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# Adiponectin: 'a metabolic ballcock' modulating immune responses and male reproduction

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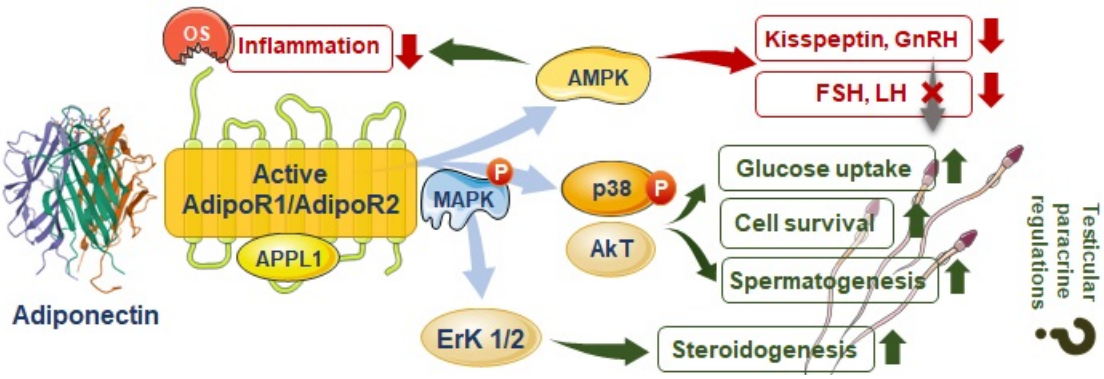
Review Article

ABSTRACT




One of the most prevalent serum adipokines, adiponectin, is well-known for its function in regulating insulin sensitivity and preventing the metabolic syndrome from developing. Adiponectin is expressed in numerous components of the testis and studies claim that adiponectin may have positive paracrine effects on testicular functions. Adiponectin, on the other hand, inhibits hypothalamic-pituitary-gonadal (HPG) axis thereby that may affect testicular testosterone production. It is a strong anti-inflammatory and antioxidant molecule that may have beneficial effects on male reproductive in addition to its metabolic functions. In obese men, reduction in adiponectin levels may partly decipher the multitudinous pathways linking obesity-mediated metabolic disturbances, inflammation, and male infertility or subfertility. This article provides an overview of the actions of adipokines in energy homeostasis, metabolic balance, inflammation, and male reproduction, hence drawing a connexon between obesity-mediated dyshomeostasis in metabolism and immune functions and male reproductive disruptions.

*Keywords: Adipokines, adiponectin, inflammation, insulin resistance, male infertility, obesity*

## INTRODUCTION

The white adipose tissue, besides a toxicant depot of triglycerides, is considered as a crucial endocrine organ generating a variety of hormones or adipokines, whose mechanism of activities has still not been entirely explained.[1] The major purpose of these adipokines is the management of energy homeostasis, while their crosstalks with various other endocrine axes in addition to their absolute impact upon various other organs are emerging with the introduction of research study in these realms.[2-6] The adipose tissue hormonal milieu is jeopardized in case of metabolic syndrome such as obesity[3, 7], whose occurrence is expediting at a worrying rate all over the world. The concurrent global decrease in male fertility[8-13], has brought about a substantial number of researches routed to uncover the precise correlation between metabolic diseases like in case of obesity and also male reproductive dysfunctions.[3,14,15]

One of the most prominent serum adipokines, adiponectin, is well-known for its function in the regulation of insulin sensitivity as well as restricting the development of the metabolic syndrome. Adiponectin has been shown to protect against the development of obesity-related illnesses. The inverse connection between plasma adiponectin levels and many inflammatory mediators, including tumor necrosis factor (TNF)-α, interleukin (IL)-8, C-reactive protein (CRP) and several chemoattractant molecules, has been demonstrated in several investigations.[16] By regulating signaling pathways in a range of cells, adiponectin reduces inflammatory responses to a variety of stimuli. Adiponectin's

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anti-inflammatory characteristics may be a key factor in its positive effects on obesity induced disorders.[17]

The expressions of adiponectin as well as its receptors in the organs involved with reproductive functions have attracted research attentions to find its involvement in regulating reproductive functions. The role of adiponectin in influencing the secretion and also release of the hormones of the prime reproduction regulating axis, the hypothalamic-pituitary-gonadal (HPG) axis, has been evidenced via several studies. Their expressions as well as functions in testicular cells have also been reported. Consequently, its high time to check out the role and also mechanism of activity by which adiponectin may affect male fertility, which may in part reveal the association of metabolic balance with male reproductive functions. This review aims to evaluate the expressions as well as properties of adiponectin as well as its receptors, its role in regulating the HPG axis, and also in influencing the essential testicular functions.

