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Endocrine approach in the treatment of obesity: Is there any space for the adiponectin action?

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Adiponectin is a hormone secreted by adipose tissue, exerting many positive effects in the human body. Its action has been widely studied, placing it into the metabolic health beneficial products of the adipose tissue. Nevertheless, adiponectin has been shown to exert some extra beneficial non metabolic actions, as well. Adiponectin levels can be related to reduced incidence of cancer in obese patients. Moreover, adiponectin has been shown to be implicated in the positive fertility outcomes of women. Some new studies have also indicated that adiponectin has a potential effect in the control of appetite, which raises a question, whether adiponectin could be accredited to be useful in the endocrine evaluation of obesity. Could these additional non-metabolic actions prove its helpfulness?

Key words: adiponectin, obesity, non metabolic actions

Nowadays, the obesity is considered to be a pandemic problem. Roughly 13% of the world population (over 650 million people) are obese and 39% (more than 1.9 billion people) are overweight. Regarding the endocrine workup of the obesity, the recently published European Society of Endocrinology (ESE) guidelines (Pasquali et al. 2020) give some new insight into the well-studied parameters of the obesity.

As widely shown, hormonal regulation in both sexes is a prerequisite for the maintenance of a normal body weight, along with all its health benefits. A detailed workup in the hormonal status of the obese patient is necessary, which often reveals various hormones that need either to be replaced or to be reduced. Nevertheless, we rarely encounter the presence of endocrinopathies responsible for excessive weight gain, while a slight increase in weight is sometimes a result of an endocrine imbalance (Seetho and Wilding 2013).

Indeed, in clinical practice, several entities should be ruled out, before initiation of the weight loss plans, either nutritionally or medically. Among the basic functions, very well described by ESE guidelines are, thyroid function, hypercortisolism, male and female gonadal dysfunction, while leptin and ghrelin offer small help (Pasquali et al. 2020). Nevertheless, we could provide some thoughts on the potential consideration of adiponectin levels measurement, as well.

As widely shown, adiponectin is an insulin-sensitizing adipokine produced mainly by adipose tissue. Its anti-inflammatory and anti-atherosclerotic effects favor the literature nickname “beneficial adipokine”. Adiponectin levels are reduced in insulin-resistant states and in obesity in general (regardless of insulin resistance) and are inversely correlated with the levels of fasting glucose, insulin, and triglycerides (Wang and Scherer 2016).

Initial thought would be that it is a waste of money measuring a hormone that shows established correlations with known and cheaper in measurement metabolic factors, so why to do it?

Metabolic health in the obese can be evaluated through various labs and exams. But, is there any

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extra benefit, apart from the metabolic health, in measuring adiponectin in the obese?

Question Nº1: Could adiponectin prove to be helpful in evaluating the risk of an obese patient suffering from cancer?

Hypothesis Nº1. Apart from the metabolic health consequences, obesity imposes a well shown danger in suffering from cancer, even sometimes in worsening the cancer prognosis (Dalamaga et al. 2012). As a molecule strongly implicated in obesity, adiponectin has further been related to oncogenesis. Of note, adiponectin mediates its actions via adiponectin receptors, Adipo R1 (mainly in muscle) and Adipo R2 (mainly in liver), whereas the third receptor, t-cadherin, has been described to mediate the adiponectin-driven muscle regeneration process (Wang and Scherer 2016).

It has been shown that adiponectin levels have been related to various types of cancers (breast cancer, endometrial cancer, colorectal cancer, pancreatic cancer, esophageal cancer, hematological malignancies, renal cancer, liver cancer, and prostate cancer) (Dalamaga et al. 2012). In the past, our team has found and measured the expression of the adiponectin receptors (AdipoR1 and AdipoR2) directly in the cancer tissue, via immunofluorescence approach (Michalakis et al. 2007). Adiponectin has been implicated in the development of cancer via a complicated cascade [including 50-AMP-activated protein kinase (AMPK), nuclear factor-kB (NF-kB), p38 mitogen-activated protein (MAP) kinase, the mammalian homologue of target of rapamycin (mTOR), c-Jun NH2-terminal kinase (JNK) and signal transduction and activator of transcription 3 (STAT3)] (Dalamaga et al. 2012). Whether this is a matter of the insulin resistance and its overexpression via IGF-1 stimulation in cancer cells by promoting cellular proliferation and inhibiting apoptosis, or via the lower adiponectin expression in cancer tissue *per se*, still remains a question (Michalakis 2019).

