IMPACT OF DIPEPTIDYL-PEPTIDASE IV INHIBITORS AS ADD-ON THERAPY TO METFORMIN ON CIRCULATING OXIDATIVE STRESS BIOMARKERS AND MICRORNAS IN PATIENTS WITH TYPE 2DIABETES: AN OBSERVATIONAL STUDY

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Introduction: Dipeptidyl peptidase-4(DPP-4) inhibitors are oral agents used for the pharmacological treatment of adults with type 2diabetes mellitus (T2DM). By preventing glucagon-like peptide 1(GLP-1) breakdown, DPP-4inhibitors enhance endogenous insulin secretion and suppress glucagon secretion, resulting in the reduction of blood glucose levels. Clinical trials demonstrated that these agents are effective in reducing glycated hemoglobin (HbA1c) with a low risk of hypoglycemia and neutral effects on weight. Oxidative stress is a key factor involved in the development and progression of T2DM and its complications and some in vitro and *in vivo* studies have proven that DPP-4inhibitors protect against oxidative stress. To date, the ability of DPP-4inhibitors to modulate oxidative damage and antioxidant defense systems has received limited attention in clinical trials; moreover, so far, several microRNAs (miRNAs) have been identified as differentially expressed in patients with T2DM compared to controls but stress-related miRNAs have not been yet investigated in relation to DPP-4inhibitors therapy.

Aims: The aim of this study was to examine the effects of add-on therapy of DPP-4inhibitors on oxidative stress markers and miRNAs in patients with T2DM who were already on routine antidiabetic treatment.

Patients and methods: This study included 40 T2DM patients (27males and 13post-menopausal females) sub-grouped according to their antidiabetic treatment. To compare the effects of DPP-4inhibitors with those of metformin on oxidative/antioxidant status, whole blood ROS, plasma advanced oxidation protein products (AOPP), advance glycation end products (AGEs) and protein carbonyls (CO) as markers of oxidative protein damage, plasma thiobarbituric acid reactive substances (TBARS) levels as a marker of lipid peroxidation, and antioxidant status measured as Ferric Reducing Ability of Plasma (FRAP), were measured by spectrophotometric methods. DNA damage will be evaluated by Comet assay and stress-related circulating miRNAs by Real-time PCR.

Results: DPP-4inhibitors treatment was associated to a trend toward reduction in protein oxidative damage markers CO and AOPP ($p=0.053$, $p=0.061$, respectively). ROS, TBARS AGEs and FRAP levels showed no significant changes. When patients were stratified for gender, males treated with DPP-4inhibitors showed significantly reduced plasma levels of TBARS ($p<0.05$), AOPP ($p<0.05$) and CO ($p<0.01$) compared to those receiving metformin alone, whereas this effect was not seen in females.

Discussion and conclusions: In conclusion, our preliminary data indicate that the treatment with DPP-4inhibitors improve oxidative damage markers in T2DM patients but these effects were significant only in males, suggesting gender related differences that deserve to be further investigated in a larger population and confirmed by multivariate statistical analyses.