## STRUCTURAL FEATURES OF ADIPONECTIN

### Adiponectin gene and protein

Adiponectin, produced by the white adipose tissues, is a peptide hormone. The two isoforms of this hormone may be referred to as adipocyte complement-related protein (30 kDa molecular weight) and gelatin binding protein (28 kDa molecular weight). In the year 1999, the name adiponectin was coined at the time of the configuration of the its nucleotide sequences.[18] The Human apM1 16kb gene includes 3 exons as well as 2 introns, which presents 3 homologous genes encoded with collagen VIII, X and C1q complements.[19] Different managing segments of apM1 gene expression have actually been noticed at the exon 1. With the contrast of other genes, apM1 does not display TATA sequences besides several transcriptional frameworks.[20] Therefore, the protein synthesis function of adiponectin can be regulated by a number of mechanisms.

A carboxy-terminal globular chain of 137 amino acids, an amino-terminal with 18 amino acids, one widely species-hypervariable-chain with 23 amino acids, and an acid-collagen-domain with 66 amino acids, 22 of which are repeat motif variations, make up human adiponectin.[21] This form of adiponectin appears to have a longer appearance. It also contains a smaller variant, which is a fragmented product of the elastase enzyme, which is produced by neutrophils and monocytes. Numerous proteolytic sites have been found in the collagen domain at various places. Adiponectin in a reduced form keeps its bulbous sphere integrity and passes on its effects to bonding receptors.[22] In comparison to human adiponectin, rat adiponectin has 247 amino acid sequences.[23] It's made up of protein complexes that travel from the adipose tissues to the bloodstream. These comprise of a segment of 67 kDa, two segments of 130 kDa, and a larger protein of 300 kDa.[24] Adiponectin stays undetectable as a monomer in natural conditions. As a result, polymerization of adiponectin is required for it to keep its native function as a protein.[25] As a result, it creates low-molecular-weight fragments, which establish hydrophobic interactions between spherical and collagen domains with unique noncovalent α-helices connections.[26] The shorter adiponectin can no longer polymerize. Longer adiponectin segments, on the other hand, can polymerize multiple times to generate medium and high molecular weight hexamers with up to 18 monomers. These adiponectin polymerizations require translational modifications afterward.[25] Hexamers are undeniably the result of disulphide linkages between two consecutive cysteines and are found in various parts of adiponectin. Various kinds of adiponectin fractions have been found to have different natural activities, according to studies. Low molecular weight adiponectin, for example, has more strong anti-inflammatory properties than high molecular weight adiponectin, which accounts for about 70% of total adiponectin circulating in normal human blood and may be responsible for insulin sensitivity.[22,27]

Adipokine circulates at high concentrations (3 to 30 µg/mL) in diverse species, contributing to 0.01% of total plasma proteins in rats, pigs, fowl, turkeys, cows, and humans.[28-31]. Proteins with low molecular weight covers about 10% of all proteins in human blood, while medium and high molecular-weight-proteins made up about 90% of total proteins in circulation.[32] The blood circulation contains a tiny quantity of spherical protein. Prior to calving, plasma adiponectin levels in the cow's blood are lowest, and at the start of lactation, they are highest. In contrast to people and rats, cow's blood has a higher concentration of high molecular weight proteins, while trimeric and spherical adiponectin is undetectable.[33, 34] Plasma adiponectin levels have been linked to a variety of reproductive problems in other species, including gestational diabetes, preeclampsia, polycystic ovarian syndrome, ovarian cancer, and so on.[35]. Adiponectin expression in humans is linked to a number of pathological factors. Its plasma concentrations are directly proportional to obesity levels and are also influenced by dietary factors. The amount of adiponectin was shown to be elevated while fasting and then reversed after a meal in studies with rats and sheep.[36, 37] It has been documented that adiponectin can be found in higher quantity in female rats and humans. However, under few definite circumstances it can be low also. Adiponectin is discovered in larger quantities in female rats and humans, according to research. It can, however, be low in a few specific conditions. Cnop et al. have revealed that adiponectin concentration was lower prior to menopause than in postmenopausal women[38], albeit no corroborating findings have yet been found. Adiponectin levels in plasma were four times higher in adult female mice than in younger mice, according to studies. Because there is a direct association between obesity and adiponectin concentration in the adipose tissues, it demonstrates that there is a direct correlation between obesity and adiponectin concentration in the adipose tissues, which could be responsible for a variety of metabolic disorders.[32,39,40]

### Adiponectin receptors

Adiponectin is predominantly activated by the seven transmembrane receptors, namely the AdipoR1 and AdipoR2, which are distinct from the other G-protein receptors. The presence of a zinc-binding motif in these receptors is critical for intracellular signal transduction.[41] AdipoR1 and AdipoR2 structurally maintained 67% of homology in amino acid sequences.[41,42] AdipoR1 bears higher affinity for spherical

adiponectin in skeletal muscles and a lower affinity for long-chain adiponectin, while AdipoR2 has a medium affinity for both spherical and long-chain adiponectin in hepatocytes.[43] Many other forms of AdipoR receptors may exist, although this has yet to be proved. Adiponectin carries its own AdipoR receptors in hypothalamus cells. Tissue macrophages have AdipoR receptors, and T-cadherin and adiponectin have biological effects on interfering RNA.[42]

