THH1

Methylation analysis of cell-free DNA - a novel method for early diagnosis of renal transplant rejection using a blood test

Mr Isaac Kim, Mr Thomas Nieto, Professor Andrew Beggs

THURSDAY - Moderated Poster Session, HALL Q, March 12, 2026, 10:00 - 11:00

Introduction

Donor-derived cell-free DNA (dd-cfDNA) has emerged as a promising non-invasive biomarker in kidney transplantation. Following allograft injury, dd-cfDNA is released into the bloodstream, and its quantification can provide an early indication of rejection. Several commercial assays now offer dd-cfDNA measurement via a blood test.

However , a key limitation of dd-cfDNA is its lack of specificity – elevated levels may also be observed in non-rejection scenarios such as infection or inflammation.

Cell-free DNA (cfDNA) methylation analysis using nanopore sequencing offers a promising approach to overcome this limitation by enabling deeper interrogation of cfDNA.

Methylation signatures can provide insights into gene regulation and the tissue or cell type of origin, potentially revealing the underlying mechanism of graft injury.

This study aims to distinguish graft rejection from other causes of transplant dysfunction using cfDNA methylation profiling in a blood test.

Methods

Patients undergoing biopsy for suspected rejection due to impaired graft function (n=46) were recruited through the Human Biomaterials Resource Centre at the University of Birmingham. Peripheral blood samples were collected, cfDNA was extracted, and nanopore sequencing was performed.

Bioinformatic analysis was conducted to assess global and differential methylation using Modkit. Cell-of-origin analysis was performed using Nanomix. Gene annotation was conducted with HOMER, and functional enrichment analysis was carried out using g:GOSt. Methylation patterns were compared to histological findings from biopsy.

Results

From the 46 patients, two cohorts were selected for analysis: 3 patients with biopsy-proven T cell-mediated rejection (TCMR), and 6 with no histological evidence of rejection.

Cell-of-origin analysis revealed no statistically significant difference in the proportion of cfDNA derived from kidney epithelial cells, B cells, erythrocyte progenitors, granulocytes, monocytes, natural killer cells, or T cells between the two groups as shown in Table 1.

Furthermore, there was no difference in global methylation of cfDNA between patients with no rejection and TCMR as shown in Figure 1.
Differential methylation analysis identified 355 CpG sites with significant differences between TCMR and the non-rejection group.

Gene annotation and pathway analysis revealed significant enrichment of genes in the phospholipase D (PLD) signalling pathway in patients with TCMR as shown in Figure 2.

Discussion

Contrary to initial expectations, cell-of-origin analysis did not reveal distinct cfDNA profiles in rejection versus non-rejection cases, suggesting that this approach alone may not reliably differentiate transplant injury mechanisms.

Nonetheless, the identification of a differential methylation signature – particularly involving genes in the PLD signalling pathway – offers promising diagnostic potential. Previous studies have implicated PLD in T cell activation, supporting the biological relevance of our findings.

In conclusion, methylation profiling of cfDNA offers a novel, non-invasive approach to distinguish TCMR from other causes of graft dysfunction in kidney transplant recipients. This method has the potential to complement or even reduce the need for invasive biopsies, enabling earlier and more targeted intervention in transplant rejection

THH2

Developing an automatic recognition & coding system for Chronic Kidney Disease in Primary Care- improving early diagnosis & detecting disease progression.

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THURSDAY - Moderated Poster Session, HALL Q, March 12, 2026, 10:00 - 11:00

Primary care plays a huge, essential role in the management of Chronic Kidney Disease (CKD). The Quality and Outcome Framework (QOF) incentivises practices to establish and maintain a register of patients with CKD categories G3a to G5. This helps identify patients early who would benefit from treatment and recognise disease progression, facilitating timely treatment or referral to secondary care. Precise coding, including both GFR status and urinary albumin:creatinine ratios (uACR), is crucial in helping us to achieve this. However, with over one in ten people in the UK living with CKD, achieving this remains a challenge in busy primary care settings. In this project, I aim to assess our current performance and create an automated process to improve it.

Of our 6000 patients, 490 met the diagnostic criteria for CKD G3a-G5. Of these, 428 were included in the CKD register, leaving 62 uncoded. An additional 47 patients were also uncoded but identified as having significant proteinuria which was diagnostic of CKD. Therefore, at least 109 patients with CKD were not included on the register, suggesting a need to improve our inclusion.

