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Running for a future without diabetes?

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Physical exercise is a commonly accepted strategy to increase the healthspan in our ageing societies and to prevent metabolic diseases such as diabetes. However, not all individuals profit to the same extent. Subjects who failed to improve in glycemic control were observed in almost all of the populations studied, and this failure is at least partially independent of other investigated endpoints, e.g. cardiorespiratory fitness, blood pressure, lipid profile, and body weight. These subjects were described as non-responders in glycemic control. However, this definition can be misleading as higher exercise loads have been shown to overcome the failure to respond in fitness parameters. Whether this can be applied to pre-diabetic subjects to improve the metabolic response is under debate. On a molecular level, improvement in glycemic control is associated with increased abundance of mitochondrial regulators and enzymes in the trained skeletal muscle, and increase in mitochondrial respiration. Mechanisms interfering with the metabolic benefit of exercise are widely unclear.

Results of an exercise intervention study in Tübingen indicate a crosstalk of inflammatory pathways with the metabolic response after training. 20 middle-aged individuals (untrained, high risk for type 2 diabetes) performed 8 weeks of cycling and walking training at 80% individual V_{O2} peak. In this structured and supervised exercise intervention study, all participants were able to improve their fitness, but 40% did not increase their insulin sensitivity. In muscle biopsies taken before and after the training period, we found a reduced up-regulation of genes pivotal for glucose and fat utilization in skeletal muscle tissue of non-responders, as well as increased transcripts pointing to local inflammation, among others TGFβ (transforming growth factor beta). In human skeletal muscle cells, TGFβ1 downregulates the abundance of important genes in energy metabolism (PPARGC1A, PRKAA2, TFAM, HADHA, CPT1B), inhibits insulin signal transduction and suppresses myotube differentiation. The data suggest that a dysregulated adaptive process in skeletal muscle leads to increased TGFβ activity and can attenuate the improvement in glycemic control. In ongoing research, the downstream effectors of TGFβ as regulator of metabolic adaptations are studied.

The metabolic dysregulations in glucose and lipid metabolism have been associated with a reduced efficiency of exercise to improve glycemic control. Comparison of the acute response of age-, BMI-, and fitness-matched type 2 diabetic subjects and healthy controls to one bout of aerobic exercise did not indicate reduced metabolic flexibility or impairment of transcriptional response.

Moreover, since the increase in mitochondrial respiration in skeletal muscle can only partly explain the improvement of glycemic control, the involvement of additional non-muscle adaptions is discussed.