The adiponectin receptors can activate a variety of cell signaling pathways, but they have no effect on phophorylase or kinase. The aimed mutagenesis of these receptors in adiponectin signaling was not disrupted by tyrosine residues.[44] As a result, the structural conformation was created by the participation of intermediary molecules during the start of transduction pathways after connecting with adiponectin receptors. The adaptor protein phosphotyrosine (APPL1), which can connect with pleckstrin homology and leucine zipper1 protein, can engage with adipoR1 and adipoR2 receptors. APPL2 is a separate protein that regulates the attachment of APPL1 protein to the adiponectin.[44] When there is no adiponectin signal, APPL2 joins with the N-terminal region of adiponectin receptors; similarly, it can create an APPL1/APPL2 dimer, which prevents adiponectin binding (Figure 1). This binding, on the other hand, aids in the separation of adiponectin from comparable dimers. As a result, APPL proteins have the ability to regulate adiponectin signalling.[42]

**Adiponectin signaling pathways**

Adiponectin activates a number of signaling pathways in different cells after binding to its receptors, including mitogen-

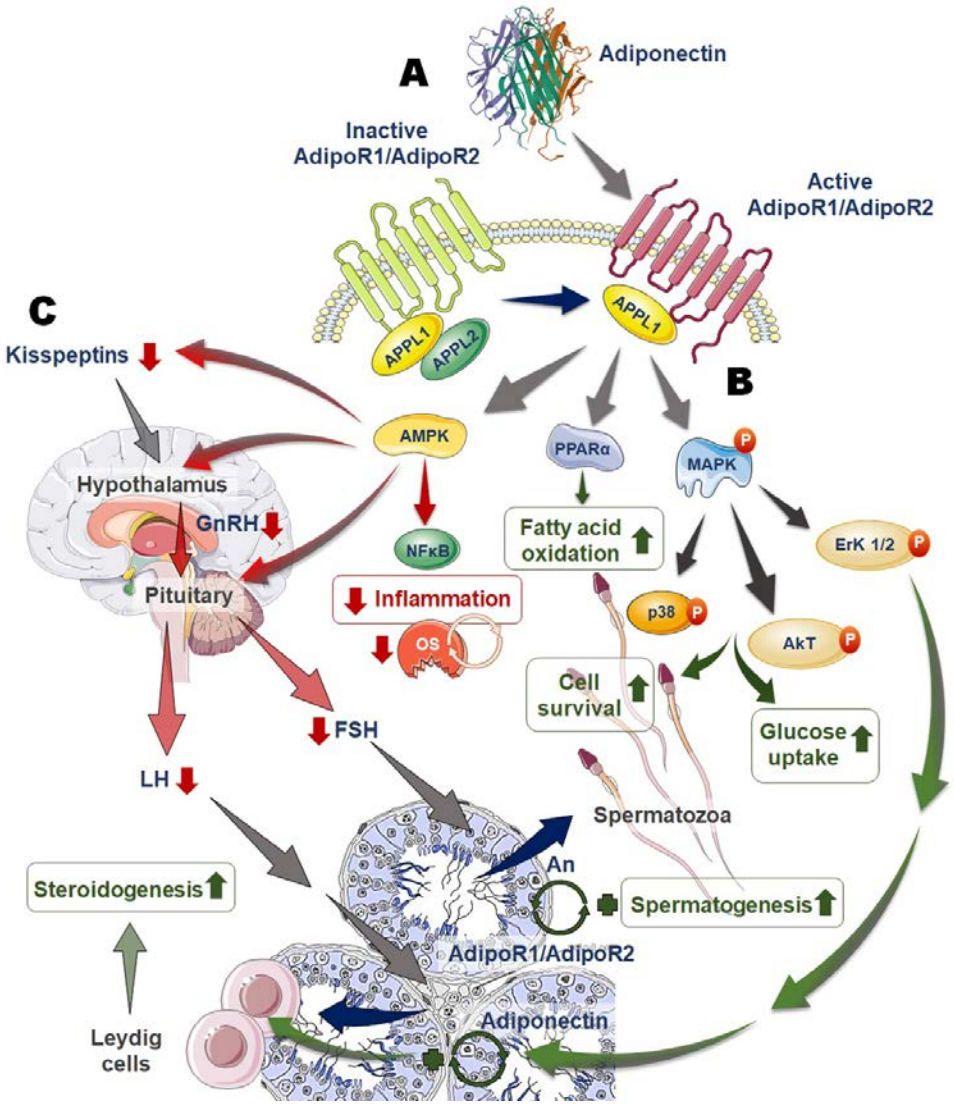


**Figure 1.** Adiponectin mode of action in linking metabolism, inflammation, oxidative stress (OS) and male reproductive functions. (A) Adiponectin acts through its receptors (AdipoR1/AdipoR2) and convert inactive dimer APPL1/APPL2 into active monomer APPL1; (B) The downstream signaling pathway can activate MAPK or PPARa or AMPK. MAPK may activate p38, AkT or ErK 1/2 and mediate cellular glucose uptake and cell survival. PPARa induces lipid metabolism and mediate positive impacts upon testicular cells. AMPK acts to inhibit NFkB and thereby downregulate inflammatory responses as well as OS. Thus, improvement of cellular metabolic status and inhibition of inflammation and OS may ameliorate male fertility; (C) Adiponectin inhibits Kisspeptin, hypothalamic GnRH and subsequently pituitary gonadotropins, LH and FSH secretion via AMP. This inhibition over the hypothalamo-pituitary-gonadal (HPG) axis may impede testicular functions. However, adiponectin and its receptors are localized in the male gonadal cells and through paracrine/autocrine actions may positively regulate steroidogenesis and spermatogenesis