Within our register, 378 patients were incorrectly coded using the correct terminology, to include both their GFR & ACR status. Most were coded broadly such as ‘Chronic Kidney Disease’ or just using their GFR result. A further 13 patients were coded as CKD stage 3 when they had actually progressed to CKD stage 4. This shows the need to improve the accuracy, consistency and maintenance of our coding.

EMIS is an electronic patient record, used by over half of all GP practices. Within it, we have the ability to create ‘concepts’, used to identify certain patient results at different thresholds. When multiple concepts are created and joined together, they can become ‘protocols’ , which works as a decision tool to automatically process patients' information in a flowchart-like sequence.

Using this, I created a CKD protocol to use GFR and uACR results to automatically identify patients who met CKD criteria. It calculates their current CKD category and then automatically codes them consistently. This not only helped identify new CKD diagnoses, but also ensured accurate maintenance of our pre-existing cohort. It even prompted users if data, such as a recent uACR, was missing to ensure collection. All clinical staff began using the tool in patient interactions (e.g. clinics, processing letters, or blood results). Within six months we saw significant improvements. Of the 109 uncoded patients, 60 remained

uncoded, showing a 45% improvement. Of the 378 incorrectly coded, 227 remained, showing a 40% improvement.

The key message is that this change happened automatically—patients weren't manually sought out, but the process was integrated into routine work. No extra resources or time were required, making it easy to apply in busy practices.What makes automation so powerful is its consistency and sustainability over time - working diligently in the background ensuring success. Once created, protocols can be shared across practices simply by downloading it, spreading benefits far and wide for all.

THH3

POCUS in Nephrology: Impact of Consultant-Delivered Point-of-Care Ultrasound During On-Call Blocks – A Snapshot Audit (2025)

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THURSDAY - Moderated Poster Session, HALL Q, March 12, 2026, 10:00 - 11:00

Background:
Handheld ultrasound devices such as the Vscan Air CL G1 Kit now enable Nephrologists to perform point-of-care ultrasound (POCUS) directly at the bedside. Unlike formal departmental scans, POCUS provides rapid, real-time insights that can guide immediate decision-making, diagnosis, and interventions. This audit describes the utilisation and impact of POCUS during four Consultant-led Nephrology on-call blocks in 2025.
Methods:
A prospective log of all POCUS scans performed by a single Consultant Nephrologist was maintained over four separate on-call weeks in 2025. Data collected included indication, scan type, management impact, requirement for formal imaging, and clinical outcomes. Patients were eligible if they had not yet undergone formal imaging at referral/admission, or if POCUS was considered likely to contribute meaningfully to their management.
Results:
A total of 23 POCUS scans were performed. Key scan types and clinical impacts are summarised below (please see table attached):

Key outcomes:
- Formal scans avoided: 6 (2 AV Fistula/4 Bladder scans)
- Reduced time to decision: 15
- Management altered: 14
- Admissions avoided: 2
- Emergency intervention expedited: 1 (biopsy bleed)
- Accuracy: POCUS diagnosis confirmed in 10/11 cases (1 misclassified, but triggered appropriate imaging)

Conclusions:
In this series, handheld POCUS by a Consultant Nephrologist improved diagnostic timeliness, expedited management, and reduced reliance on formal imaging. In several cases, it prevented admissions and treatment delays. These findings highlight the value of consultant-delivered POCUS in enhancing patient safety, streamlining care, and easing pressure on hospital imaging resources. The project aligns closely with the GIRFT programme and NHS England Renal Transformation Agenda, both of which emphasise improved assessment pathways, reduced unnecessary admissions, and optimal use of specialist expertise.

Addendum:
The author received formal ultrasound training in Germany and is a UK-accredited Focused Acute Medicine Ultrasound (FAMUS) supervisor. For governance purpose, all cases where

ultrasound is standard of care were subsequently confirmed by formal sonographer-performed imaging.

