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Adipokines as immune modulators in inflammation mediated male infertility

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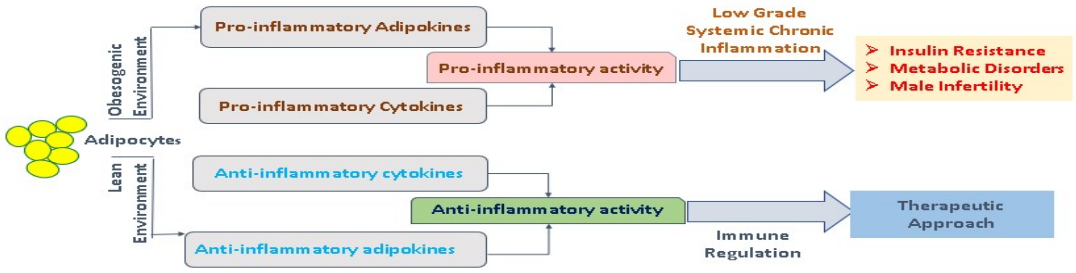
ABSTRACT



Extensive research on adipose tissue has considered it as immune-metabolic endocrine organ consisting of a variety of immune cells, playing an important role in pathology of obesity. The immune components of adipose tissue are said to mediate both innate and adaptive immunological responses. Adipokines secreted from adipocytes are known to play a significant role in maintaining metabolic homeostasis. An imbalance between pro- and anti-inflammatory adipokines on adipose tissue results in insulin resistance and the development of metabolic syndrome. Excess of proinflammatory adipokines on adipose tissue during obesity may result in reproductive dysfunction of which inflammation mediated male infertility is of great importance. The impact of adipokines on male reproduction/male fertility has received much attention nowadays. Adipokines can be possible molecular targets for the treatment of obesity-induced male infertility. This review aims to accentuate the understanding of how adipokines may act as immune-modulators, which might lead to unveiling of therapeutically relevant mechanisms that govern adipose tissue inflammation, and thereby inflammation induced male infertility.

Keywords: Adipokines, adipose tissue, inflammation, immune-modulation, male infertility

INTRODUCTION

Immunity and metabolism are intertwined mechanisms that are of growing importance in research. Obesity and type 2 diabetes (T2DM), which appear to be non-immunological in origin, are now known to be related to immune dysregulation, raising the possibility that metabolic changes can be triggered by or result from decreased self-immune tolerance. According to the World Health Organization (WHO), obesity is defined as "abnormal or excessive fat accumulation that presents a risk to health"[1] and is considered to be a major contributor in various chronic degenerative, inflammatory and autoimmune diseases including type 2 diabetes mellitus, cardiovascular diseases, osteoarthritis, rheumatoid arthritis, atherosclerosis, fatty liver disease etc.[2,3] The immune system plays an important role in pathology of obesity and extensive research is going on since long to identify the therapeutic regulating factor for obesity.

Adipose tissue was exclusively recognized as a fat storage organ up to mid-1990s[4] but currently extensive research on adipose tissue has considered adipose tissue to be an immune-metabolic endocrine organ[5-8,9] consisting of adipocytes of different stages of development, as well as fibroblasts, endothelial cells and a variety of immune cells, like macrophages, neutrophils, eosinophils, mast cells, T and B cells.[10] Besides, energy storage and thermal insulation, the adipose tissues are known to perform various immune and endocrine functions.[11-13] The different types of adipose tissue are white, brown, beige/brite and pink adipose tissue[13,14] and

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all of them are known to have endocrine properties.[15] It has been reported that activation of beige or brown adipocytes and the subsequent increase in energy expenditure can lower body fat mass and potentially lower adipose tissue inflammation.[16] It is also noted that white adipose tissue (WAT) produces and secretes a variety of pro and anti-inflammatory factors known as 'adipokines,' which is thought to be a link between obesity-related external factors and the molecular events that lead to inflammation, autoimmune conditions and finally metabolic syndrome. The pink adipocytes are known to secrete leptin-a proinflammatory adipokine.

