Adipocytokines

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Adipocytokines are hormonally active molecules that are believed to play a key role in the regulation of crucial biological processes in the human body.

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1. Introduction

According to the newest data, 30.5% of European women are overweight (body mass index (BMI) > 25 kg/m^2), and a stunning 15.9% of them are diagnosed with obesity (BMI > 30 kg/m^2), which forces obstetricians to face with the state of an obesity epidemic and obesity-related diseases among their patients [1]. Moreover, the pregnancy itself is connected with increased insulin resistance and promotes the worsening of multiple metabolic parameters. The exact pathophysiological mechanism of numerous pregnancy complications such as gestational hypertension, preeclampsia (PE), gestational diabetes (GDM), or fetal growth abnormalities is quite elaborate, however, its incidence among obese patients is significantly elevated [2][3][4].

Obesity is a pathological condition considered to be mainly associated with bad lifestyle habits—high caloric intake and the lack of physical activity—leading to morphological changes in the structure of adipose tissue [5]. Excessive body weight promotes adipocyte hypertrophy and the occurrence of the local cellular hypoxia, which together contribute to the development of the state of chronic low-grade inflammation [6]. This results in increased migration and the presence of immune cells, such as macrophages and lymphocytes, in pathologically re-modelled adipose tissue due to increased adipocyte apoptosis promoted by hypoxia [7]. The increased infiltration of immune cells exposed to persistent hypoxia and increased oxidative stress destroys the balance between secretion of anti- and pro-inflammatory cytokines [8]. In response to the presence of those stressors, the synthesis of various adipocyte-specific molecules, such as leptin and adiponectin, is altered compared to lean individuals. It has been found that adipokine secretion patterns are strictly linked with the excessive body weight, percentage of hormonally active adipose tissue, and inflammatory status [9]. However, these changes can be reversed through a reduction of both subcutaneous and visceral fat levels [10][11].

Adipokines belong to the group of protein hormones and cytokines secreted by adipocytes, immune cells, fibroblasts, and other hormone-secreting cells originating from the adipose tissue. Adipocytes release hundreds of signaling molecules that are responsible for the regulation of the local and systemic cellular activities through their autocrine, paracrine, and endocrine activity [12][13]. It has been established that adipokines play a key role in the regulation of many crucial processes in the human body, like glucose and lipid metabolism, insulin sensitivity, appetite, immune response, and inflammation [14]. Due to their engagement in these processes, adipokines may be treated as potential targets for novel therapeutic strategies in numerous medical conditions [15].

A dysregulation in adipokine production is known as a characteristic feature of obesity and occurs in a variety of obesity-related diseases. Furthermore, those abnormalities are treated as partial causative factors in the pathogenesis of several metabolic, inflammatory, and neoplastic diseases [16]. The abnormal leptin-to-adiponectin ratio is often observed in test results of individuals diagnosed with impaired glucose tolerance, dyslipidemias, and high blood pressure [17][18]. Without any predominant changes in daily habits and diet, those conditions lead straight to the development of the metabolic syndrome [19]. Patients affected by metabolic syndrome are often diagnosed with type 2 diabetes and advanced atherosclerosis, which makes them more susceptible to micro- and macro-vascular diseases and puts them at risk of death from cardiovascular events like stroke or heart attack [20].

While there are still multiple possible hypotheses regarding the mechanisms of pregnancy-related complications, such as gestational hypertension, preeclampsia, gestational diabetes, or fetal growth abnormalities, the discovery of the adipose-derived hormones sheds new light on those conditions. Current studies tried to analyze the contribution of adipocyte-specific peptides to the pathogenesis of those complications. Moreover, it seems essential to assess the possible benefits

of routine adipokines concentration measurements performed in patients with uncomplicated pregnancies. Those assessments could establish their utility as potential early markers of gestational complications. Standard measurements of adipokine levels in a few mentioned high-risk pregnancy complications may also influence the choice of proper treatment strategies. Finally, adipokines open promising perspectives for the invention of new drugs that could be used during gestation.

