ABSTRACT

Background: Type 2 diabetes (T2D) is one of the greatest challenges of modern medicine, affecting 425 million people worldwide. The pathogenesis of T2D is grounded in the inability of tissues to import and metabolize glucose, known as insulin resistance (IR), as well as in diminished secretion of insulin from the pancreas. The precise mechanisms leading to these pathological states remain unclear. Physical activity is an effective method to prevent and treat (T2D), but its effectiveness in patients at different stages of glucose metabolism dysregulation and the mechanisms of its beneficial effects have not been precisely elucidated. Skeletal muscle is a major contributor to overall glucose homeostasis in the body and is chiefly responsible for the efficacy of exercise intervention in ameliorating the burden of T2D. However, few studies have investigated the transcriptional signature of glucose metabolism dysregulations in skeletal muscles and how exercise affects it. Thus, the aim of this project was to identify the transcriptional signature of dysregulated glucose metabolism in skeletal muscle and its response to three-month exercise intervention in humans by profiling the transcriptome, using next generation sequencing (NGS).

Materials and methods: For this project we included 35 sedentary males, aged 35-65 years, with BMI 26-33 kg/m^2, divided into three groups: 15 normoglycemics, 12 prediabetics and 8 subjects with type 2 diabetes, treated with metformin only. RNA samples were obtained from biopsied Vastus lateralis muscles, before and after a 3-month supervised exercise intervention. The exercise intervention occurred thrice weekly and consisted of mixed aerobic (60-70% of individual's VO2max) and strength (60-70% of the repetition maximum for each exercise) activities, performed three times per week. Selected groups of patients did not differ in age, BMI, number of performed trainings or diet during the intervention. mRNA sequencing was performed with Illumina HiSeq 4000 platform.

Results: The baseline gene expression analysis indicated that significant differences in gene expression in skeletal muscles were observed between type 2 diabetics and the two remaining groups. Differentially expressed genes related mainly to oxidative phosphorylation and the electron transport chain in mitochondria, and to a much smaller degree to impaired protein synthesis. We found no differences between prediabetics and normoglycemics in baseline gene expression. We found that the exercise intervention was equally effective in all three diagnostic groups; however, the effect of intervention did not overcome baseline metabolic differences among the groups. Moreover, changes in genes related to mitochondrial function predominated the transcriptional response to the exercise intervention in all three studied groups.

Conclusions: Our results suggest that main defects of type 2 diabetes pathogenesis in skeletal muscles is related to mitochondrial dysfunction and that physical activity mediates its beneficial effects through activation of mitochondria-related pathways. Moreover, a lack of differential gene expression in skeletal muscle between patients with prediabetes and normoglycemia implies that early stages of insulin resistance may predominantly affect the liver. Additionally, we showed that there is no impairment of response to exercise in type 2 diabetic nor prediabetic subjects, compared to normoglycemics.