Adipokines are molecules similar in structure to cytokines which possess pro and anti-inflammatory properties and play a significant role in integrating systemic metabolism and immune function. Individuals with normal metabolic status are known to have a balance between pro and anti-inflammatory adipokines[17] whereas an imbalance between pro- and anti-inflammatory adipokines on adipose tissue results in insulin resistance and the development of metabolic syndrome.[18] The adipokines, are classified as hormones, growth factors, angiogenic factors, and cytokines[19] and they act through an endocrine, autocrine or paracrine manner. A good number of adipokines are known to directly play significant role in metabolic homeostasis.[20,21] Among the large number of adipokines, the most studied adipokines are leptin, adiponectin, resistin, interleukin (IL)-6, IL-1β, tumor-necrosis factor (TNF), anti-inflammatory IL-10, and transforming growth factor (TGF)-β etc.[22] It has been reported that during obesity the number of adipocytes is increased due to adipogenesis[23] and it has impact upon modulation of immunological responses. Body fat distribution is known to be an important factor in obesity and visceral fat accumulation is linked with levels of some adipokines which in turn may induce chronic inflammation.[24]

Scientific researches have reported that excess of adipose tissue during obesity along with adipokines may result in reproductive dysfunction. About 20% of the body weight in males is due to WAT constituting the adipocyte, pre-adipocytes, macrophages and lymphocytes and they act as an important mediator of inflammation and metabolism. Proinflammatory cytokines are secreted mainly by non-adipose cells in adipose tissue.[25] The proliferative and differentiating action of cytokines determines the biological activity of germ cell.[26] It is evident that obesity has impact on the function of the cells involved in spermatogenesis.[27] Obesity and its mediators have a negative impact on semen parameters, including sperm concentration, motility, viability and normal morphology. Several adipokines (leptin, adiponectin, resistin, chemerin, visfatin, vaspin, and progranulin etc) and certain cytokines have already been detected in semen.[28] A decreased testosterone production by Leydig cells is observed in obese or overweight men due to higher levels of circulating leptin and this causes impaired spermatogenesis.[29] Obese men have increased leptin concentrations which lead to low serum testosterone concentrations and abnormal seminal parameters.[30] In obese men, the levels of serum adiponectin are elevated and it bears an inverse association with testosterone.[31] Visfatin, secreted by visceral adipose tissue, is detected in the testis and increased Visfatin concentrations causes increased concentration of serum testosterone, increased body and testis weight, and is negatively correlated with blood glucose concentrations.[30] Resistin and chemerin also have a deleterious effect on spermatogenesis as well as on the semen parameters. Sperm morphology is improved when adiponectin level was increased.[32] Resistin shows a correlation with IL-6, TN-α suggesting that resistin might play a regulatory role in the inflammation of the male reproductive system.[30]

Apart from these adipokines, Ghrelin, a peptide hormone secreted by the stomach although not an adipokine, is known to increase in obesity. It exerts strong inhibitory effects on proinflammatory cytokines, including interleukin 1 beta (IL-1β), interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α), following inflammation. This is also present in Leydig and Sertoli cells and inhibits the proliferative activity of immature Leydig cells.[29] In addition, Orexin also known as hypocretin (one of the non-classical metabolic hormones) stimulates testosterone production by increasing the activities of the steroidogenic enzymes in Leydig cells.[33] Orexins A and B (hypocretins 1 and 2) are two GPCR binding hypothalamic neuropeptides derived from a common precursor (prepro-orexin).[34] A few studies have suggested that orexin A exhibits anti-inflammatory properties and are known to regulate energy homeostasis.[35] Obesity is linked with reduced levels of orexins and thereby causes disbalance between energy homoeostasis and reproductive functions in men.[36] Thus, correlation between the circulating concentration of adipokines on sperm quality is evident.

Obesity involves chronic inflammatory responses together with endocrine disruptions. Excessive deposition of visceral adipose tissues induces Th1-lymphocyte and M1-macrophage to cause pro-inflammatory responses[37] by modulating cytokines, adipokines and myokines that adversely affect numerous tissues, including the hypothalamus, cardiac, hepatic, pancreas and testes. Male infertility and hypogonadism are associated with obesity-induced systemic inflammation. Inflammatory mediators of this immune response include various adipokines like leptin, resistin etc and cytokines like interleukin IL-1β, IL6, IL8, IL12, tumour necrosis factor-alpha (TNFα), interferon gamma (IFNγ), transforming growth factor-beta (TGFβ), macrophage inflammatory protein (MIP-1), and neuroendocrine hormones.[37]

