

Abstract Type : Poster

Abstract Submission No. : PO-1177

Effect of dipeptidyl peptidase-4 inhibitors on urinary exosome microRNAs in type 2 diabetes

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Objectives: Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of antidiabetic agents that prevent the degradation of the incretin hormones glucagon-like peptide-1 and gastric inhibitory peptide. The effects of DPP-4 inhibitors on renal outcomes are inconsistent, but preclinical studies suggested renoprotective effects of DPP-4 inhibition. To show the effect of DPP-4 inhibitors on renal microenvironment, we investigated the difference of urinary exosomal microRNAs expression between type 2 diabetic patients using sulfonylurea and those using DPP-4 inhibitor.

Methods: Type 2 diabetic patients using metformin with one of other oral antidiabetic agents including sulfonylurea or DPP-4 inhibitor (Gemigliptin) more than 3 months were enrolled. Non-diabetic control were also recruited. After separation of urinary exosomal miRNAs from the urine samples, twelve participants with adequate quality of miRNAs, four from each group, were selected. The miRNA expression was evaluated using the NanoString nCounter technology, and differentially expressed miRNAs between Sulfonylurea group and Gemigliptin group were investigated.

Results: A total of 57 participants including 34 Gemigliptin group and 23 Sufonylurea group were enrolled. Mean age of this cohort was 53.4 ± 11.6 years, and 36 (63.2%) participants were men. From the cohort, four participants of each group were extracted after matching of age and gender. In the analysis with NanoString technology, nineteen urinary exosomal miRNAs were upregulated, and one miRNA were downregulated in Gemigliptin group compared to Sulfonylurea group. From the literature review, 6 urinary exosomal miRNAs (Table 1), were suggested to have renoprotective effects.

Conclusions: Our study showed the different expression pattern of urinary exosomal miRNAs between sulfonylurea use and DPP-4 inhibitor use. We plan to validate the expression of candidate miRNAs using quantitative PCR, and these results will provide more solid results.

Table 1. The list of urinary exosomal miRNAs which was upregulated in patients using DPP-4 inhibitor and the references showing their roles in diabetes

miRNAs	References
let-7c-5p	<ul style="list-style-type: none">• Clin Lab. 2018 May 1;64(5):709-718.• Diabetes. 2015 Sep;64(9):3285-93.
miR-30d-5p	<ul style="list-style-type: none">• Cardiovasc Diabetol. 2019 Aug 30;18(1):113.
miR-23a-3p	<ul style="list-style-type: none">• J Clin Endocrinol Metab. 2018 Apr 1;103(4):1447-1458.
miR-10a-5p	<ul style="list-style-type: none">• J Nephrol. 2018 Dec;31(6):813-831.
miR-26a	<ul style="list-style-type: none">• Eur Rev Med Pharmacol Sci. 2019 Aug;23(3 Suppl):304-311.
miR-26b-5p	<ul style="list-style-type: none">• J Med Biochem. 2018 Dec;37(4):499-506