A Brief Insight about Obestatin possible relation with Diabetes Complications

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Conflict of interest: None declared

Funding: No funding sources

Abstract

Obestatin is a hormone linked to the regulation of appetite in humans reducing food intake, body weight gain, gastric emptying and suppression of intestinal motility and it could be a useful marker of the nutritional status reflecting adiposity and insulin resistance. Obestatin positive effects on glucose and lipid metabolism candidates this peptide as a potential therapeutic tool in pathological conditions such as insulin resistance and diabetes. Studies in humans have shown that blood obestatin levels are significantly lower in obese subjects and correlate negatively with BMI, insulin, glucose and the HOMA IR. At present, the causative role of obestatin in this complex process is unknown. Although it is tempting to speculate about the potential role of obestatin in pathologic retinal angiogenesis, further results are needed. A worrisome and fragmental clinical finding is that obese patients may develop diabetic retinopathy long before the clinical manifestation of diabetes shows up. Whether this may be explained by change in obestatin level is an open question. The use of obestatin peptide as a regenerative agent for traumatic peripheral nerve damage offers a novel approach to address .Beyond its established role in myogenesis, obestatin singularly enhance both the speed and extent of recovery of motor behavior after crush injury to the sciatic nerve, as analyzed by sciatic functional test. These benfits were associated with regulation of the SC plasticity to direct the differentiation, axonal regrowth, and remyelination.

Keywords: Obestatin, Diabetes.

Tob Regul Sci. ™ 2023;9(1): 2937-2942
DOI: doi.org/10.18001/TRS.9.1.202

Introduction:

At a low glucose concentration, obestatin potentiated the insulin response to glucose At a high glucose concentration, obestatin inhibited the insulin release At a high glucose concentration, the

beta cells are less responsive to obestatin than at a normal glucose level, and the glucose concentration bathing the beta cell appears to be a critical factor for the insulinotropic activity of obestatin **(1).**

Obestatin is a hormone linked to the regulation of appetite in humans reducing food intake, body weight gain, gastric emptying and suppression of intestinal motility and it could be a useful marker of the nutritional status reflecting adiposity and insulin resistance **(2).**

Obestatin is derived by post-translational cleavage of the same peptide precursor (preproghrelin) as ghrelin, which is a peptide mainly released from the stomach **(3).** In several studies in adult humans, decreasing concentrations of obestatin were associated with diabetes and impaired glucose regulation and the insulin-sensitivity surrogate homeostasis model assessment (HOMA) of insulin resistence (IR) indicating an important role for obestatin in body weight regulation **(4).**

Obestatin has been reported to have important effects on endothelial cells such as decreasing vascular cell adhesion molecule-1 expression and increasing oxidized low-density lipoprotein binding to macrophages **(5)** Therefore, it was suggested that obestatin may also have a potential function in the regulation of blood pressure **(6).**

In a study by **Zorlu et al., (7)**, they sought to determine the relationship between circulating omentin-1 and obestatin levels and macroalbuminuria in patients with type 2 diabetes. This study found that Serum obestatin levels were significantly higher in patients with macroalbuminuria.

Obestatin positive effects on glucose and lipid metabolism candidates this peptide as a potential therapeutic tool in pathological conditions such as insulin resistance and diabetes. Studies in humans have shown that blood obestatin levels are significantly lower in obese subjects and correlate negatively with BMI, insulin, glucose and the HOMA-IR **(8).** Another study results suggested a rise in serum obestatin levels in type 2 diabetes patients with macroalbuminuria compared with type 2 diabetes patients with normoalbuminuria (NA) **(7).** Albumuniria was reported to reflect a local (renal) endothelial dysfunction and low-grade inflammation **(9).** So, it may be expected a decrease in serum obestatin levels in patients with MA. In the same study it was also found that serum obestatin levels positively correlated with albumin levels in urine samples (**7).**Thus, it may be contemplated that there is an association between albumin and obestatin in terms of pathophysiological pathways.**Vicennati et al., (10)**and **Zhang et al., (11)** reported lower ghrelin and oppositely higher obestatin levels in obese patients. So, these two peptides may be working opposite each other as reported initially and a decrease in ghrelin levels may result in an increase in obestatin levels in patients with IR, low grade inflammation or T2DM.