During obesity, the immune profile of the adipose tissue is changed, shifting to a chronic low-grade inflammatory state, which gradually becomes systemic and drives insulin and metabolic disease.[38,39, 40-45] Adiponectin, due to its antiinflammatory property, downregulates the expression of TNF-α, IL-6 and IL-18 genes, thus protecting the system from the harmful effect of proinflammatory cytokines by suppressing NFkB action. Adipose tissue inflammation is driven by innate and adaptive immune cells. The reproductive tract inflammation induced due to obesity and metabolic syndrome inversely correlates with indicators of hypogonadism and decreased semen quality.[46] Moreover, oxidative and endoplasmic reticulum stress induced due to hyperglycemia can cause inflammation that may result in glycation end-products and sperm DNA fragmentation (SDF)[47]. Circulating IL-6 is usually considered as a biomarker of inflammation and significant correlation is observed between seminal IL-6 and various semen parameters like spermatozoid concentration, progressive motility, and sperm vitality.[48] Another inflammatory marker C-reactive

protein, is also markedly elevated in obesity-associated reproductive tract inflammation.[37] These observations suggest about possible involvement of the seminal adipokines in regulating the fertility potential in men with metabolic syndrome.

Nowadays, immunemodulation is a key issue in tissue homeostasis and is defined as change in the body's immune system, caused by agents that activate or suppress immune responsiveness.[49] Natural compounds that are known to influence the immune system by either affecting the functions of immune cells or antibody secretion to control the infection and to maintain immune homeostasis are known as immune modulators and these compounds can be utilised in the future immunotherapeutic strategies.[50] Currently immune modulators can be both biological or synthetic in nature and they can stimulate, suppress or modulate any of the components of the immune system including both innate and adaptive parts of the immune response. Natural adjuvants, synthetic agents, antibody reagents are used as immunosuppressive and immunostimulative modulators.[49] Currently, cytokines and chemokines are also known to regulate immune responses by signaling, through membrane receptors.[51]

The purpose of this review is to discuss about the probable immune-modulatory role of adipokines, as well as their associated signaling pathways that may be of particular importance in the development of effective therapeutic strategies for inflammation mediated male infertility due to obesity.

ADIPOSE TISSUE: ITS TYPES AND BIOLOGICAL FUNCTIONS

Adipose tissue is a type of connective tissue and is composed of adipocytes, pre-adipocytes, fibroblasts, stromal cells and macrophages[11,12]. It is also considered to be an endocrine organ that secretes various adipokines involved in metabolic regulation and inflammatory processes[52]. The endocrine function of adipose tissue was unknown since long, [13,14]. All four types of adipose cells (white, brown, beige/brite and pink varieties) are known to have endocrine properties. White adipose tissue (WAT), acts as energy storage organ also exerts multiple immune, metabolic, and endocrine functions[42,53]. WAT is divided into two regional and functional depots. Visceral (vWAT) and subcutaneous white adipose tissues (sWAT).[11-13] vWAT is related to insulin resistance, inflammation, dyslipidemia, obesity and T2DM caused by the pathogenic expansion of WAT.[11,12,54] The brown adipose tissue (BAT) is located in specific depots, of human and mice and is responsible for thermogenesis.[55] White adipocytes can be differentiated into brown-like adipocytes in WAT in a process called **beiging,**[56] whereas, during chronic positive energy balance, the brown adipocytes are differentiated into WAT by a process called **whitening.**[13,57] The pink adipocytes are abundant ~~in~~ in the adipose organs during pregnancy and lactation.[58]

Contribution in immune metabolism:

Immune mechanisms and metabolism are two intimately connected phenomena and are known to mutually co-regulate each other[38,39]. Immune responses require metabolic adaptation at the cellular and organism level.[38,59, 60] while metabolic dysregulation, like obesity, leads to immune activation.[38,-41] Many of the interactions between the metabolic and immune systems appear to be coordinated by a complex network of soluble mediators that are produced by immune cells as well as adipocytes (fat cells) in the body. White adipose tissue (WAT) consists a broad array of immune cells, namely, adipose tissue macrophages, neutrophils, eosinophils, mast cells, T and B cells, dendritic cells (DC), mast cells, natural killer cells (NK) cells, innate lymphoid cells (ILC).[10,55] In WAT of lean individuals, tissue homeostasis is maintained by coordinated interaction between adipocytes and immune cells finally leading to tissue homeostasis. In this case, the main resident T cell population - eosinophils and T regulatory cells (T_{reg}) secrete anti-inflammatory cytokines (IL-10 and IL-4) and thus an anti-inflammatory phenotype of the adipose tissue macrophages (i.e. M2 or alternatively activated macrophages) is maintained. M2 macrophages upregulate production of the anti-inflammatory cytokine IL-10 and downregulate synthesis of pro-inflammatory cytokines. As a result, a tolerogenic environment[10,61] is maintained. Functionally, M2 macrophages ~~are~~ also helps in the repairing of injured tissues and the resolution of inflammation.[62]

