# Summary of the manuscript

The manuscript “TNF-α and Tryptophan Degradation Progressively Increase as Kidney Function Declines in Type 2 Diabetic Patients” by Debnath et al. reports cross-sectional study on patients with diabetic nephropathy. They measured tryptophan (TRP) and its downstream metabolites in kynureine pathway (designated as TRP metabolites, i.e. KYN, KYNA, 3-HKYN, QUINA) and found that reduction of TRP and increase in the downstream metabolites are correlated with progression of diabetic nephropathy.

# Major comments

Most discussions are based only on correlation analyses among clinical variables, metabolite levels and inflammatory markers. Thus, I feel that more evidences may be necessary to justify causalities they inferred.

For example, the authors suggest that the reduction of TRP and increase in the levels of downstream metabolites were due to accelerated TRP breakdown, and this suggestion is basically based on the anti-correlation between level of TRP and those of downstream metabolites. It is better to have some more evidences (in addition to KYN/TRP ratio) that the breakdown is indeed accelerated. For example, how was IDO actually activated? What was the mechanism behind it? Did expression level of IDO go up?

# Minor comments

* p.9 lines 214-215 What does R^2=-0.95 mean? R-square value should always be positive.
* p.9 lines 210-211, lines 217-218 Probably the authors are repeating the very similar statement.
* p.9 mico- should be micro-
* Table 1 Authors give clinical characteristics for all study participants altogether, but in addition to it, they should also give same statistics within each stage (Only stage-dependent BMI is given in the next table).
* Table 3 What statistical tests do the authors use to calculate p-values of Spearman’s correlation coefficients? Did they do multiple-testing corrections?
* I could not see variances from Figure 2. I suggest the authors to plot actual values (actual eGFR values and Metabolite levels) and superimpose the smoothing lines onto them.