THH4

Integrating POCUS into a Nurse-Led Renal Service: Enhancing Care for AKI and CKD Patients

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THURSDAY - Moderated Poster Session, HALL Q, March 12, 2026, 10:00 - 11:00

Introduction:

Acute Kidney Injury (AKI) remains a significant patient safety concern, associated with increased length of stay (LOS), mortality, and healthcare costs, additionally with Chronic Kidney Disease (CKD) cases projected to rise,GIRFT (2021) and NHS England renal transformation agenda (2023) recommend streamlining renal assessment pathways, reducing unnecessary admissions, improving patient flow, and optimising use of specialist skills. Developing responsive, nurse-led renal services is essential to improve early diagnosis and intervention (NHS England, 2023, NICE, 2024). Point-of-care ultrasound (POCUS) was introduced as a bedside diagnostic tool to enhance real-time clinical decision-making within this nurse-led model.

Method:

Our nurse-led AKI service, established in 2014, reviews all AKI stage 2 and 3 alerts within the acute hospital. Since then, the service has expanded to include Advanced Nurse Practitioners (ANPs), which facilitated the creation of a dedicated renal assessment unit. To support NICE AKI guidelines and the NHS England renal transformation agenda—both emphasising early diagnosis and timely intervention—one ANP was trained to use a handheld ultrasound device (Vscan Air CL G1) by a FAMUS-accredited Consultant. This training involved attending an online course (123sonography POCUS focus class for kidneys and urinary tract scanning) formal teaching sessions with a mentor who is formally trained in ultrasound scanning, observing scans for one week, and then performing scans under supervision for an additional week, following a competency framework. Currently, the team depends on bladder scans and formal renal ultrasounds, which often result in delays in clinical decision-making. To address this, a four-week pilot was conducted where an ANP used handheld POCUS to assess 15 patients presenting with AKI, with ongoing mentoring from a FAMUS-accredited Consultant, formally trained in ultrasound scanning. All POCUS scans are currently followed by formal departmental ultrasounds or reviewed by a Consultant experienced in ultrasound.

Discussion:

The pilot has demonstrated that POCUS is a valuable diagnostic adjunct for the nurse-led renal service. POCUS contributed directly to timely, patient-centred interventions. Key benefits observed include:

For Patients:

Faster diagnosis and treatment.

Reduced wait times and improved experience.

Quicker discharges

For Staff:

Enhanced ANP autonomy and skillset.

Increased diagnostic confidence at the bedside.

For the Trust:

Greater efficiency in patient flow.

Potential for reduced LOS and long-term cost savings.

Patient feedback, although limited was positive, with a third reporting increased reassurance and improved understanding of their care

Conclusion & Future Plans:

POCUS implementation in the nurse-led renal service has enhanced patient care, supported real-time clinical decisions, and demonstrated potential for improved patient experience and flow and ultimately cost-efficiency. Preliminary data indicates that 6/15 patients had a change in management and as a direct result of POCUS and it aided clinical decision making in 100% of cases. The goal is to train the remaining six team members and to develop SOPS for when POCUS can guide management vs when formal imaging is still required to enable wider use across the hospital. For this reason, we will develop an audit cycle to review the accuracy of POCUS vs formal imaging. The goal being to prevent delays in diagnosis and treatment of AKI. This supports a sustainable, patient-centred model that enhances safety, efficiency, and care quality in AKI and CKD management.

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THH5

A quality improvement project to improve glucose monitoring and glycaemic control in patients commenced on high-dose steroids within a renal setting

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THURSDAY - Moderated Poster Session, HALL Q, March 12, 2026, 10:00 - 11:00

This quality improvement project was grounded in my perception that patients receiving steroids were not having their blood glucose monitored. A scoping review of the literature to establish the mismanagement of steroid-induced hyperglycaemia/diabetes (SIH/D) showed that implementation and follow-up of capillary blood glucose monitoring (CBG) is poor (Limbachia and Dhatariya, 2021; Ostrowska-Czyżewska et al., 2024). Inadequate monitoring, despite national guidance (Roberts et al., 2018), places patients at unnecessary risk of hyperglycaemic complications, such as end-organ damage and cardiovascular disease (Mauri and Badireddy, 2015). It was noted that for patients commenced on high dose steroids within a renal outpatient department, the implementation of the national guidance (Roberts et al., 2018) was not followed correctly placing patients at risk of SIH/D and its complications (Kleinhans et al., 2024).

