wales (NSW), between 01/07/2000 and 31/07/2010. These patients were linked using probabilistic linkage to the NSW hospitalisation database and the NSW death registry, allowing measurement of hospital usage and mortality. Postcodes and the Accessibility Remoteness Index of Australia were used to separate patients into urban living in highly accessible areas and rural residents (living out of highly accessible areas). We compared all-cause mortality between the two groups. Risk was adjusted for age, gender, diabetes, cardiovascular disease, peripheral vascular disease (PVD), chronic lung disease (CLD), cerebrovascular disease and indigenous status. We also adjusted for late referral, RRT modality and type of dialysis access at baseline.

Results: Of the patients identified by ANZDATA, 95% linked with the hospitalisation database resulting in 10,505 ESKD patients with 2,384,218 admission records allowing a median follow up of 4.8 years (IQR 2.0 to 8.2). Of these, 1,527 (15%) were rural and 8,978 (85%) were patients urban residents. Rural versus urban residents had less cardiovascular disease (39% vs. 35%; p=0.008), PVD (29% vs. 23%; p=0.001) and CLD (19% vs. 14%; p=0.001) and significantly more identified as being indigenous (10.9% vs. 2%; p=0.001). Rates of diabetes (30% vs. 31%; p=0.51) and late referral (23% vs. 22%; p=0.18) were similar. 79% of patients had no CV diagnosis as their first recorded diagnosis, but it was less common (67% vs. 70%; p=0.007) in the rural cohort compared to the peri-toreal dialysis (32% vs. 28%; p=0.003). Median unadjusted survival in rural residents from 1st July 2000 or start of RRT was 3.8 years (IQR 1.9-7.5) while in urban residents it was 4.3 years (IQR 2.0-8.4; p=0.006). In univariate analysis, rural residence increased mortality by 17% (HR 1.17: 95% CI 1.08-1.26, p<0.001) and multivariable adjustment for age, gender, co-morbidities and indigenous status did not change this (HR 1.17: 95% CI 1.08-1.26, p<0.001). Adjusting further for late referral, modality of RRT and type of dialysis access somewhat attenuated the increased risk (HR 1.14: 95% CI 1.01-1.28; p=0.04).

Conclusions: Rural ESKD residents have a significant mortality disadvantage compared to urban residents in NSW. Further work exploring factors related to geography and health service utilisation such as timely access to specialist services are necessary to better understand the factors driving this difference.

ASSOCIATION OF SERUM AND DIALYSATE SODIUM AND SODIUM GRADIENT WITH MORTALITY IN INCIDENT HEMODIALYSIS PATIENTS: RESULTS FROM THE INTERNATIONAL MONITORING DIALYSIS OUTCOMES (MONDO) INITIATIVE

Jochen G. Raimann1, Len A. Usvyat2, Olymka Vega-Vega3, Lars Penne4, Jeroen Kooman5, Frank Van Der Sande5, Stephan Thijssen1, Daniele Marcelli6, Bernard Canaud6, Nathan W. Levin1, Yuedong Wang7, Peter Kotanko1 and The MONDO Initiative8
1Renal Research Institute, New York, NY, 2Fresenius Medical Care NA, Waltham, MA, 3National Institute of Medical Sciences, Mexico City, Mexico, 4University Medical Center, Amsterdam, The Netherlands, 5Maastricht University Medical Centre, Maastricht, The Netherlands, 6Fresenius Medical Care, Bad Homburg, Germany, 7UC Santa Barbara, Santa Barbara, CA, 8MONDO Initiative, New York, NY

Introduction and Aims: Hemodialysis (HD) with dialysate sodium concentrations (DNa+) higher than serum Na+ (Sn) results in diffusive Na+ flux into the patient, increased post HD SN+, thirst and fluid intake. The current literature on the relationship between SN+, DNa+, sodium gradient (GNa+; defined as DNa+ minus SN+) and mortality is controversial. Research by DOPPS claimed benefits for higher DNa+ (2-5). In fully adjusted analyses the risk of death increased in close parallelism with the number of background CV events and four established biomarkers which have been solidly associated to CV risk in this population -namely asymmetric dimethylarginine (ADMA), interleukin-6 (IL-6), norepinephrine (NE) and brain natriuretic peptide, (BNP) - for predicting mortality in a large cohort of dialysis patients.

Methods: We studied 270 patients on chronic dialysis (220 on HD and 50 on CAPD) with a mean age of 61±15 years (55% males and 16% diabetics) without congestive heart failure at enrollment. The cohort was followed up for an average time of 4.5 years (range 0.02-12.8 years).

Results: One hundred and twenty-two patients had CV comorbidities (45%). Sixty-seven patients had 1 CV comorbidity (myocardial infarction in 9 cases, stroke/TIA in 6 cases, anginal episodes in 36 cases and peripheral vascular disease in the remaining 16 cases), and 55 patients had 2 or more than 2 CV comorbidities (range 2-5). In fully adjusted analyses the risk of death increased in close parallelism with the number of background CV comorbidities, the hazard ratio (HR) of death being highest when patients had SN+ of greater 137 mmol/L, the mortality risk was the same over a wide range of DNa+, in patients with lower SN+, higher DNa+ levels were associated with poorer outcomes.

(P for trend=0.005). ADMA [HR (1 SD): 1.27, 1.09-1.47, P=0.002], NE [HR (1 SD): 1.21, 1.03-1.42, P=0.02], IL-6 [HR (1 SD): 1.11, 1.01-1.22, P=0.02], BNP [HR (1 SD): 1.27, 1.11-1.44, P<0.001] and CRP [HR (1 SD): 1.17, 1.04-1.33, P=0.01] significantly predicted all-cause mortality independently of traditional risk factors (Framingham) and factors peculiar to ESKF (albumin, Hb, calcium, phosphate and duration of dialysis). Remarkably, on both univariate (P=0.025) and multivariate (P=0.037) analyses, the burden of background CV comorbidities significantly amplified the effect of ADMA on the death risk, the hazard ratio for mortality of a fixed increase in this methilarginine (1 SD, i.e. 2.0 µMol/L) being closely dependent on the number of background CV comorbidities (Figure). Intriguingly, no such an effect modification was found for norepinephrine, IL-6, BNP and CRP (all P=NS).

Conclusions: In dialysis patients, the burden of background CV comorbidities amplifies the death risk associated to circulating levels of ADMA but not that of biomarkers of inflammation, sympathetic activity and left ventricular mass and function. The specificity of such an effect modification further emphasizes the central role of endothelium in the high CV risk in the dialysis population and underlines the importance of taking into account background CV comorbidities for the interpretation of the mortality-ADMA link.