Neovascularization in retina and choroids is regulated, in a large part, by diverse mechanisms; most of them are regulated by growth factors and growth inhibitory factors secreted by RPE cells. Among these factors, angiogenic factors have been most closely linked to induction of neovascularization in the eye **(12).** Expression of these factors appears to be under regulation of

different metabolic signals that determines the link connecting metabolic disorders with retinal status as happens for diabetic retinopathy. At present, the causative role of obestatin in this complex process is unknown. Although it is tempting to speculate about the potential role of obestatin in pathologic retinal angiogenesis, further results are needed.

In the early stage of diabetic retinopathy, the damage of retinal ganglion cells (RGC) already exists, promoting the development of the disease. Obestatin was found to prevent H_2O_2-induced damage in RGC-5 cells . Moreover, GLP-1R is closely related to the function of obestatin in RGC-5 cells **(12).**

Under normal conditions, the hRPE (human retinal pigment epithelium cells) related activities are preserved by a balanced proliferative–antiproliferative surroundings as well as by a balance between adhesive and counter-adhesive molecules that maintain RPE cells adhered to Bruch's membrane **(13).** In the development of proliferative retinopathies, such as proliferative vitreoretinopathy (PVR), RPE cells migrate from their physiological location to the preretinal and subretinal spaces where they dedifferentiate to myofibroblasts and then begin to proliferate.

Several growth factors and cytokines appear to be responsible for the evolution of such a disease. In fact, several factors such as PDGF **(14),** TNF-α**,** HGF**,** IL-1, IL-6 **(15),** IL-8, MCP-1, MCSF **(15),** EGF **(16),** TGF-β1**,** or FGF**,** are increased in the vitreous body, sub-retinal fluid as well as in the epiretinal membranes of patients with PVR **(17).** PVR might thus be interpreted as a result of a cascade of interactions among cytokines and growth factors with the intraocular cell populations, mainly RPE cells, and non-habitual cells, such as macrophages and lymphocytes, that enter in the vitreous cavity when the ocular barriers break down **(18).** Therefore, obestatin is included to the list of factors that regulate the hRPE cell proliferation.

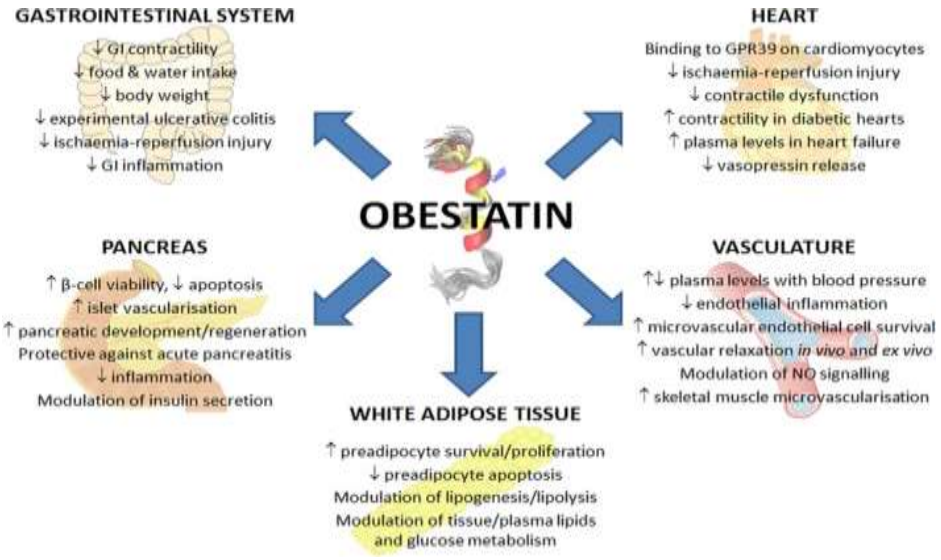

Figure 1: Summary of the reported pathophysiological effects of obestatin. Obestatin targets several tissues, including the GI system, pancreas, WAT, the heart and vasculature, where it exerts diverse biological actions relevant to the metabolic and cardiovascular complications of diabetes. **(19)**

