

**Weight reduction decreases TNF- $\alpha$  and increases IL-6 gene expression in lymphocytes in subjects with metabolic syndrome - the GENOBIN study**

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**Background and Aims:** Obesity has been considered as a proinflammatory state. Inflammation has been implicated in metabolic syndrome (MS), type 2 diabetes and cardiovascular diseases. Weight loss may have an effect on expression of genes related to inflammation in adipose tissue, and genes like tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin (IL)-6 have been found to be increased in the adipose tissue of obese subjects. However, expression of these genes in immune cells is poorly described. We sought to evaluate how long-term weight reduction affects expression of genes related to inflammation in lymphocytes.

**Materials and Methods:** We carried out a randomized clinical trial in 75 40–70 year-old overweight or obese men and women with the MS. The subjects entered one of three lifestyle interventions - weight reduction (WR), aerobic training or resistance training - or the control group. Subjects randomized to WR participated in an intensive 12 wk weight loss period in which they met a clinical nutritionist for 5 times. During the following weight maintenance phase 13–34 wks, they met the clinical nutritionist twice. Blood samples were taken at the beginning, at wk 12 and at the wk 34. Lymphocytes from 24 subjects from the WR group intervention were isolated with the use of Lymphoprep kit. Total RNA was extracted and converted to cDNA for quantitative real-time PCR gene expression analysis. The Ethics Committee of Kuopio University Hospital approved the protocol according with the standards of the Helsinki Declaration.

**Results:** A significant reduction in weight ( $P < 0.001$ ), waist circumference ( $P < 0.001$ ), body fat (BF;  $P < 0.001$ ), BF% ( $P < 0.001$ ) and fasting plasma glucose (FPG;  $P < 0.001$ ) was observed in the WR group at wk 34 compared with wk 0. Gene expression levels of TNF- $\alpha$  were lower at wk 34 than at wk 0 [median 23.4% (95% CI: 1–24),  $P < 0.05$ ]. Conversely, IL-6 expression increased at wk 34 compared with wk 0 [median 9% (95% CI: –5–35),  $P < 0.05$ ]. Changes in both genes were significantly correlated between each other ( $r = 0.61$ ,  $P = 0.002$ ). Change in IL-6 expression was significantly correlated to changes in BF

( $r=-0.42$ ,  $P=0.042$ ), in BF% ( $r=-0.49$ ,  $P=0.014$ ) and in FPG ( $r=-0.44$ ,  $P=0.035$ ). Even when adjusting for changes in weight or waist circumference, correlations between changes in IL-6 expression with FPG and BF changes remained significant.

**Conclusion:** Weight loss in subjects with MS decreased TNF- $\alpha$  gene expression and paradoxically increased IL-6 gene expression in lymphocytes. The increase of IL-6 expression was correlated with decreases in body fat and fasting plasma glucose levels. Although the literature seems to support a decrease in gene expression of proinflammatory cytokines such as IL-6 with weight reduction, the immunomodulatory effects of weight loss on gene expression in lymphocytes may be more complex.

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