2. Clinical Applications of Adipokines Measurements in Various Pathologies

2.1. Leptin

Leptin is a peptide hormone secreted mainly by the white adipose tissue, with its most important functions including regulation of energy homeostasis, metabolism, and neuroendocrine function [21]. Leptin was reported to be elevated even in physiological pregnancy, steadily increasing throughout its course [22]. Leptin was the first described adipokine linking the adipose tissue with reproduction [23]. This protein is also expressed by the placental tissue and fetal adipose tissue. Ninety-five percent of leptin produced in the placenta is delivered into maternal circulation where it promotes excessive weight gain during pregnancy [24][25][26]. Hence, leptin is often considered to be responsible for pregnancy-associated energy balance changes [27]. Furthermore, reproductive functions, such as embryo implantation and development, have also been found to be influenced by its expression. In turn, mouse model studies reported infertility caused by leptin deficiency, with the affected animals rescued by exogenous administration of this protein [28]. Leptin was also found to stimulate gonadotropin hormone expression, as well as act as a puberty permissive factor under the influence of steroid hormones [29]. It was further reported to affect ovarian function, linking follicular alterations with obesity [30]. Additionally, a significant role of leptin was suggested in embryo implantation, as the protein and its receptors are expressed in blastocysts and can be extracted from embryo-conditioned media [31][32].

2.2. Adiponectin

Adiponectin is a 30 kDa adipokine most abundantly secreted by adipocytes, with reported antidiabetic, anti-inflammatory, and cardioprotective functions [33]. Its expression was shown to exhibit significant sexual dimorphism, with males characterized by notably lower levels of this protein than females [34], while its action is exerted through two functionally different receptors, AdipoR1 and AdipoR2. It is one of the hormones that were, in a number of studies, associated with the development of obesity [35]. Its reduction plays a significant role in diseases associated with excessive weight, as it counteracts insulin resistance and inflammation [36]. Hence, administration of recombinant adiponectin was a subject of a number of therapeutic interventions [37]. Furthermore, adiponectin is one of the most studied adipokines within the context of pregnancy. It was found that adiponectin, independently from maternal BMI, modulates the glucose homeostasis, promoting the increased insulin sensitivity [38][39].

Most studies suggest that in normal pregnancies, plasma levels of this protein did not significantly differ between non-pregnant and first trimester pregnant women, decreasing towards the end of pregnancy and falling again postpartum [40]. This inverse correlation with the gestational age of the fetus is not observed in overweight women. This dependency can be explained with the need for maternal pregnancy-related fat deposition and the downregulation of adiponectin expression in response to increasing adipose mass [41][42][43][44]. Hence, despite that singular studies based on a small size sample group question the correlation of adiponectin level with gestation advancement, the general consensus states that concentration of this protein decreases significantly between the first and third trimester of pregnancy. Nevertheless, the physiological range of this protein's serum levels during gestation is not yet established [40]. Finally, adiponectin was implicated in a range of other diseases, such as hypertension, chronic kidney diseases, atherosclerosis, chronic obstructive pulmonary disease, diabetic retinopathy and cancer, as summarized by a number of existing excellent reviews focused solely on this adipokine [36][37].

2.3. Visfatin

Visfatin is a protein produced predominantly by the visceral adipose tissue, with its tissue and circulation levels significantly increasing in obesity [45]. Visfatin levels are, also, higher in pregnant compared to non-pregnant controls [46]. During normal pregnancy, the plasma concentration of this protein changes, reaching a peak between 19 and 26 weeks of gestation. In normal pregnancies of obese women, visfatin levels were unchanged [47]. Decreased placental visfatin expression was associated with poor glycemic control and macrosomia in women with type 1 diabetes [48]. However, the physiological range of visfatin in normal pregnancy remains undetermined, with the variation between studies mostly dependent on the characteristics of the studied group [49].

2.4. Resistin

Resistin is a pro-inflammatory adipokine that is predominantly expressed by mononuclear cells, as well as adipocytes and most importantly, placental trophoblastic cells during pregnancy [50][51]. Resistin impairs glucose uptake by adipocytes, increases plasma glucose concentration, and thus decreases insulin sensitivity [50]. It is also known as a factor inducing the production of inflammatory cytokines and cell adhesion molecules [52]. The plasma resistin levels in pregnant women at term are significantly higher than those in age-matched non-pregnant controls. Because, adipose resistin expression remains unchanged during pregnancy, it suggests that the placenta is likely a major source of resistin in the maternal circulation [53][51]. Moreover, high resistin level could further affect the placental transfer of glucose by decreasing the expression of trophoblastic cell surface glucose transporters, GLUT-1 [54]. Some authors linked the high resistin concentrations with the increase in insulin resistance during the latter half of pregnancy, which may suggest its potential indirect role in the regulation of fetal growth. Those effects could be caused by increased insulin secretion and its pro-growth activity [55].

