ROLE OF ADIPONECTIN IN OBESITY AND METABOLIC DISORDER INDUCED OVARIAN DYSFUNCTION

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Abstract

Adipokines are cellular signaling proteins produced by adipose tissue and are nowadays the focus of extensive research. They play roles in a variety of processes including inflammation, modulation of energy and appetite, lipid and glucose metabolism, insulin sensitivity, endothelial cell function, angiogenesis, blood pressure regulation, and hemostasis. An increase in white adipose tissue in obesity, namely its visceral depot, affects the production and secretion of adipokines and are associated with metabolic and cardiovascular diseases due to reduced sensitivity to insulin, low angiogenic potential, and increased lipolytic activity. Adiponectin may influence ovarian physiology by affecting genes essential for ovarian follicular development and ovarian reserve, including kisspeptin and AMH. Adiponectin dysregulation may be one of the possible mechanism responsible for reduced insulin sensitivity in PCOS. This review attempted to highlight the inflammatory aspect of obesity and metabolic disorder and the role of adiponectin in the pathophysiology of ovary under metabolic dysregulation.

Keywords : adipokines,adiponectin, inflammation,obesity,insulin,polycystic ovary.

Introduction :

Adipose tissue is a major tissue to provide excess nutrient storage for triacylglycerols .White adipose tissue (WAT) is acknowledged as a dynamic endocrine organ capable of producing and releasing various bioactive polypeptides known as adipokines. Adipokines are molecules which share structural similarities with cytokines and have both pro-inflammatory and anti-inflammatory properties (Cornier *et al*.,2008). They play a crucial role in integration and maintaining equilibrium of systemic metabolism with immune function. In individuals with normal metabolic health, there is a balance between pro-inflammatory and anti-inflammatory adipokines. However, an imbalance in these adipokines in adipose tissue can lead to various metabolic disturbances including insulin resistance. Adipokines are categorized into hormones, growth factors, angiogenic factors, and cytokines, and they exert their effects through endocrine, autocrine, or paracrine signaling (Ouchi *et al*.,2011).

Many adipokines are directly involved in maintaining metabolic homeostasis. Among the numerous adipokines, leptin, adiponectin, resistin, interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF), anti-inflammatory IL-10, and transforming growth factor (TGF)-β are particularly well-studied. Adiponectin circulates in different multimer complexes

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and molecular weights .Following translation, it can be modified into several forms: trimers, hexamers, and high molecular weight (HMW) formations, which have varying biological effects (Krause *et al*.,2019).. Recent findings indicate that several endoplasmic reticulum (ER)-associated proteins, such as ER oxidoreductase 1-α (Ero1-α), ER resident protein 44 (ERp44), disulfide-bond A oxidoreductase-like protein (DsbA-L), and glucose-regulated protein 94 (GPR94), play crucial roles in the assembly and secretion of these higher-order adiponectin complexes. (Achari and Jain.,2017).

During obesity, the increase in the number of adipocytes due to adipogenesis affects immune responses. Body fat distribution is a significant factor in obesity as visceral and omental fat accumulation are linked to elevated levels of certain adipokines, which can trigger chronic inflammation. (Mraz and Haluzik, 2014). Obesity and excess weight are significantly involved in the decline in the natural fertility of mammals. Recently research has highlighted the roles of adipokines in fertility and reproduction. as adipokines such as leptin, adiponectin, visfatin, chemerin and resistin are able to regulate the functions of gonads and the hypothalamic-pituitary axis. (Ouchi *et al*.,2011).Adiponectin receptors are present in many reproductive tissues, including the central nervous system, ovaries, oviduct, endometrium, and testes. Adiponectin influences gonadotropin release, normal pregnancy, and assisted reproduction outcomes. In this review the role of adiponectins in connection with the pathophysiology of female reproductive system is discussed (de Heredia *et al.,* 2012).

Obesity induced inflammation : Obesity, like other states of malnutrition, is known to impair the immune function, altering leucocyte counts as well as cell-mediated immune responses. Alternatively a modified immune function contributes to the pathogenesis of obesity (de Heredia *et al.,* 2012). Obesity-associated increase in the production of leptin (pro-inflammatory) and the reduction in adiponectin (anti-inflammatory) seem to affect the activation of immune cells. Additionally Non-esterified fatty acids (NEFA) seems to induce inflammation through various mechanisms (such as modulation of adipokine production or activation of Toll-like receptors). Excess nutrient and adipocyte expansion trigger endoplasmic reticulum stress and hypoxia occurring in hypertrophied adipose tissue stimulates the expression of inflammatory genes and activates immune cells. Adiponectin is markedly reduced in obesity and rises with prolonged fasting and severe weight reduction (Kubota *et al*.,2007).

The exact molecular mechanisms of obesity-associated Type II Diabetes mellitus are still unclear, however low-grade chronic inflammation is an important factor in the pathogenesis of obesity-associated Type II Diabetes mellitus in humans and rodent animal models . While the liver and muscles exhibit only mild inflammatory responses and no substantial changes observed in immune cell numbers in obesity, adipose tissue depots are particularly susceptible to significant immune cell infiltration and inflammation. This contributes to systemic inflammation and insulin resistance in both obese rodents and humans (Zatterale *et al.,* 2019).