Neovascularization in retina and choroids is regulated, in a large part, by diverse mechanisms; most of them are regulated by growth factors and growth inhibitory factors secreted by RPE cells. Among these factors, angiogenic factors have been most closely linked to induction of neovascularization in the eye (12). Expression of these factors appears to be under regulation of different metabolic signals that determines the link connecting metabolic disorders with retinal

At present, the causative role of obestatin in this complex process is unknown. Although it is tempting to speculate about the potential role of obestatin in pathologic retinal angiogenesis, further results are needed. A worrisome and fragmental clinical finding is that obese patients may develop diabetic retinopathy long before the clinical manifestation of diabetes shows up. Whether this may be explained by change in obestatin level is an open question (20).

The use of obestatin peptide as a regenerative agent for traumatic peripheral nerve damage offers a novel approach to address .Beyond its established role in myogenesis, obestatin singularly enhance both the speed and extent of recovery of motor behavior after crush injury to the sciatic nerve, as analyzed by sciatic functional test. These benfits were associated with regulation of the SC plasticity to direct the differentiation, axonal regrowth, and remyelination. The fact that obestatin expression increases in the distal region where dedifferentiated SCs switch off the myelination program, supports a regulatory role not only on SC proliferation to replace lost cells but also on the collective migration of SCs to drive nerve repair. Thus, obestatin may be included to the group of extrinsic and/or intrinsic signals that modulate and balance negative and positive factors to control SC proliferation and their transition to a differentiating state during peripheral myelination (21).

Defects in SC generation and differentiation during regeneration may cause a failure in myelinogenesis, contributing to SC deterioration associated with motor disabilities. However, functional recovery after obestatin treatment in peripheral nerve injury was observed. Obestatin expression is up-regulated in the distal nerve stumps. This type of signal may be understood as a trophic factor to promote axonal survival and regulate neuronal elements. This fact would be related to a stereotypical spatial organization and dynamics of the axon cytoskeleton that ensure the elongation and steering of injured peripheral axon (22). Regenerating axons need to carry out de novo growth to reach their targets. In a study showed that obestatin signaling protects neuromuscular synaptic loss and, therefore, counteracts atrophy of hindlimb skeletal muscles innervated by motor neurons (20). Although the obestatin/GPR39 system has been thought of as a regulator of myogenesis, its involvement in crucial aspects of peripheral nerve regeneration was under study.

Obestatin signaling regulates SC plasticity to promote and guide axonal repair. On the other hand, obestatin preserve neuromuscular synapses by regulating the axonal transport of mitofusin 2 (Mfn2), calpastatin, and possibly other cytosolic proteins to inhibit localized calpain activation, axon degradation, and neuromuscular synaptic loss. In summary, glial obestatin-mediated paracrine and autocrine stimulation constitutes an attractive target for therapeutic approaches of

wide range of diseases including, but not limited to, aging- and disease-related skeletal muscle atrophy **(20).**

Considering the reasonably consistent alteration of circulating levels of obestatin in patients with metabolic disease (the majority of which display reduced concentrations), together with its established actions on the GI system, pancreas and adipose tissue, and emerging evidence supporting beneficial effects of obestatin treatment in experimental T1DM and T2DM, it is clear that this peptide demonstrates vast potential as a novel therapeutic target that is worthy of further investigation in the context of metabolic dysfunction linked with obesity and diabetes. **(20).**

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