Question Nº2: Could adiponectin prove to be helpful in the prediction of an improved fecundity in an obese woman, with or without ART, regardless of Insulin Resistance?

Hypothesis Nº2. Adiponectin seems to be strongly implicated in fertility, mainly in women and especially in the women suffering from PCOS, a rather common feature of obese women presenting with menstrual irregularities and infertility. So, the well accepted and popular Oral Glucose Tolerance Test (OGTT) in the obese females reveals sometimes an extensive insulin resistance, which further stimulates the ovary to produce androgens or worsens the quality of the follicle. Adiponectin levels are reduced, as expected, in the state of marked insulin resistance, but on the same time, adiponectin receptors are expressed in the pituitary, the ovaries, the oviduct and the endometrium, possibly explaining part of the effect of insulin. Moreover, adiponectin has been shown to increase along with successful oocyte retrieval that leads to a successful pregnancy (but not during the stage of the stimulation phase) in pregnancies achieved via Assisted Reproductive Techniques (ART) (Michalakis and Segars 2010).

Question Nº3. Could adiponectin prove to be helpful in mediating central appetite effects and on parallel reduce the depressive symptoms in an obese patient?

Hypothesis Nº3. The last years, the human gut has surprisingly been related to the appetite center of the brain. The brain (mainly via the hypothalamic arcuate nucleus – ARC) interprets various peripheral and neural signals to regulate energy homeostasis, thus maintaining the balance between food intake and energy expenditure. All signals are transduced to an orexigenic (appetite stimulating) circuit via agouti-related peptide (AgRP) and neuropeptide Y (NPY) neurotransmitters, and an anorexigenic circuit (appetite suppressing), via cocaine- and amphetamine-regulated transcript peptide (CART) and pro-opiomelanocortin (POMC) neurotransmitters. Adiponectin has been implied to be a part of the "fat-centric hypothesis" (Kubota et al. 2007), since adiponectin levels in the cerebrospinal fluid (CSF) are increased during the fasting periods along with the stimulation of AMPK locally in the brain, further increasing orexigenic NPY towards the need for food. In states of overfeeding, the adiponectin levels are decreased, while during obesity, the adiponectin levels do not respond to the overfeeding, possibly showing a partial resistance (Kubota et al. 2007).

Moreover, intracerebroventricular (ICV) administration of adiponectin resulted in an increased energy expenditure, increased thermogenesis, and consequent reduction in body weight. Indirect actions of adiponectin administration may include the increased effect of leptin on thermogenesis (Qi et al. 2004), while the experimental use of an adiponectin receptor agonist, prevented the corticosterone-induced obesity

and reversed the corticosterone-driven depression state, at least in mice (Nicolas et al. 2018).

Conclusions

So, should we measure adiponectin in everyone presenting with the obesity? Are there any more specific criteria? Are the adiponectin levels partially predisposed genetically, in relation to the weight gain of the mother in different trimesters of gestation? Excessive weight gain of the mother in the first trimester of pregnancy, seems to be related to lower adiponectin levels for the newborn, predisposing to an overweight or obese environment in the future (Rifas-Shiman et al. 2017). On the other hand, regardless of weight gain of the mother, the adiponectin levels are low in the majority of obese subjects in adult life.

Thus, the measurement of adiponectin levels could be beneficial in newborns whose mothers had an excessive weight gain in the first trimester of gestation, or in obese adults.

In medicine, quick answers are sometimes needed. The quick answer says that "adiponectin value for money ratio" favors towards not using its measurements in a routine screening. Could we perhaps sometimes give it a chance?

"Food for thought". Rephrasing, at least the "thought for food" seems to be influenced by adiponectin.

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