Overall, the project was successful with 92% of patients post-intervention found to undertake CBG readings correctly and as per guidance (Roberts et al., 2018) compared to 9.1% pre-intervention . This project finds that CBG monitoring is easy to embed in practice. Patients can use and understand CBG monitoring, it's implications; and it provides both a cost-effective and cost-saving measure to prevent diabetes related complications and harm (Alshannaq et al., 2024).

The patients with the highest number of risk-factors were found to be at the highest risk of developing SIH. Patients with one-two risk factors did not always develop hyperglycaemia. This confirms that CBG monitoring is therefore indicated as risk factors alone are not a reliable predictor for SIH. The project was deemed successful as two patients were at significant risk of hyperglycaemic complications, which would not have been identified early were it not for the implementation.

THH6

Transplant Kidney Biopsy: Is It Time For A Better Alternative?

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THURSDAY - Moderated Poster Session, HALL Q, March 12, 2026, 10:00 - 11:00

Introduction

Rejection occurs in 10-15% of patients within the first year following kidney transplantation. Biopsy of the transplanted kidney remains the gold standard for diagnosing rejection. However, due to its invasive nature, biopsy carries rare but serious risks, including graft loss and mortality. Interpretation is also subject to inter-rater variability, influenced by sampling, processing and evaluation techniques.

This study reviewed the use of transplant kidney biopsy at Queen Elizabeth Hospital Birmingham (QEHB) to evaluate its diagnostic utility and whether there is a case for a better alternative.

Methods

We retrospectively reviewed the last 100 consecutive transplant kidney biopsies performed in 2024 at QEHB.

Results

These 100 biopsies were performed over a 157-day period and involved 74 unique patients. Of these, 64% were male, with a median age of 48 years.

Biopsy indication:
- 53% for transplant dysfunction
- 28% for delayed graft function
- 18% to assess response to rejection treatment
- 1% at transplant re-exploration

Complications:
The complication rate requiring intervention was 1%. This consisted of a transfusion of 1 unit of blood on days 1 and 3 post-biopsy for a same patient.

Histological findings:
- 49%: no rejection
- 28%: confirmed rejection
- 13%: borderline rejection
- 6%: insufficient

- 4%: uncertain

Histological adequacy:
- 85%: adequate
- 15%: inadequate

Biopsy burden:
Repeat biopsies were required in 4% of cases. Among the 74 unique patients, the median number of biopsies per patient - over the lifetime of their current graft - was 2 (range: 1-5).

Discussion

Our findings demonstrate that the complication rate of kidney transplant biopsies at QEHB is low and consistent with published data. Of 100 cases reviewed, 10 biopsies did not yield a definitive diagnosis. In 4 of these, a concomitant diagnosis could not be excluded, while in 6 cases, biopsy inadequacy limited diagnostic certainty. Nevertheless, repeat biopsy was required in only 4 cases, indicating that in 96% of instances, clinicians were able to make acceptable management decisions by integrating biopsy results with the broader clinical context.

Limitations of this study include the lack of patient-reported experience, as well as the absence of cost analysis and turnaround time evaluation. We are also unable to determine the long-term clinical impact of inconclusive biopsy results.

While kidney transplant biopsy remains a cornerstone of post-transplant monitoring and decision-making, its invasive nature, occasional diagnostic limitations, and associated burden suggest that a non-invasive, cost-effective, and patient-friendly alternative would be a welcome advancement in the field.

THH7

Ketohexokinase C is Downregulated and Fructose Metabolism is Reduced in Chronic Kidney Disease

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THURSDAY - Moderated Poster Session, HALL Q, March 12, 2026, 10:00 - 11:00

Fructose is a monosaccharide sugar prevalent in the Western diet, consumption of which has been linked with chronic kidney disease (CKD), both mechanistically and at a population level. This can be attributed to the unrestrained activity of the rate limiting enzyme in the 'Fructolytic' pathway, Ketohexokinase-C (KHK-C). This activity results in ATP depletion, uric acid production, inflammation and fibrosis. In addition, de novo production of fructose by the kidney, via the 'polyol pathway' during tissue hypoxia, links fructose with CKD progression irrespective of dietary intake. KHK-C is thus an important component underlying the pathophysiology of CKD.