In obese individuals, the adipose tissue expands (hypertrophy) and new adipocytes are formed irrespective of age and gender (hyperplasia).[63-67] The expansion of adipocytes results in inadequate vascularization and hypoxia in the obese adipose tissue[68,69]. The mechanical stress created due to adipocyte expansion causes contact with the surrounding matrix and cells[70]. Increased adipocyte cell death is observed due to such hypoxia and mechanical stress on adipocytes lead to recruitment of pro-inflammatory macrophages, T and B cells[10] and deposition of fibroblasts[71-75]. As a result, T cells become activated with a reduced number of T_{reg} cells and there is a phenotypic switch of the macrophage from M2 to M1 (classically activated macrophage). This results in accumulation of necrotic adipocytes forming 'crown-like structures' and producing large amounts of pro-inflammatory cytokines, such as **IL-6** and TNF-α[9] etc, express inducible nitric oxide synthase (iNOs) and produce reactive oxygen species (ROS) and nitrogen intermediates[62] . The accumulation of adipose tissue macrophages is proportional to adiposity in both humans and mice,[76,77] and a reduction in the number of adipose tissue macrophages may result due to sustained weight loss accompanied by a decrease in the proinflammatory profiles of obese individuals.[78] Macrophages are more abundant in visceral adipose tissue than subcutaneous adipose tissue.[79] Fibroblasts ~~are also~~ present in adipose tissue are known to produce extracellular matrix components.

It is evident that for normal metabolic function, interaction between the adipocyte derived anti-inflammatory factors adiponectin and secreted frizzled-related protein 5 (sFRP5) and the pro-inflammatory factors, TNF and wNT5a derived from macrophages within adipose tissue is required. During obesity,TNF and wNT5a are upregulated whereas adiponectin and sFRP5 are downregulated[80-82]

WAT secretes adipokines, such as leptin, adiponectin, LCN2 and PGRN which are considered to be the crucial regulators of the innate and adaptive immune system.[83-84] Brown/beige adipocytes also secrete hormones and growth factors and Pink adipocytes secrete leptin besides milk components.[11,13,14]

In obese individuals, the development of a large immune-cell infiltrate in the adipose tissue is regarded to be one of the crucial

factor in obesity induced inflammation and are assumed to be the result of a massive attraction exerted by adipocytes toward immune cells, (i.e., macrophages, neutrophils, natural killer cells, and dendritic cells). [85,86]

The criteria for a pathological condition to be classified as 'autoimmune' are: (1) infiltration of an organ by immune cells and subsequent tissue damage; (2) the presence of circulating autoantibodies and subsequent complement system activation; (3) the clonality of TCRs from infiltrating immune cells; (4) the secretion of pro-inflammatory Th1 cytokines; (5) quantitative or qualitative alterations of regulatory T (Treg) cells; the presence of the above-mentioned factors has been seen in obese individuals. [87,88] In conjunction with one another, these findings may support the concept that obesity is an immunological condition. The discovery of various adipokines has provided yet another link between adipose tissue and immune cells, strengthening the relationship between the two. However, by acting as cytokines, adipokines are able to modulate immunological functions and inflammatory processes throughout the body.

