Preventing type 2 diabetes: When genes fail to respond

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It is widely accepted that physical exercise lowers the risk of developing diabetes. Yet in one in five participants in related studies this positive effect fails to materialize. Researchers and clinicians involved in a collaborative translational project launched by the German Center for Diabetic Research between the Helmholtz Zentrum München and the University Hospital Tübingen have now discovered what occurs in the muscle of these so-called "non-responders". The results of their research were published recently in the *Diabetes* journal.

Regular physical activity is a highly effective means of lowering the risk of developing diabetes. However, patients respond in very different ways. In about one in five participants in so-called training intervention studies, the positive metabolic impact of physical exercise actually fails to occur.

A team of researchers led by Prof. Cora Weigert of the University Hospital Tübingen, who heads a department at the Institute of Diabetes Research and Metabolic Diseases (IDM), a research unit of the Helmholtz Zentrum München at the University of Tübingen, have now examined the reasons behind this. To this end, 20 middle-aged subjects completed an endurance training program over eight weeks consisting of cycling and walking at the Sports Medicine in Tübingen (Head: Prof. Andreas Nieß). "All participants were at high risk to develop type 2 diabetes. The aim was to improve their insulin sensitivity and to lower their diabetes risk", explains Dr. Anja Böhm from the IDM and first author of the study. "Before the training intervention, none of the participants were very physically active."

Messenger substance inhibits glucose and fat burning

Together with Prof. Martin Hrabě de Angelis and Prof. Johannes Beckers from the Institute of Experimental Genetics (IEG), Helmholtz Zentrum München, the researchers examined molecular changes in the skeletal muscle. While the anticipated positive effects on genes important for glucose and fat burning were evident in the muscles of those participants whose insulin sensitivity had improved, the respective adjustments in the muscles of the "non-responders" were reduced.

However, analyses of the muscles of the "non-responding" participants revealed that the messenger substance TGF-beta was activated after training. Experiments with human skeletal muscle cells subsequently conducted by Dr. Christoph Hoffmann of the University Hospital Tübingen confirmed that TGF-beta inhibits transcription of the genes that are important for glucose and fat burning and reduces insulin sensitivity.

No carte blanche for couch potatoes

"At the moment we are still trying to understand what causes TGF-beta to be activated in the muscle of some participants. There is some evidence that a different training program where the intensity or length of training is adapted to an individual's ability to respond to physical exercise would be successful, and would help to prevent diabetes," says Prof. Weigert. But the results should not be understood as a carte blanche for couch potatoes, she adds. "I myself am convinced that everyone – given a suitable training program – can lower their personal diabetes risk!"

More information: Anja Böhm et al. TGFβ contributes to impaired exercise response by suppression of mitochondrial key regulators in skeletal muscle, *Diabetes* (2016). DOI: 10.2337/db15-1723