

### Impact of chronic kidney disease on corneal neuroimmune features in type 2 diabetes

**Aims:** To determine the impact of chronic kidney disease (CKD) on corneal nerve measures and dendritic cell counts in type 2 diabetes.

**Methods:** In vivo corneal confocal microscopy (IVCCM) was used to obtain corneal nerve parameters and compare them in 29 participants with type 2 diabetes with CKD (T2DM-CKD) and 29 with type 2 diabetes without chronic kidney disease (T2DM-no CKD), along with 30 healthy controls. Corneal dendritic cell densities were compared between the T2DM-CKD and T2DM-no CKD groups which were matched for diabetic neuropathy (DPN) status.

**Results:** There was a significant difference in corneal nerve fibre density ( $p < 0.01$ ) and corneal nerve fibre length ( $p = 0.04$ ) between T2DM-CKD and T2DM-no CKD groups. The two diabetes groups had reduced corneal nerve parameters compared to healthy controls (all parameters:  $p < 0.01$ ). Immature central dendritic cell density ( $p = 0.048$ ) and mature central dendritic cell density ( $p = 0.016$ ) were higher in the T2DM-CKD group compared to the T2DM-no CKD group, as well as total central dendritic cell density [10.4 (4.3–16.1) and 3.9 (2.1–21.0) cells/mm<sup>2</sup>, respectively,  $p = 0.028$ ].

**Conclusions:** The study showed that central corneal dendritic cell density is increased in T2DM-CKD compared to T2DM-no CKD, despite the similar DPN severity. This is accompanied by a loss of central corneal nerve fibres. The findings suggest more active inflammation concurrent with greater corneal neuropathy in diabetic CKD compared to type 2 diabetes alone and raise the possibility of additional local factors exacerbating central corneal nerve injury in presence of diabetic CKD.

**Comments.** The overlap of type 2 diabetes and CKD is considered a major risk factor for development of both microangiopathic and macroangiopathic complications. However, it is not known whether this greater corneal nerve loss in diabetic CKD occurs in the setting of increased corneal inflammation as measured by corneal dendritic cell density. IVCCM is now considered the gold standard measure of small fibre structure and aids in the diagnosis of early diabetic polyneuropathy (DPN). Readers will be aware of the large body of evidence which suggests the early loss of corneal neural parameters heralds the onset of DPN in both type 1 and type 2 diabetes. Normative values of IVCCM indices have been drawn up in healthy controls to assist in the interpretation of outcomes in diabetes subjects. This study, however, brings up the interesting observation that there is a role of CKD in altering central corneal dendritic cell density which might affect the outcomes and interpretation of IVCCM indices. In this study, there was a significant reduction of corneal nerve fibre density (CNFD), and length (CNFL) but no difference in branch density (CNBD), inferior whorl length (IWL) and average length (IWL + CNFL/2) in the T2DM-CKD group as compared to the T2DM-no CKD group.

Limitations of this study: This is a single centre study with a small number of subjects. This might lead to bias of results and inconsistency between the IVCCM comparator outcomes. CKD has been defined as eGFR  $< 60$  ml/min/1.73m<sup>2</sup> but the data has now been divided between various CKD stages (e.g. CKD 3a, 3b, 4 etc.). Future scope of work: The readers of this report might be stimulated to do the following: 1) Look into their own established type 2 datasets and see if there is an influence of CKD on the IVCCM outcomes and report it to the Neurodiab community in the next Neurodiab meeting in 2023; 2) a multicentre prospective study could be set up to prospectively explore the relationship between baseline CKD and IVCCM in both type 1 and type 2 patients and follow these patients up annually to see if there is concordance in changes of eGFR with changes in IVCCM indices.

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**Reference.** Asiedu K, Markoulli M, Tummanapalli SS, Chiang JCB, Alotaibi S, Wang LL, Dhanapalaratnam R, Kwai N, Poynten A, Krishnan AV. Impact of Chronic Kidney Disease on Corneal Neuroimmune Features in Type 2 Diabetes. *J Clin Med.* 2022 Dec 20;12(1):16. doi: 10.3390/jcm12010016. PMID: 36614815; PMCID: PMC9820846. <https://www.mdpi.com/2077-0383/12/1/16>