SEDENTARY-TIME: EFFECT ON PRO- AND ANTI-INFLAMMATORY CYTOKINES PLASMA LEVEL AND ON URINARY METABOLIC SIGNATURES IN PATIENTS WITH TYPE 2 DIABETES ENROLLED IN THE IDES 2 (ITALIAN DIABETES AND EXERCISE STUDY-2) CLINICAL TRIAL.

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Physical inactivity, i.e. an insufficient amount of physical activity (PA) according to current guidelines, and sedentary behavior, i.e. a large amount of time spent in a sitting or reclining posture, have become the major determinants of the epidemic of obesity and type 2 diabetes. Recent findings from individuals with type 2 diabetes indicate a significant association between sedentary (SED)-time and metabolic risk, independently of several confounders, including time spent in moderate-to-vigorous-intensity PA.

On this base, this study aimed to evaluate the effect of different sedentary-time levels (i) on plasma pro- and anti-inflammatory cytokines level and (ii) on urinary metabolic signatures. We have analyzed samples collected at the baseline visit from patients with type 2 diabetes enrolled in the IDES-2 (The Italian Diabetes and Exercise Study 2) clinical trial. All patients were physically inactive and sedentary, but on the basis of their sedentary level, we selected and compared two different groups: patients at the first quartile of SED-time (n=38) and patients at the fourth quartile of SED-time (n=40).

By ELISA analysis on plasma samples, we analyzed the levels of two pro-inflammatory cytokines (IL-6 and TNF-alpha) and three anti-inflammatory cytokines (IL-1RA, IL-4 and IL-10). Our results showed that the different SED-time do not induce significant differences for IL-6 and TNF-alpha, whereas statistically relevant higher levels of IL-1RA ($p<0.0247$) and IL-10 ($p<0.0123$) were observed in the group with the lower SED-time. For IL-4, this difference was significant just considering male population.

Urinary metabolic fingerprints were defined by comprehensive two-dimensional gas chromatography implemented with a parallel dual secondary column-dual detection by mass spectrometry and flame ionization detector (e.g., GC×2GC–MS/FID).

The high separation power, the enhanced sensitivity and improved system loadability enabled to define highly informative 2D patterns corresponding to the distribution of low molecular weight metabolites (aminoacids, sugars, metabolic acids, amines etc). Advanced fingerprinting 2D data interpretation, based on targeted and untargeted features, was adopted to extract information about analytes distribution across samples. Fingerprinting results were firstly analyzed by Principal Component Analysis (PCA); that failed on clearly clusterize patients groups. By supervised Linear discriminant analysis (LDA) some meaningful differences were revealed with a decisive gender effect on the female sub-population. In particular, it was observed a statistically relevant up-regulation of several urinary metabolites in females belonging to the lower sedentary group in comparison with more sedentary female. These metabolites included glycine ($p=0.05$), threonine

(p=0.018), phenylalanine (p=0.014), valine (p=0.028), succinic acid (p=0.039), malonic acid (p=0.028), xilitol (p=0.023) and ribitol (p=0.028).

Our results demonstrated that a less extended sedentary time is associated to higher levels of plasma anti-inflammatory cytokines. In addition, we showed that sedentary-time reduction impacts on some urinary metabolites in females, the more sensitive gender.