In cardiac tissue, hypoxia induces KHK-C expression via a HIF-1α mediated isoform switch. Subsequent cardiac 'fructolysis' is associated with cardiomegaly and dysfunction which is abolished by KHK-C knockdown. Progressive CKD is characterised by renal hypoxia; it is therefore important to establish the expression profile of KHK-C in CKD. This is pertinent given the introduction of HIF-stabilising Prolyl Hydroxylase inhibitors to clinical practice. Furthermore, if upregulated in CKD, pharmacological inhibition of KHK-C presents an appealing strategy to slow disease progression.

Hypothesis: Renal KHK-C is upregulated in CKD, and its expression is mediated via HIF1α.

A previously validated Wistar rat model of adenine-induced CKD was used to establish a 'Control' and 'CKD' group of rats. Plasma, urine and kidney tissue were collected at the study end point. Creatinine Clearance (CrCl) was calculated using urine creatinine (µmol/L), urine volume (ml) and plasma creatinine (µmol/L) measurements. KHK, Megalin, HIF1α and HIF2α protein were quantified by Western Blot analysis. RT-qPCR was used to quantify KHK-C and KHK-A mRNA. RNA-Sequencing data of 24 human kidney biopsy samples ('North Dublin Renal BioBank') were identified for in silico validation, patient eGFR and Percent Tubular Atrophy and Interstitial Fibrosis (%TIF) being matched to each sample. Relative expression of KHK as well as other genes of interest were calculated using the 'GEO2R' tool and adjusted for %TIF and eGFR.

Unexpectedly, KHK protein was significantly decreased in CKD compared with controls (N=4, P=0.001). This remained significant when adjusted for Megalin (N=4 P=0.008). In addition, both KHK-A and KHK-C mRNA were downregulated in CKD (N=5, p=0.0001 and 0.0002). A significant positive linear association was observed between CrCl and KHK protein in Wistar rats (N=9, P<0.0001). The same association was evident in silico between eGFR and KHK RNA adjusted for %TIF in human kidney (N=24 P=<0.0001).

Furthermore, downstream markers of KHK-C activity and Polyol Pathway associated genes were downregulated in lower eGFR when adjusted for %TIF (N=24, P<0.0001).
Western blot analyses did not identify a significant difference in HIF1α or HIF2α protein between groups.

Contrary to our hypothesis, these findings demonstrate a downregulation of the principal fructose metabolising enzyme in CKD. There is no evidence to implicate HIF1/2α or an isoform switch. This is at odds with previous experimental data linking fructose metabolism with kidney injury and may represent a compensatory response limiting associated ATP depletion and inflammation in the chronic setting. These findings have implications for current understanding of disease progression and future pharmacotherapy.

THH8

Why do Alport kidneys get leakier during pregnancy?

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THURSDAY - Moderated Poster Session, HALL Q, March 12, 2026, 10:00 - 11:00

Alport syndrome is a rare inherited disease caused by variants in the collagen 4 coding genes, a key component of basement membranes. It is characterised by hearing loss, ophthalmological changes, haematuria, proteinuria and progressive kidney dysfunction. Proteinuria can transiently increase during pregnancy up to 10-fold in Alport patients, compared with 2-fold increases in most other kidney diseases. The underlying aetiology of this, and long-term impact on patient health, remains unknown. We aimed to take a multi-omics approach to identify differences in glomerular composition and structure which could be contributing to the clinically observed differences in proteinuria.

Individual glomeruli from wild type and Alport (COL4A5 heterozygote) pregnant and non-pregnant mice were analysed using time-of-flight secondary ion mass spectrometry (ToF-SIMS), a form of unbiased imaging mass spectrometry which enables simultaneous, glycomics, lipidomics and metabolomics. Following ToF-SIMS, sections were stained using Periodic Acid-Schiff stain and brightfield imaged to identify morphological changes (Holscher et al., 2023).

A significant increase in chondroitin sulphate (CS) was observed between wild type pregnant and non-pregnant mice only (Figure 1a). CS is a glycosaminoglycan and is a major component of the endothelial glycocalyx, a known modulator of vascular permeability. We hypothesize that this increase is a physiological compensatory mechanism which functions to mitigate the impact of increased blood flow and pregnancy related growth factors on the glomerular filtration barrier and renal health. The absence of this increase in an Alport pregnancy suggests a two-hit challenge to the glomerular filtration barrier is occurring, whereby the inherent disruption to the glomerular basement membrane is further compounded by the lack of increase in CS, resulting in severely exacerbated proteinuria. No significant metabolomic or lipidomic changes were observed between groups (Figure 1b/c). Histological analysis identified a reduction in glomerular diameter and a change in glomerular shape in Alport pregnant tissue compared to non-pregnant (Figure 1d). Taken together, this supports that Alport is primarily a disease of the extracellular matrix.