activated protein kinase and extracellular signal-regulated kinases 1/2, serine/threonine-protein kinase, and adenosine monophosphate (AMP)-activated protein kinase (AMPK). The transcript factor and the peroxisome proliferator-activated receptor-alpha can both be phosphorylated by adiponectin. As a result, adiponectin may be able to regulate various signalling pathways in a range of bodily activities.[42,43]

Adiponectin acts through its receptors (AdipoR1/AdipoR2) and convert inactive dimer APPL1/APPL2 into active monomer APPL1. It has been shown to activate the MAPK or PPARa or AMPK. MAPK may activate p38, AkT or ErK 1/2 and mediate cellular glucose uptake and cell survival. PPARa induces lipid metabolism and mediate positive impacts upon testicular cells. AMPK acts to inhibit NFkB and thereby downregulate inflammatory responses as well as OS. [42,43]

## ADIPONECTIN ON ENDOCRINE REGULATION

### Adiponectin and hypothalamus

Adiponectin receptors expression are found in the hypothalamus of various species, including humans.[45, 46] Its high concentration in the cerebrospinal fluid could imply autocrine or paracrine effects along the hypothalamic-pituitary axes.[47, 48] It is evident that peripheral intravenous adiponectin treatment causes a concomitant rise in adiponectin levels in the cerebrospinal fluid in mouse models, indicating that it can pass the blood-brain barrier.[48, 49] Adiponectin levels have also been shown to rise during fasting and then fall following refeeding.[36]

As previously stated, hypothalamic GnRH neurons are the primary regulators of the reproductive axis, which regulates pituitary gonadotropin secretion and release. Adiponectin reduces hypothalamus GnRH secretion by activating AMPK46, according to in vitro experiments.[50] Adiponectin decreased GnRH secretion and suppressed KISS1 mRNA expression in a matured immortalised murine hypothalamic GnRH neuronal cell line (GT1-7 cells) in experiments.[51,52] Kisspeptins are hypothalamic neuropeptides that are reported to mediate the physiological beginning of puberty by inducing hypothalamic GnRH by binding to their receptors (KISS1-R). As a result, it's possible that adiponectin reduces GnRH release by interfering with the kisspeptin-mediated GnRH inducing signal. The adiponectin receptor, AdipoR2, is abundantly expressed in mouse GnRH neurons, suggesting that adiponectin may activate the protein kinase Cζ/liver kinase B1/AMPK signalling pathway to rapidly decrease GnRH neuronal activity.[53]

### Adiponectin and anterior pituitary

Adiponectin along with its receptors have been discovered in the pituitary lobes in humans and animals, in the same way they have been found in hypothalamic neurons.[54,55] Adiponectin has been discovered in all pituitary cells responsible for the generation of reproductive hormones such LH, FSH, thyroid-stimulating hormone, and growth hormone in humans.[5,54] Adiponectin receptors expressions were detected in various pituitary cells, including gonadotrophs, thyrotrophin, and somatotrophs, but not in lactotrophs or corticotrophs.[54] *In vitro* studies have revealed that adiponectin downregulates both basal and GnRH-mediated LH production in rodents pituitary cells.[56] Furthermore, adiponectin has been shown to suppress GnRH receptor gene expression.[57] The stimulatory effects of adiponectin on FSH release from swine primary pituitary cells have been discovered.[55] GnRH and insulin-mediated LH and FSH releases are said to be modulated by adiponectin. Adiponectin has no effect on LH and FSH secretion by primary-pituitary-cell-cultures, as shown in a study on nonhuman primates.[58] However, the majority of research have shown the expressions and activities of adiponectin and its receptors in the hypothalamus and pituitary, influencing the secretion and release of critical reproductive hormones, GnRH, LH, and FSH, as discussed above. As a result, adiponectin plays a significant part in the modulation of reproductive processes by modulating the hypothalamic-pituitary axis. It has been proposed that FSH aids in the onset of spermatogenesis by acting on its receptors on testicular Sertoli cells, and that it also aids in the maintenance of spermatogenesis when combined with high intratesticular testosterone. LH regulates androgen production or steroidogenesis by acting on its receptors on testicular Leydig cells, as is well known.

