**Title:** Periodontitis severity contributes to CKD and CKD progression through increased oxidative stress

**Objectives**: Gum disease (periodontitis) is the sixth most prevalent condition in humans and, in its severe form, affects 11% of adults worldwide. Periodontitis associates with increased systemic inflammatory and oxidative stress and we hypothesised that these pathways may contribute to the severity and progression of CKD. To address this, we quantified the direct and indirect effects of periodontitis severity on renal function and risk of progression to kidney failure, using structural equation models (SEMs).

**Methods**: We recruited 770 patients with stage 3-5 pre-dialysis CKD. Levels of periodontal inflammation were calculated using the periodontal inflamed surface area (PISA) score, which provides an estimate of the surface area of inflamed periodontal tissues. Renal function was assessed using the CKD-EPI equation for estimated glomerular filtration rate (eGFR), with the addition of albumin:creatinine ratio (ACR) for calculating kidney failure risk. Multivariable linear regression analyses were employed to investigate associations between PISA score, eGFR and markers of inflammation and oxidative stress. SEMs were created to unravel potential pathways by which periodontitis may influence renal health and vice-versa.

**Results**: The mean age of participants was 63 years (S.D. 16 years), 61% were male, 48% never-smokers and 37% had diabetes. Path analysis using SEM (Figure 1) revealed an indirect effect of increase in PISA score, via oxidative stress, on decreasing renal function such that a 10% increase in PISA score equated to a 2.5% decrease in eGFR (95% CI: 0.4-4.6% p=0.021) which translated to a 7.5% (95% CI: 1.0-14.0% p=0.023) increase in 2-year risk of kidney failure. There was no significant direct/indirect effect of eGFR on PISA score.

**Conclusion**: Here we confirm our causal hypothesis that, in this large, well characterised cohort, a decline in periodontal health results in a decline in kidney function via an increase in oxidative stress burden. If treating periodontal disease reverses this deleterious effect, patients with CKD may have differing treatment pathways depending on their periodontal health status.

**Figure 1:** Graphical representation of structural equation model (SEM).

Inflammation, Oxidative stress, SES and Diabetes- latent variables; rest –observed variables

BMI- body mass index; BP- systolic blood pressure; CRP- c-reactive protein; FLC- free light chains; HbA1C- glycated haemoglobin; SES- socio-economic status.