The use of multi-omics enables a more holistic approach to the identification of the molecules of interest to improve the fundamental understanding of why Alport patients experience severe proteinuria during pregnancy. Translation of this approach to liquid biopsies such as blood and urine could provide less invasive tests for patients, improve the identification, prediction and prognosis of individuals who go on to experience severe proteinuria and advance our understanding of glomerular adaptations to disease.

THH9

The hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat increases pulmonary artery systolic pressure and enhances cardiopulmonary responses to hypoxia

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THURSDAY - Moderated Poster Session, HALL Q, March 12, 2026, 10:00 - 11:00

Introduction
Anaemia is common in patients with chronic kidney disease (CKD) and the novel hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) such as roxadustat offer a therapeutic alternative to erythropoietin. However, HIF is the master regulator of transcriptional responses to hypoxia and known to have profound effects on integrated physiology – the pulmonary circulation, and its sensitivity to hypoxia, in particular. Given that CKD patient numbers are predicted to rise, and with the popularity of HIF-PHIs increasing, there have been calls by the expert community for a better understanding of the pleiotropic non-erythropoietic actions, and potential adverse effects, of these novel agents. Notably, there has been a case report of severe pulmonary hypertension associated with roxadustat. We have therefore conducted the first study in humans investigating the effects of a HIF-PHI (roxadustat) on ventilation and pulmonary vascular tone, both with and without concomitant hypoxia.

Methods
We performed a randomised double-blind crossover placebo-controlled study of 12 healthy volunteers (nine male; aged 25 +/- 8 years, mean +/- SD) taking a single 200 mg dose of roxadustat. For six hours after the dose participants underwent serial transthoracic echocardiography (TTE) to estimate pulmonary artery systolic pressure (PASP). The participants then breathed through a mouthpiece and end-tidal forcing was used to control alveolar oxygen and CO2 levels. Pulmonary ventilation was measured, and PASP determined with TTE, during acute hypoxia (SpO2 ~92%). This was repeated after two hours of sustained hypoxia in a chamber (which induced acclimatisation).

Results
After a single 200 mg dose of roxadustat, estimated PASP increased significantly over the course of six hours (Figure 1; $p < 0.001$). This peaked at five hours, with a roxadustat-induced increase of 4.2 mmHg (95% CI, 3.0 – 5.3 mmHg; $p < 0.001$). Both ventilation and PASP were increased by hypoxia - roxadustat significantly augmented these responses, both before and after sustained hypoxia. Several participants commented on their marked work of breathing during hypoxia, which for some approached their limit of tolerance. Peak hypoxic-PASP after sustained hypoxia and roxadustat was 41.1 mmHg (95% CI, 38.2 - 43.9 mmHg) compared with 34.5 mmHg for control (95% CI, 30.8 – 38.2 mmHg; $p < 0.01$).

Discussion

HIF-PHI have gained worldwide interest for the treatment of renal anaemia in large numbers of patients, and the list of potential applications is increasing. We have completed the first integrative physiology study of any HIF-PHI in humans, and shown that a single dose of roxadustat is sufficient to significantly augment pulmonary vasoconstrictor and ventilatory responses to hypoxia. This underscores the central role of HIF in the calibration and homeostasis of the respiratory and cardiovascular systems. Furthermore, it emphasises the urgent need to better understand the effects of sustained HIF-PHI dosing in patients with CKD. Activation of the HIF pathway, sustained hypoxia, and iron deficiency (common in CKD) all increase the sensitivity of the pulmonary circulation to acute hypoxia, and it will be important to determine whether HIF-PHI are an appropriate treatment choice for patients with significant respiratory disease and/or pre-existing pulmonary hypertension, for example.

