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Answer to reviewer

Dr. Kushiyama et al reviewed linking UA metabolism to diabetic complications. Although authors reviewed well, several points should be addressed before publication. Especially, the association between UA and disease progression is independent of diabetic control.

1. Authors described T2DM onset and UA levels. And they also showed that diabetic complications were associated with UA levels. I believe that it is important that diabetic complications were associated with UA levels, independent of diabetic controls. Therefore, authors should describe the statistical analysis, i.e., univariate analysis or multivariate analysis, independent of diabetic control or not.

We described what you pointed out in our paper(ref 59), therefore we added a sentence as follows:

Our data shows the association between UA and disease progression is independent of diabetic control in multivariate analysis.

2. In page 5, authors described the transporter of UA in kidney. However, there is no description of genetics on hyperuricemia. Recently, GWAS identified 18 new loci associated UA concentrations (Nat Genetics 45; 145, 2013). In addition, ABCG2 is important in hyperuricemia as decreased extra-renal urate excretion (Nature Communication 3: 764, 2012).

We added sentences

There are many studies about genetic variations exhibiting hyperuricemia. Among genes introduced above, variants of GLUT9 (SLC2A9)[11, 12], NPT (SLC17A1)[13], ABCG2 (BCRP) variant[14], are well established and proved to be important in hyperuricemia as a result of decreased extra-renal urate excretion. Genome-wide association study (GWAS) is applied for detecting loci affecting serum UA level. Recent report identified 18 new loci (18 new regions in or near TRIM46, INHBB, SFMBT1, TMEM171, VEGFA, BAZ1B, PRKAG2, STC1, HNF4G, A1CF, ATXN2, UBE2Q2, IGF1R, NFAT5, MAF, HLF, ACVR1B-ACVRL1 and B3GNT4) associated UA concentrations[15]. Not only transporters, but also transcriptional factors, signaling receptors, enzymes are

involved in serum UA level.

3. Authors claimed that the SUA is low due to increased urate clearance in patients with diabetes (page 6). This sentence may mislead the readers. It is only observed during the hyperfiltration phase.

We modified the sentence as below:
Shichiri et al. showed that glomerular hyperfiltration also occurs in non-insulin-dependent diabetes mellitus (NIDDM) and that it lowers SUA levels by increasing the renal clearance of urate during the hyperfiltration phase[50].

4. Authors claimed that UA production was increased in the Cr doubling group (page 10). The reference is now in press. Therefore, I cannot evaluate this sentence.

We added DOI: 10.1111/jdi.12243 in ref. 59. It has already been published electronically.

5. Authors described the association between UA and inflammasome. Recently, many interesting papers have been reported (Nature immunology 2013;14:454, The EMBO journal 2013;32:2336). Authors should refer and comment.

So we did:
UA crystals can injure organelle such as lysosomes, and damaged organelle selectively sequestered by autophagy[100]. If mitochondria is damged, autophagosome is driven via microtubule to NLRP3 inflammasome[101]. Colchine treatment expresses the anti-inflammatory effect for gout by inhibiting microtubule-driven spatial arrangement, not by inhibiting UA crystalizaion. Therefore uric acid crystal in inflammatory cells of atherosclerosis lesion might activate inflammation, while solvent uric acid acts as antioxidant. Microtubule-driven spatial arrangement might be a possible target for diabetic complication derived from UA crystals.

Thank you for your kind review to improve our paper.