### Adiponectin and gonadal hormones

There is mounting evidence linking adipose tissue-derived hormones, factors, and other metabolic hormones to male reproductive activities.[59-65] Studies have also revealed a link between adiponectin and steroid hormones, such as gonadal ablation in adult male mice, which lead to enhanced blood adiponectin levels, which were reversed after testosterone treatment.[66,67] Hypogonadism caused an increase in serum adiponectin concentrations in humans, which was reversed by androgen supplementation.[68] There is a link between testosterone and adiponectin, according to a rat study. According to the findings, exposure to isoflavones throughout the developing phase enhanced the levels of serum adiponectin while decreasing circulating testosterone levels.[69] By activating the peroxisome proliferator-activated-receptor-signalling pathway, porcine testicular extract increased the stimulation of adiponectin secretion in adipose tissue.[70] These findings could suggest that further in-depth studies on adiponectin may improve the understanding of the link between metabolic balance and reproductive functions.

## ADIPONECTIN IN TESTIS AND SEMINAL FLUID

Semen, also known as seminal fluid, is a male bodily fluid that contains spermatozoa and has been found to contain adiponectin at concentrations 66 and 180 times lesser compared to serum in men and bulls, respectively.[35,71] Furthermore, Seminal adiponectin concentration positively associate to those in blood plasma, implying that it is transported from blood to testicular cells across the blood-testis barrier.

### Adiponectin on semen quality

Adiponectin receptors are also expressed in spermatozoa, according to Kawwass et al.[72] AdipoR1 was found to be largely expressed in the sperm equatorial and acrosome areas, while AdipoR2 was mostly expressed on the equatorial line and in the sperm head region.[73,74]

Adiponectin concentrations in plasma and abundance of its receptor mRNA expressions in spermatozoa were found to be positively linked with female counterparts' conception rates in bulls' studies.[73] The presence of adiponectin receptors in ram sperm, as well as the concentration of adiponectin in the seminal fluid, was linked to sperm motility parameters.[75] Seminal adiponectin concentrations in humans are favourably correlated with sperm count, sperm concentration, and sperm morphology.[71] Adiponectin and its receptors are said to decrease, followed by capacitation, suggesting that adiponectin has a direct function in sperm motility regulation.[71]

## ADIPONECTIN ON TESTICULAR INNATE IMMUNE REGULATION

### Adiponectin and regulation of innate immune cells

Adiponectin is found to be a potent modulator of immune responses and as elaborately discussed in the following sections: it mediates its anti-inflammatory roles by suppressing the actions of inflammatory immune cells. It may have a role in protecting testicular cells from cytokines produced by testicular immune cells during inflammation, as explained in the

*Monocytes/macrophages*

AdipoR1 and AdipoR2, the most common adiponectin receptors, have been shown *in vivo* and *in vitro* to have key functions in modulation of inflammation, lipid and glucose metabolism, as well as in OS.[42, 76-79] T-cadherin is a cell surface-anchored-glycoprotein that attaches to adiponectin and enhances adiponectin signaling, but this is not a receptor which can bind to and transduce intracellular signaling.[80] Numerous signaling pathways following adiponectin receptors activation, including AMPK, $Ca^{2+}$, ceramide, PPARα, and S1P, have been shown to have insulin-sensitizing effects by adiponectin.[77,81,82] The signalling events underlying adiponectin's control of immune cell activity, on the other hand, are still unknown. Although AdipoR1, AdipoR2, and T-cadherin are prevalent in monocytes and macrophages, it is yet unclear if these receptors have a role in regulating adiponectin's anti-inflammatory activity in macrophages.[78, 83, 84] AdipoR1 binds mostly to globular adiponectin (gAd) and inhibits NF-κB activation and the generation of pro-inflammatory cytokines in macrophages.[84-86] AdipoR2 is necessary for complete adiponectin-mediated M2 polarisation, on the other hand.[87] T-cadherin is also induced by cold exposure, rather than AdipoR1 or AdipoR2, and is required for adiponectin's stimulatory effects on M2 macrophage proliferation.[83] Suppression of AdipoR1, AdipoR2, or T-cadherin, on the other hand, has no influence on adiponectin-stimulated apoptotic THP-1 cell uptake.[88] These data imply that adiponectin regulates macrophage growth and function via receptors that are currently unknown. Adiponectin appears to regulate macrophage growth and function through a number of intracellular signalling pathways. To begin, NF-κB signalling mediated by Toll-like receptors (TLRs) is important for adiponectin mediated regulation of functions and proliferation of M1 macrophage.[76, 89, 90] Adiponectin also increases endotoxin tolerance in primary macrophages by activating the Erk pathway.[91] In contrast to its anti-inflammatory properties, adiponectin reportedly also may mediate pro-inflammatory response by activating the NF-κB and Erk pathways, which upregulate pro-inflammatory cytokines such as IL-6, TNF-α, and IL-8.[89, 92-94] However, adiponectin's pro-inflammatory activity is temporary, contributing to LPS tolerance and ultimately dampening LPS-facilitated cytokine generation in macrophages with constant adiponectin exposure, implying that chronic adiponectin produces LPS resistance.[89, 92] gAd therapy significantly reduced LPS-induced TNF-α-mRNA stabilisation and hindered the potential of LPS to promote TNF-α transcription.[92, 95] Furthermore, adiponectin triggers macrophages to produce anti-inflammatory cytokines, IL-10 in via cAMP-dependent pathways.[95] Adiponectin-induced M2 macrophage proliferation is mediated by the Akt pathway, in addition to the NF-κB, Erk, and cAMP pathways.[83] In the future, it will be determined if adiponectin stimulates these signalling pathways in macrophages in an adiponectin receptor-mediated process.