2.5. Irisin

Irisin is a novel secreted myokine, encoded by the fibronectin type III domain-containing protein 5 (FNDC5) precursor gene. Functional studies of irisin demonstrated that its metabolic role was to mediate exercise-related energy expenditure by turning white adipose tissue (WAT) into brown adipose tissue (BAT) in response to activation of the peroxisome proliferator-activated receptor-gamma coactivator-1 α (PGC-1α) [56]. Irisin is cleaved and secreted mostly from skeletal muscle after exercise, but low levels may also be found in the pancreas, liver, and adipose tissue [56][57][58][59]. Irisin is expressed in the female reproductive system, including the ovary, as well as in the placenta and in neonatal cord blood serum [60][61].

In healthy eumenorrheic women, serum irisin levels vary throughout the menstrual cycle, being higher in the luteal phase than in the follicular phase, with an approximately 26% increase of these levels. The rise of irisin in the luteal phase suggests that it might be involved in the ovulation cycle. Furthermore, serum irisin levels were found to rise during normal pregnancy. Additionally, irisin levels are higher in middle and late pregnancy with respect to early pregnancy in healthy women, with an increase in levels of approximately 16% and 21%, respectively [60][62].

2.6. Omentin

Omentin was initially described in intestinal Paneth cells and has been implicated in the gut defensive mechanisms against pathogenic bacteria [63]. There are two homologs, omentin-1 that is the major circulating form, and omentin-2. This adipokine is preferentially produced and secreted by visceral adipose tissue (VAT) and is predominantly expressed in VAT stromal vascular cells [63]. Yang et al. noted that in vitro experiments revealed that omentin enhances insulin-stimulated glucose uptake in human adipocytes and presents insulin-sensitizing properties [64]. Omentin is also expressed in the heart, lungs, ovary, and placenta. Omentin-1 was shown to be downregulated by insulin and glucose, resulting in decreased levels in overweight women suffering from polycystic ovary syndrome [65]. Moreover, decreased omentin-1 levels were found in patients suffering from obesity and diabetes [66]. Briana et al. also reported that omentin is detectable in the serum of infants and it is mainly derived from fetal and/or maternal tissues. Thus, a positive correlation between maternal and fetal omentin-1 concentrations was found, implying a transplacental transport of this adipocytokine. In addition, the placenta most probably does not contribute to circulating concentrations of omentin-1, as its concentrations do not decline after placental elimination. It was also demonstrated that there are relatively high concentrations of omentin-1 in umbilical serum samples. Therefore, omentin-1 is hypothesized to play a similar role in energy homeostasis [67]. It is worth keeping in mind that glucose acts as a main source of energy during prenatal development and growth. Insulin in turn is well-known for increasing the uptake of circulating glucose by fetal muscle and adipose tissue. Therefore, despite the fact that there is no available information about a potential role of omentin-1 in fetal growth, enhanced growth-promoting effect through its insulin-sensitizing action may be attributed to high levels of omentin-1 in the fetus.

2.7. Chemerin

Chemerin is a hormonally active protein that is suspected to be associated with a range of metabolic, inflammatory, and cardiovascular diseases [68][69]. Chemerin is expressed in various human tissues, and also in the placenta. However, its expression is mainly pronounced in the liver and subcutaneous and visceral adipose tissue. [70][71][72]. Its concentration in peripheral blood correlates well with BMI and obesity [73]. Pregnancy is a state of increased chemerin secretion, which rises throughout the gestation [70][74][75]. Nonetheless, its involvement in the regulation of physiological pregnancy is not fully elucidated yet. However, it is thought that chemerin may play a significant role in the pathophysiology of various gestational complications.

2.8. Apelin

Apelin is a peptide hormone widely expressed in various human tissues. Apelin and its receptors (APJ) are thought to be involved in the regulation of numerous physiological processes [76], making the Apelin/APJ axis a promising target for implementing novel therapeutic strategies for a range of metabolic and cardiovascular diseases [77][78]. It was reported that the state of physiological pregnancy is associated with a significant reduction in apelin secretion [79].

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