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IGFBP-3 Interacts with the Vitamin D Receptor in Insulin Signaling Associated with Obesity in Visceral Adipose Tissue

Inmaculada Moreno-Santos [1,2,†], Daniel Castellano-Castillo [1,2,†], María Fernanda Lara [3], Jose Carlos Fernandez-Garcia [1,2], Francisco Jose Tinahones [1,2,*] and Manuel Macias-Gonzalez [1,2,*]

1 Unidad de Gestión Clínica Endocrinología y Nutrición, Instituto de Investigación Biomédica de Málaga (IBIMA), Complejo Hospitalario de Málaga (Virgen de la Victoria)/Universidad de Málaga, 29010 Málaga, Spain; morenosantos.inma@gmail.com (I.M.-S.); danie__cc@hotmail.com (D.C.-C.); josecarlosfdezgarcia@hotmail.com (J.C.F.-G.)
2 CIBER Pathophysiology of Obesity and Nutrition (CB06/03), 29010 Málaga, Spain
3 Department of Urology, Complejo Hospitalario de Málaga (Virgen de la Victoria)/Universidad de Málaga, 29010 Málaga, Spain; fer76lc@hotmail.com
* Correspondence: fjtinahones@uma.es (F.J.T.); manuel.macias@ibima.eu (M.M.-G.); Tel.: +34-951-032-648 (M.M.-G.); Fax: +34-27-951-924-651 (M.M.-G.)
† These authors contributed equally to this work.

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Abstract: Adipose tissue has traditionally only been considered as an energy storage organ. Nevertheless, the importance of this tissue in systemic physiology and, especially, in systemic inflammation has been highlighted in recent years. Adipose tissue expresses proteins related to vitamin D (VD) metabolism, and it has been proposed that it can act as a VD storage tissue. The active form of VD, 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$), is able to modify adipocyte and adipose tissue physiology via the VD receptor (VDR), decreasing the expression of pro-inflammatory cytokines in adipose tissue. Moreover, VD deficiency and VDR has been reported to be associated with obesity and diabetes. However, the results of the different studies are not conclusive. Insulin growth binding proteins (IGFBPs) have been identified in adipose tissue, but their roles are poorly understood. Therefore, the objective of this study was to analyze the plasma levels of VD and the gene expression of VDR in the adipose tissue of subjects with morbid obesity (MO) and with different degrees of insulin resistance (IR), as well as the functionality of direct interaction between IGFBP-3 and VDR, which could explain its inhibitory role in adipogenesis. Our results show a novel role of the VD system in the regulation and activation of IGFBP-3 in visceral adipose tissue (VAT) of patients with MO, as a new and alternative mechanism proposed in the insulin signaling associated with obesity.

Keywords: vitamin D; VDR; IGFBP; insulin resistance; morbid obesity and adipose

1. Introduction

Adipose tissue has long been identified as the main storage site for vitamin D (VD) [1]. In addition, it has been shown that VD regulates adipogenic gene expression, and is active in adipocytes at all levels. VD reduces the release of cytokines and the inflammation of the visceral adipose tissue (VAT) through the inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling. Obesity is associated with VD deficiency [1]. Furthermore, recent studies have shown that the vitamin D receptor (VDR) is expressed in adipocytes. VDR is a transcription factor which binds to specific VD response elements (VDREs) within the regulatory regions of its primary target genes [2]. Retinoid x receptor α (RXRa) is also a ligand-dependent transcription factor, whose functions by dimerizing