THH10

Significant telomere-shortening in diabetes within the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA): investigating the impact of kidney disease

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THURSDAY - Moderated Poster Session, HALL Q, March 12, 2026, 10:00 - 11:00

Introduction

Chronic kidney disease (CKD) prevalence is increasing globally and is predicted to become the 5th leading cause of death by 2040 [1]. Increasing diabetes incidence is contributing to this increasing CKD prevalence [2, 3], with 30-40% of individuals with diabetes going on to develop CKD [4]. The aging global population is also contributing to the increasing CKD prevalence, as renal decline occurs with advancing age [5]. Telomere shortening is a hallmark of aging and a potential biomarker that may provide insights to the molecular mechanisms underlying age-related decline in kidney function [6, 7].

Methods

Average telomere length (ATL, kilobases) across chromosomes was measured in the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA) via quantitative polymerase chain reaction (Absolute Human Telomere Length Quantification Assay kit and Roche LightCycler 480 II) [8]. Eleven outliers were removed with ATL less than Quartile 1 minus 3*the interquartile range (IQR), or greater than Quartile 3 plus 3*IQR. Type 2 diabetes (T2D) was defined as: random blood glucose ≥11.1 mmol/L, HbA1c ≥ 6.5% or a self-reported physician T2D diagnosis. CKD was defined as eGFR < 60 ml/min/1.73m2 (determined from serum creatinine). Individuals were categorised as Controls (no T2D and no CKD), CKD only, T2D only, or CKD and T2D. Individuals with type 1 diabetes (T1D) were excluded. In total, 1,676 participants were included in this study (51.8% female, mean age 64).

Results

Table 1 shows the number of individuals within each category. The density plot in Figure 1 shows that individuals with CKD (with and without T2D) had significantly shorter ATL compared to controls ($p<0.038$, Wilcoxon rank, Bonferroni adjustment). ATL differed significantly across groups for both sexes (Figure 2, $p<0.027$, Kruskal-Wallis rank sum), but pairwise comparisons were only significant when comparing the CKD and control group in males ($p=0.02$, Wilcoxon rank, Bonferroni adjustment). In a linear model adjusted for age, sex, smoking, BMI and batch, ATL was not significantly associated with CKD, but was significantly associated with T2D ($p=0.012$), with a borderline significant pairwise comparison between control and T2D groups, accounting for covariates ($p=0.058$).

Discussion

Results suggest that T2D was independently associated with ATL shortening after accounting for covariates; an association not observed after covariate adjustment in individuals with both T2D and CKD, or CKD alone. Hill et al. 2024, summarised a selection of studies investigating the association between TL and CKD (including CKD cases with and without diabetes), highlighting inconclusive results [7]. Scope exists to further expand this analysis to all 2,971 individuals with ATL measurements within NICOLA, increasing power to detect more subtle disease-specific effects. This is important as group sizes were smaller for CKD, and T2D with CKD groups. Moreover, novel tools such as long-read sequencing of telomeres may provide a higher degree of resolution to further understand the potential bi-directional relationship between CKD and telomere shortening, independent of diabetes.

THH11

Serum miRNAs as novel biomarkers and modulators of rapidly progressing chronic kidney disease in patients with diabetes

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THURSDAY - Moderated Poster Session, HALL Q, March 12, 2026, 10:00 - 11:00

Background and Aims:

Chronic kidney disease (CKD) is common in diabetes, occurring in around 40% of patients. Without treatment, CKD can lead to end stage renal disease (ESRD), which requires costly dialysis and transplantation. The current methods for rapid identification of patients prone to accelerated CKD progression are limited, as they are based on measuring estimated glomerular filtration rate (eGFR) over prolonged periods of time, as well as albuminuria, which can be variably reliable. Therefore, there is a clinical need for novel biomarkers that can predict rapid CKD progression earlier.
The aim of this study was to determine whether serum microRNAs (miRs) can be used as biomarkers to identify diabetes patients prone to rapid CKD progression, and to identify potential pathophysiological mechanisms that underpin rapid CKD progression.

Methods:
Next Generation Sequencing established the miR profiles in sera from patients with type 2 diabetes classed with either slow or fast progressing CKD by their eGFR (annual eGFR decrease≥ 3ml/min/1.73m2/year; n=17; obtained from the Salford Kidney Study sample collection). Significantly dysregulated miRs were identified in fast-progressing patients, and their levels were validated by quantitative PCR in a larger cohort of stable and fast-progressing CKD patients (n=70).
Bioinformatic analysis based on miR databases and Ingenuity Pathway Analysis platform (Qiagen) was used to identified target genes of interest linked to a select miR panel. The 3'UTR of those target genes were synthesised and cloned into the pmiRGlo dual-luciferase target miR expression vector (Promega, UK), and then transfected into human embryonic kidney cells (HEK293).
Stably transfected luciferase-expressing HEK293 clones were exposed to miR mimics to establish the interaction between the 3'UTR of the target genes and the miR panel.