*Lymphocytes*

Innate-like lymphocytes, which include gamma delta-T (gdT)-cells, natural killer T (NKT)-cells, group 2 innate lymphoid cells (ILC2), B1 cells, and marginal-zone B-cells, are essential immune system components which can mediate adaptive as well as innate immunity. Various kinds of innate-like lymphocytes, including NKT cells and ILC2, are found in metabolic tissues, which include adipose tissue, and possess critical roles in both inflammation and metabolism.[96-98] ILC2s and NKT cells in adipose tissue are consistently lowered in obese mice or human subjects, whereas gdT cell density is consistently raised, demonstrating a link between obesity and these innate-like lymphocytes.[97-101] As a result, ILC2s, NKT cells, and gdT cells have provided innovative therapeutic options for metabolic disorders. By targeting innate-like cells, adiponectin is thought to modulate energy and metabolic homeostasis. ILC2s were first discovered in the lungs, where they are activated in response to allergens by thymic stromal lymphopoietin (TSLP), and epithelial cell-derived cytokines (IL-25, IL-33). Type-2 immune responses are orchestrated by activated ILC2s.[102-104] ILC2s were discovered in adipose tissues as a conserved feature of obesity just recently, and they have been demonstrated to stimulate fat browning and inhibit occurence of obesity.[97, 98] For example, ILC2s release the type-2 cytokines IL-5 and IL-13, which promote eosinophil maturation and infiltration while activating M2 macrophages as well as eosinophil maturation and infiltration. Following that, both M2 macrophages and eosinophils induce conversion of white to brown adipose tissue.[98, 105] ILC2s induced by IL-33, on the other hand, secrete methionine-enkephalin peptides which target the white adipose tissue and promote their browning and thermogenesis.[97] Furthermore, cold stress increases the population of ILC2 in white adipose tissue with IL-33.[97] However, it is unknown whether ILC2s are recruited to or generated in adipose tissue. The modulation of the role of ILC2 in adipose tissue is similarly unknown from a mechanistic standpoint. Adiponectin stimulates M2 macrophage proliferation, which leads to a browning effect and increased energy expenditure.[83] In response to persistent cold, a well-known stimulus to promote fat browning,

adiponectin insufficiency has only slight influence on the ILC2 population and downstream cytokines such as IL-13 and IL-4 in the white adipose tissues.[83] Adiponectin knockout (KO) mice, on the other hand, show higher thermogenesis and energy expenditure, according to two other studies.[106, 107] Furthermore, it has been demonstrated that acute cold stress activates ILC2s in adipose tissue.[97] ILC2 population and activity are both dramatically reduced during chronic stress, suggesting that downstream effects of chronic stress may be responsible for ILC2 suppression in adipose tissue.[83] These contradictory findings underscore the need for more research into adiponectin's actual physiological roles in regulating immune responses and energy expenditure. NKT cells found in human adipose tissue play critical part in metabolic regulation.[96, 108] In human obesity, invariant NKT cells are reduced, and they protect against metabolic syndrome-induced inflammatory conditions with the aid of inflammatory cytokines (such as IL-4 and IL-10).[108] Nevertheless, total adipose tissue T-lymphocytes count rises as obesity progresses.[109, 110] Despite the fact that these is lack of proper evidence to support the actions of adiponectin on NKT cell functions, studies show that plasma B cells mobilization is aided by adiponectin and it also facilitates production of the 'B-cell-derived peptide PEPITEM' inhibiting the migration of the memory T-cells.[111] Furthermore, B-cells express AdipoR1 and AdipoR2, which may mediate adiponectin's suppressive action on B-cell-specific PEPITEM synthesis and secretion.

Remarkably, gdT cells, a kind of adipose-resident-innate-like lymphocyte that promotes diet-induced inflammation and insulin resistance, are significantly connected with obesity.[99, 100] gdT cells, which have the gd+T-cell receptor (TCR), make up a small percentage of total T-cells and are mostly CD42 and CD82. Some gdT cell subsets have anti-tumor and immunoregulatory properties.[112] A new study found that adiponectin insufficiency causes a significant increase in dermal gdT cells as well as acute skin inflammation by promoting IL-17.[113] This research further shows that adiponectin inhibits inflammatory cell recruitment and IL-17 production in the skin via AdipoR1, but not AdipoR2-dependent cellular autonomous mechanisms.[113] However, it is unclear if adiponectin affects the activities of adipose-resident-gdT cells.