Excessive nutritional intake leads to hypertrophy and hyperplasia of adipocytes, causing cellular stress that triggers oxidative stress and inflammatory responses in adipose tissue. These inflammatory responses become self-sustaining, increasing local and systemic levels of pro-inflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β, and CC-chemokine ligand 2 (CCL2), which contribute to insulin resistance (Murakami *et al*.,2013).. Alongside the production of inflammatory adipokines in adipose tissue, factors associated with obesity, such as hyperlipidemia, hyperglycemia, hypoxia, oxidative stress, and endoplasmic reticulum (ER) stress, can also induce insulin resistance in peripheral tissues and activate inflammatory signaling pathways within adipose tissue.(Zatterale *et a*l.,2019). Excess nutrients leading to hyperlipidemia and hyperglycemia trigger mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and oxidative stress. These conditions activate stress-responsive signaling molecules, such as JNK and IKKβ. In addition to IRS serine-307 phosphorylation, the JNK and IKKβ signaling pathways enhance the expression of inflammatory genes in target tissues, thereby increasing systemic inflammation (Magkos *et al*., 2016). Saturated free fatty acids and gut-derived bacterial lipopolysaccharide (LPS) also activate Toll-like receptor 4 (TLR4), leading to the activation of NF-κB and JNK, which further contribute to inflammation and insulin resistance Additionally, inflammation in adipose tissue is driven by inflammatory adipokines produced by adipocytes and by pro-inflammatory immune cells that infiltrate the tissue (Choi and Cohen., 2017).

Subcutaneous adipose tissue is highly effective at differentiating adipocytes and expanding cell size to store large amounts of triacylglycerol. This ability helps minimize lipid accumulation in visceral adipose tissue, the liver, and muscles. When subcutaneous adipose tissue cannot efficiently convert excess carbohydrates into lipids for storage—often due to reduced expression of genes like SREBP-1 and ChREBP—it is linked to diabetes in obese individuals (Luo and Liu 2016). In contrast, visceral adipose tissue is linked to a higher risk of insulin resistance and exhibits greater infiltration of monocytes and production of IL-6 compared to subcutaneous adipose tissue, which contributes to inflammation in obese individuals. Ectopic lipid accumulation in the liver and muscles is also associated with insulin resistance induced by obesity. Elevated levels of diacylglycerol (DAG), which result from incomplete triacylglycerol synthesis or the breakdown of triacylglycerol into DAG, have been suggested to impair insulin signaling by activating protein kinase C in muscle Similarly, DAG accumulation in the liver is linked to hepatic insulin resistance (da Silva Rosa *et al*., 2020). In line with this, mice deficient in ATGL, which have a reduced ability to convert triacylglycerol to DAG, demonstrate improved glucose tolerance and insulin sensitivity (Choi and Cohen., 2017). Increased ceramide levels have also been associated with insulin resistance .(Luo and Liu.,2016). However, it remains unclear whether DAGs or ceramides directly mediate insulin resistance at the cellular level or if they are part of the broader inflammatory pathways associated with obesity.

Adiponectins and female reproductive system : In females, adiponectins regulates steroidogenesis in ovarian granulosa and theca cells, oocyte maturation, and embryo development. Additionally, adiponectin receptors have been identified in placental and endometrial cells, indicating that this adipokine may be vital for embryo implantation, trophoblast invasion, and fetal growth.In ovary adipokines can regulate folliculogenesis, ovulation, and steroidogenesis in paracrine and autocrine manners. Moreover, adipose tissue-derived adipokines can be involved in ovarian functions directly through affecting the pituitary-hypothalamus axis as the central regulator of ovarian functions or indirectly by regulating energy balance and metabolisms (Jafari-Gharabaghlou *et al*., 2021). The presence of adiponectin receptors in GnRH neurons and pituitary cells, along with its effects on GnRH, LH, and FSH release, indicates that adiponectin plays a crucial role in regulating fertility through the hypothalamic–pituitary axis in both males and females.Adiponectin may play a role in ovarian physiology through its impact on genes crucial for ovarian follicular development and ovarian reserve, such as kisspeptin and AMH. (Merhi *et al*.,2019). In vitro studies have highlighted that adiponectin exerts an inhibitory effect on GnRH secretion by hypothalamic cells via AMPK activation . Specifically, in GT1-7 cells (a subset of GT1 cell lines), adiponectin not only reduces GnRH secretion but also decreases the transcription of KISS1 mRNA. (Thundyil *et al*., 2012). The receptors of adiponectins are found in reproductive tissues, such as the ovaries, oviduct, endometrium The Adipo R1,Adipo R2 receptors are present in endometrial tissue and a variation of Adipo R1 and Adipo R2 was observed throughout the menstrual cycle. The expression was maximum at the middle of the secretory phase (Merhi *et al*., 2019). .