Results:
Six miRs were significantly upregulated in serum of fast-progressing patients and correlated with demographic and clinical parameters.
A backwards stepwise regression model created using the miR expression levels and the patient demographics, successfully stratified patients as fast progressors with an accuracy of 86%.

Bioinformatic analysis identified three key gene targets of the six upregulated miRs. Those receptors are involved in inflammation, cell proliferation and regeneration, and can therefore play a role in the progression speed of CKD.
Interference experiments with miR mimics and luciferase reporter vector constructs containing the 3'UTR of the three genes expressed in HEK293 cells demonstrated that the miRs downregulated the luciferase expression. Incubation of the six miR mimics with non-transfected human proximal tubular cells (HK-2) resulted in reduced mRNA levels of the three receptors, thus confirming their interaction in a native cell culture model.

Conclusion:
A biomarker panel of 6 miRs has been identified and validated in an extended patient cohort. A model created using the miR panel demonstrated a predictive power of 86% for identification of fast-progressing CKD patients. It was confirmed that the six miRs regulate the mRNA expression of three key receptors. The identification of the roles of these dysregulated miRs and their gene targets in fast-progressing CKD in type 2 diabetes might eventually enable development of novel therapeutic treatments to halt the progression of CKD.

THH12

Investigating the role of DNA methylation in podocyte dysfunction in Diabetic Kidney Disease

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Background: Diabetic Kidney Disease (DKD) occurs in up to 40% of people with diabetes and is the leading cause of chronic kidney disease worldwide. The role and regulation of DNA methylation (DNAm) in DKD is increasingly appreciated; with numerous studies now showing associations between DNAm and disease. However, the causal role of DNAm in specific cell types involved in disease pathogenesis is not well established. Podocyte loss or injury is one of the earliest features observed in DKD and a predictor of DKD progression. Understanding the mechanisms underlying podocyte dysfunction in DKD is therefore of clinical importance; with the potential to identify novel therapeutic targets.

This study aims to further investigate the causal, mechanistic role of DNAm changes in diabetic podocytes using laboratory models, integrated with 'multi-omics' data from human kidney.

Methods and Results: Conditionally immortalised human podocytes were exposed to a diabetic, insulin-resistant environment in vitro, and DNAm was measured at 850,000 genomic loci (CpGs) using the Illumina EPIC array. 11,803 differentially methylated CpGs were identified in 'insulin-resistant' vs 'control' podocytes (3,424 hypermethylated / 8,379 hypomethylated, FDR<0.01). Notably, our enrichment analysis highlighted a significant over-representation of pathways related to 'Type 2 Diabetes' and 'Insulin Resistance'. Integration with sample-matched transcriptomics data allowed us to map 921 differentially methylated CpGs (FDR<0.05) to 181 differentially expressed transcripts (FDR<0.05), including examples of podocyte-enriched genes such as CACNA1C. To prioritise CpGs for further functional analysis, we used human kidney single-nucleus 'multiome' sequencing data (snATAC-seq and snRNA-seq) data from the 'Kidney Precision Medicine Project' (KPMP). We found 3,214 of our differentially methylated CpGs overlapped with podocyte-enriched regions of open chromatin (snATAC) and linked to 572 podocyte-expressed genes (snSEQ). We further performed 'Mendelian Randomization' analyses to infer causal relationships between kidney DNAm, kidney gene expression and albuminuria, using mQTL and eQTL data derived from over 500 human kidneys in The University of Manchester 'Human Kidney Tissue Resource'. This highlighted potential causal associations between over 100 insulin-resistance-driven methylation events and albuminunria.

Conclusion: This work provides an overview of DNAm changes occurring in insulin resistant podocytes and prioritises DNAm events for follow-up mechanistic study. Ongoing work aims

to further characterise the role of prioritised differentially methylated CpG sites, using CRISPRa/i.