*Eosinophils*

Following staining with eosin, eosinophil granulocytes, also known as eosinophils, appear brick-red and are parts of immune system accounting for allergen-triggered inflammation and parasite infection.[114,115] Eosinophils move and infiltrate in adipose tissue accounting for atypical macrophage activation and cold stimuli-mediated adipose tissue browning.[116-118] Adiponectin suppresses allergic airway inflammation by inhibiting the eosinophils recruitment in the airways.[119] Furthermore, adiponectin inhibits eosinophil recruitment by regulating CCL11/eotaxin, a macrophage-derived chemokine.[119] Though AdipoR1 and AdipoR2 are both found in human eosinophils, it is unclear whether adiponectin affects eosinophil activity via an adiponectin receptor-mediated signalling pathway.[120] Furthermore, whether adiponectin regulates the activity of adipose resident eosinophils has yet to be determined.

*Neutrophils*

Neutrophils is the most profuse immune cells in blood and is among the main first-order defense against pathogenic microbes, relocating to eliminate infectious agents by phagocytosis, secretion of cytokines, 'neutrophil extracellular traps' (NETs), and reactive oxygen species (ROS).[121] Adiponectin in its full length suppresses neutrophil phagocytosis by inhibiting NADPH oxidase and ROS generation in an AMPK-activation pathway.[122] Adiponectin decreases the formation of ceramide in the neutrophil membrane and thereby prevents neutrophil death via AMPK.[123] Additionally, adiponectin therapy reduces Escherichia coli neutrophil phagocytosis by blocking the PI3K/PKB pathway and activating Mac-1.[123] These findings indicate that adiponectin has a deleterious effect on neutrophil activity.

*Dendritic cells*

Dendritic cells (DCs) are specialised antigen presentation cells (APCs) that are required for the development of immunity and tolerance. Obesity in mice increases both the number and activity of DCs.[124, 125] Adiponectin appears to influence the function of DCs, although it is still debatable whether adiponectin affects DC function favourably or adversely. Tsang et al. (2011) demonstrated that adiponectin therapy decreases co-stimulatory molecule production and hinders allogenic T cell activation in murine-bone-marrow-derived-DCs, implying that adiponectin inactivates DCs.[126] On the other hand, another study discovered that adiponectin promotes DC development and activation.[127] In addition, adiponectin induces DC activation via the phospholipase C g/JNK/NF-kB pathway, resulting in Th1 and Th17 polarisation, a mechanism that is dependent on the adiponectin receptor.[127] The opposite conclusion may be reached as a result of the variable doses and durations of adiponectin administration. As a result, additional research is required to elucidate the mechanism behind adiponectin's regulatory involvement in DCs.

**Adiponectin and inflammation**

Adiponectin, through its receptors AdipoR1 and AdipoR2, is thought to regulate both spermatogenesis and steroidogenesis.[128, 129] Adiponectin inhibited the steroidogenic acute regulatory protein in Leydig cells, demonstrating direct activities of adiponectin on Leydig cells to downregulate androgen production.[69]

Adiponectin may activate intracellular signalling cascades involving proteins including AMPK, peroxisome proliferator-activated receptor-alpha, and mitogen-activated protein kinase when it binds to its receptors.[43] The modulation of testicular activities, specifically steroidogenesis, is important for this signalling system.[130] The significance of adiponectin in regulating testosterone synthesis is suggested by the stimulation of the testicular signalling pathway relevant for steroidogenesis by adiponectin.

Adiponectin's ability to maintain insulin sensitivity by inducing testicular glucose absorption is another important component of its activity.[128] Intratesticular glucose level is well established to be one of the key regulators of important testicular activities such as steroidogenesis.[131] Exogenous adiponectin administration to aged mice improved testicular mass and

function by increasing insulin receptor expression, inducing antioxidative enzyme activity, testosterone biosynthesis, and testicular glucose and lactate uptake via an increased tumour of glucose and lactate transporter proteins.[129]

Adiponectin also has anti-inflammatory characteristics, which protect Leydig cells from cytotoxicity caused by inflammatory cytokines and chemokines. As a result, adiponectin serves as a testicular defence against pro-inflammatory mediators such macrophage-derived TNF-α, interleukin-1, and interferon-γ on steroidogenesis.[132]

Adiponectin signalling in male gonadal tissue appears to be vital for various testicular processes, but further research is needed to determine the exact role of adiponectin-mediated pathways in male reproduction.

## Adiponectin in Linking Energy Balance, Immune System and Testicular Functions

Obesity decreases sperm motility in rats.[133] Obesity induces male subfertility/infertility due to poor sperm quality,[133] indicating that obesity might affect male fertility. Furthermore, OS at the testicular level, which is prevalent in obese people, can lead to reduced spermatogenesis and sperm impairment.[134] Indeed, it has been hypothesized that increased OS, reduced testosterone levels, and altered spermatogenesis may affect testicular functions, resulting in subfertility in men.[135,136]