In humans, adiponectin has been shown to inhibit the proliferation of both normal and ectopic endometrial cells in a dose- and time-dependent manner. An important role of adiponectin signal was established during human embryonic implantation. It was also been observed that the endometrium of women with frequent implantation failure expresses reduced Adipo R1 and Adipo R2 compared to normal women of reproductive age. Adiponectin also exerts anti-inflammatory effect in the endometrium by inhibiting the production of proinflammatory cytokines IL 6,IL 8 and monocyte chemotactic protein 1.(Barbe *et al*.,*2019*). Uterine leiomyoma cells also have been confirmed to express both AdipoR1 and AdipoR2, and adiponectin significantly inhibits the proliferation of uterine Eker leiomyoma tumor 3 (ELT-3) cells in rats (Ruiz *et al*.,2019).

Obesity, metabolic disturbances and ovarian pathology : role of adiponectin

Recent studies conducted in human and animal models for obesity, diabetes, and atherosclerosis have reported on the potential role of adiponectin and adiponectin receptors for these metabolic diseases. Reduced serum levels of adiponectin have been linked to chronic inflammation in various metabolic disorders, including type 2 diabetes, obesity, atherosclerosis, and non-alcoholic fatty liver disease, where adiponectin's anti-inflammatory properties have been observed. These anti-inflammatory effects are primarily mediated through the targeting of macrophages. (Hui *et al*., 2015, Luo and Liu.2016). Adiponectin can inhibit the growth of myelomonocytic progenitor cells and affect the function of mature macrophages by impairing their phagocytic ability, decreasing TNF-α production, and reducing the expression of class A scavenger receptors (Luo and Liu., 2016). Adiponectin can enhance insulin sensitivity by increasing the expression of PPARα, which in turn regulates genes like CD36, ACO, and UCP-2 in the liver. (Achari and Jain.,2017). Additionally, adiponectin supplementation has been shown to reduce glucose production in primary rat hepatocytes. Thiazolidinedione medications improve glycemic control by elevating adiponectin levels in type 2 diabetes patients, adiponectin transgenic models, and also in knockout mice (Nawrocki *et al.,*2006).

PCOS is the commonest endocrine disorder in women, affecting 5–10% of females of reproductive age. PCOS is frequently associated with insulin resistance, abdominal obesity and an increased risk of developing type 2 diabetes (Moghetti., 2016). Localization of some adipokines (in particular, adiponectin, resistin, visfatin, and chemerin) , their receptors and their role in the female reproductive tract including ovary, placenta, and uterus are studied in detail and it has been found that in women with PCOS. Adiponectin signaling in adipose tissue seems to be impaired with decreased expression of Adipo R1and Adipo R2 which suggests that adiponectin dysregulation may be one of the possible mechanism responsible for reduced insulin sensitivity. In women with PCOS, there is an upregulation of receptors in both subcutaneous and visceral fat tissues compared to those without PCOS. While these receptors are present in both types of fat, their expression is higher in subcutaneous fat . For all women, the expression of adipoR1 is positively correlated with insulin levels, the androgen index (testosterone/SHBG × 100), and testosterone, and negatively correlated with Sex Hormone Binding Globulin (SHBG) (Mannerås-Holm *et al* .,2014). Notably, treating tissue with testosterone and estradiol increases the expression of these receptors. Previous studies have shown that high levels of sex steroids (testosterone and estradiol) and low levels of SHBG are associated with insulin resistance.It had also been observed that adiponectin concentration in follicular fluid was decreased in PCOS women. (Groth., 2010). In polycystic ovaries a lower proportion of theca cells expresses adiponectin receptors and granulose cells also showed a reduced expression of adiponectin,APPL 1,Adipo R1 and Adipo R2,possibly affecting follicular development and selection of a dominant follicle (Tao Tao *et al*.,2019). It has also been shown that adiponectin messenger RNA (mRNA) expression is significantly lower in women with PCOS compared with weight-matched women without PCOS. This decreased expression, which occurs in both subcutaneous and visceral fat tissue, is consistent with the lower levels of circulating adiponectin levels that are seen in women with PCOS (Bernick *et al*.,2017).

Conclusion

Obesity is thought to play a crucial role in the development of PCOS especially in women who are genetically predisposed to PCOS and are overweight.Metabolic disorders are commonly associated with ovarian dysfunction specially PCOS and include hyperinsulinemia, dyslipidemia and type II diabetes, which are associated with the development of cardiovascular disorders and diseases. The connection between adiponectin and PCOS is complex, primarily because adiponectin levels can vary independently of adiposity in women with PCOS, unlike in women without the condition. Adiponectin concentrations have been shown to fluctuate with changes in fat mass in both healthy women and those with ovarian dysfunction. The observed relationship between adiponectin and androgen levels in PCOS suggests a distinct interaction specific to this condition. It is proposed that the upregulation of adiponectin receptors in the adipose tissue of women with impaired ovarian steroidogenesis might be a compensatory response to insulin resistance, indicating a unique aspect of anovulation and ovarian steroid dysregulation,. This is in contrast to the normal decrease in both adiponectin levels and receptor expression with obesity.

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