**EFFECT OF VITAMIN D ON INSULIN SENSIBILITY AND MYOSTEATOSIS IN A MURINE MODEL OF DIET-INDUCED INSULIN RESISTANCE**

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Increasing evidence support the hypothesis that vitamin D could exert pleyotropic effects far beyond the preservation of mineral and skeletal homeostasis. In particular, epidemiological studies pointed out to a strong association between vitamin D deficiency and type 2 diabetes (T2DM) prevalence and, consistently, vitamin D levels have been negatively correlated with BMI and pre-diabetic status. However, the role of vitamin D supplementation in the prevention or progression of T2DM is currently under debate, and a causal relationship is still lacking. This study aimed to evaluate the effect of vitamin D administration in a murine model of diet induced insulin-resistance focusing on the skeletal muscle, a tissue that play a crucial role in the maintenance of glucose homeostasis.

Male C57DL/6 mice (n=40) were provided with a standard diet or High Fat-High Sugar Diet (HFHS) for 4 months. Subsets of animals were treated with Vitamin D (7 □g•kg-1, i.p. three times/week) for the last 2 months. Body weight and food intake were recorded weekly. At the end of the treatment, glucose tolerance test was performed. The expression of markers of lipogenesis and phosphorylation of insulin signalling intermediates were evaluated by western blot on gastrocnemius specimens. The expression of RAGE receptor and AGE protein adducts were also evaluated by immunoblotting. Gastrocnemius fat accumulation was detected by oil red staining.

HFHS diet induced body weight increase, hyperglycemia and impaired glucose tolerance. HFHS animals showed an impaired insulin signalling and a marked fat accumulation in the skeletal muscle. Vitamin D administration reduced body weight and improved systemic glucose tolerance. In addition, vitamin D restored the impaired muscle insulin signalling and reverted myosteatosis evoked by the diet. These effects were associated to decreased activation of NF-□B and lower levels of TNF-alpha, a well known proinflammatory cytokine involved in the insulin resistance development. Consistently, a significantly decreased activation of the SCAP/SREBP lipogenic pathway and lower levels of CML protein adducts and RAGE expression were observed in skeletal muscle of animals treated with vitamin D.

Our data demonstrated that vitamin D administration improved insulin resistance due to chronic exposure to HFHS diet. In addition, our results indicated that selective inhibition of some signalling pathways (including NF-□B, SCAP/SREBP and CML/RAGE cascades) within the skeletal muscle significantly contributed to its beneficial effects.