Adiponectin concentrations in seminal plasma are three times greater than in blood serum in normal-weight males.[71] Furthermore, adiponectin levels in seminal plasma are linked to sperm concentrations, sperm count, and spermatozoa with normal morphology.[71] Obesity causes adiponectin levels in seminal plasma to decrease, similar to blood serum concentration. The source of adiponectin in seminal plasma, on the other hand, is unknown. Since adiponectin has ameliorating impact on obesity-induced metabolic disruptions decrease in adipokines levels in advance obesity leads to the development of metabolic disorders such as glucose and lipid metabolism dysregulations, insulin resistance, and type-2 diabetes.[40, 88, 101] These in turn initiate a positive feedback cycle where metabolic disorders stimulate obesity and vice versa, resulting in induction of various pro-inflammatory adipokines and cytokines that inflict direct or indirect adverse effects upon male fertility, mainly via systematic inflammation and OS.[18, 88, 101, 137, 138]

Adiponectin bears essential roles in sperm functions and morphology, which helps to improve male fertility. In fact, bulls with robust fertility parameters had greater blood adiponectin levels and sperm mRNA expressions for adiponectin and its receptors.[73] Adiponectin was found in abundance in the sperm tail of bull, whereas AdipoR1 was mostly found in the mid region and acrosome sites, and AdipoR2 was mostly found in sperm-head and on the mi- line.[73] Adiponectin along with its receptors express in spermatozoa before as well as after capacitation [73] suggesting that adiponectin may play a role in sperm capacitation. As a result, the generation of fertilizable sperm is aided by adiponectin-mediated paracrine activities in the testis (Figure 1).

Adiponectin's capacity to control steroidogenesis has been shown in a variety of steroidogenic tissues.[29,139,140] Dexamethasone has been found to suppress adiponectin synthesis in the testis,[139] indicating that stress-induced cortisol may inhibit adiponectin autocrine/paracrine functions in testis. As demonstrated by *in vitro* study using rosiglitazone on rat testicular cells, that transcription factor PPAR is implicated in the inhibition of adiponectin actions in testis.[139] Adiponectin enhanced phosphorylation of ERK1/2, p38, Akt, and AMPK in rat granulosa cells at a baseline level.[29] However, no similar signalling pathways have been identified for adiponectin-dependent steroidogenesis regulation in Leydig cells. Adiponectin may influence steroidogenic genes expressions (such as that of Star, Cyp11a1, and Cyp19a1) in chicken, pigs, rodents and human ovaries,[29,141,142] suggesting that adiponectin may also alter steroidogenesis in Leydig cells via steroidogenic gene regulation. Low to intermediate dosages of adiponectin (10 and 100 ng/mL) inhibited baseline testicular testosterone synthesis in male rats as a result of decreased StAR protein expression.[139] Because adiponectin has been shown to inhibit KISS1 gene transcription in hypothalamic cells via downregulation of SP-1, which regulate steroidogenic genes,[143] it may be possible that adiponectin acts on Leydig cells to regulate steroidogenic gene expression by inhibiting the transcriptional activity of SP-1. Furthermore, PPAR transcription factors may be implicated in the transcriptional control of steroidogenic genes in Leydig cells, as they are regulated by adiponectin in other cell types.[144, 145] Several steroidogenic promoters have been shown to possess SP-1 and PPAR regulatory elements in common. The importance of these regulatory components in regulating testosterone synthesis from Leydig cells, however, has yet to be determined.

AdipoR1 and AdipoR2 expression has recently been shown in the mouse TM3 and mLTC Leydig cell lines, where adiponectin protects against pro-inflammatory cytokines such as TNFα.[145] This is accomplished by blocking the NFkB signalling pathway via enhanced AMPK phosphorylation mediated by AdipoR1.[145] TNFα and IL-1b, two pro-inflammatory cytokines, have been found to impair Leydig cell steroidogenesis and function.[146] As a result, adiponectin may have a role in protecting Leydig cells from cytokines produced by macrophages in the testis during inflammatory circumstances.

## Conclusion and Future Perspectives

Obese and overweight men are susceptible to suffer from male infertile/subfertile. This occurs owing to numerous factors (genetic, physical, endocrine, immunological, redox imbalance etc.) that contribute to hormonal disruption and dysregulation of the HPG axis in obese men rendering them vulnerable to infertility. Adiponectin represents the most common and well-researched adipokines, found high levels in serum. Its functions as positive regulator of metabolic syndrome and insulin sensitivity are widely documented. In order to control numerous functions of testicular cells, testicular adiponectin may serve as a paracrine/autocrine factor. Adiponectin along with its receptors are found to be profusely expressed in testicular cells, including

Leydig cells, germ cells and are found in the epididymis, which supports this theory. Adiponectin's effects in the testes have been demonstrated to enhance spermatogenesis and sperm maturation. However, adiponectin has negative impact on hypothalamic GnRH secretion, pituitary LH and FSH secretion, and testicular testosterone. Besides its metabolic effects, adiponectin is a potent ant-inflammatory and antioxidant molecule that may also contribute to ameliorative effects upon male reproduction. Thus, adiponectin may help to understand the diverse mechanisms that link metabolic disruptions, inflammation and male infertility.

**Conflict of Interest**

Authors declare no conflict of interest.

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