ADIPOKINES: ROLE IN INFLAMMATION AND METABOLIC DISEASE

Adipokines are low MW, bioactive proteins produced by the adipose tissue that play a crucial role in energy metabolism[89] and are currently considered as key players in inflammation and immunity[3]. Adipokines, are not only synthesized and secreted by adipocytes, but other cells such as macrophages, lymphocytes, and fibroblasts also synthesize and secrete them [25,90]. These adipokines act at endocrine, paracrine, and autocrine levels[91] influencing secretion of cytokine, chemokines, hormonal and growth factors, as well as interfering with actions of insulin and lipid and glucose metabolism. Adipokines are categorised as hormones, growth factors, angiogenic factors, and cytokines[18] and the main adipokines include leptin, adiponectin, resistin, tumor-necrosis factor, interleukin 6, chemokine (C–C motif) ligand 2, interleukin 10, transforming growth factor-β etc.[18] . Adipose tissue secretes different patterns of adipokines, depending on its location[91]**.** It is evident that in human males most of the adipokines and their receptors are expressed in testis especially in seminiferous tubules and more specifically in Leydig and Sertoli cells[92]. Adipokines like leptin, adiponectin, resistin, chemerin, visfatin, vaspin, and progranulin along with certain cytokines have already been detected in semen.[32]

Functionally adipokines can be categorized as proinflammatory and anti-inflammatory in nature. Proinflammatory adipokines are those which are highly expressed during obesity and Type 2 diabetes, and the anti- inflammatory adipokines are of opposite in nature.

Proinflammatory adipokines

The proinflammatory adipokines are upregulated in the obese The proinflammatory adipokines are upregulated in the obese state, and these proteins are known to promote obesity-linked metabolic diseases. In addition to leptin, TNF and IL-6, more recently identified adipokines that promote inflammation include resistin, retinol-binding protein 4 (RbP4), lipocalin 2, IL-18, angiopoietin-like protein 2 (ANGPTL2), CC-chemokine ligand 2 (CCL2), CXC-chemokine ligand 5 (CXCL5) and nicotinamide phospho ribosyltransferase (NAMPT) or visfatin. This leads to the development of a chronic inflammatory state and contributes to metabolic dysfunction[93].

The proinflammatory functions of various adipokines and their metabolic regulatory pathways are discussed below.

Leptin:

Leptin is a 16 kD a nonglycosylated peptide hormone, consisting of 167 amino acids[94] and is the product of the *obese gene* (ob)[93]; also known as *LEP* gene, located on chromosome 7q31.3 and mainly expressed and produced by white adipose tissue. Leptin is secreted mainly by the subcutaneous adipose tissue[3,95] and is involved in expansion of adipose tissue and total body fat[96]. The tertiary structure of Leptin consists of four alpha helices connected by two long and one short loop[28] and is structurally similar to the family of helical cytokines that includes IL-2 and growth hormone 1, and is thought to have pro-inflammatory activities[93]. Leptin is known to modulate lipid metabolism, hematopoiesis, thermogenesis, and ovarian β-cell function.[97]

The human gene of the leptin receptor (*LEPR*) is located on chromosome 1p31, and investigations have revealed that genetic alterations of *LEPR* and obesity are interlinked[98]. Binding of Leptin to its receptor, LEPR, results in the activation of the (JAK)/signal transducer and activator of transcription (STAT) pathway. JAK2 (Janus kinase 2) with LEPR phosphorylates LEPR tyrosine residues which in turn phosphorylates members of the STAT family that translocate to the nucleus, regulating genetic transcription[18]. By activating the JAK2 (Janus kinase 2)–STAT3 (signal transducer and activator of transcription 3) pathway, Leptin increases the production of TNF and IL-6 by monocytes and CC-chemokine ligands (namely, CCL3, CCL4 and CCL5) by macrophages[99].

Obesity causes defective transport of leptin across the blood–brain barrier and impaired signaling in neurons and other target cells and thus is associated with leptin resistance. Leptin resistance may also be due to a defect in the leptin-receptor gene[100] and hyperleptinemia in response to pro-inflammatory stimuli[93] followed by leptin resistance may be possible consequences in immune-cell activation[101]**.**

Leptin induced expression of proinflammatory cytokines in macrophages and T cells, and activation of the inflammation pathways used by proinflammatory cytokine receptors, like mitogen-activated protein kinases (MAPKs), JAK-STAT3, and phosphatidylinositol-4,5-bisphosphate 3-kinase suggest that leptin is positively a mediator of inflammatory responses[93,102] **.**

Resistin

Resistin is known to ~~is for its capacity to~~ interfere with the action of insulin, leading to insulin resistance[103] and hence the name. It is a 12.5 kDa polypeptide secreted by adipocytes in rodents and by macrophages in humans[104] and is present in two quaternary forms: an abundant high-molecular weight hexamer and a less abundant, but more bioactive, trimer, which strongly induces hepatic insulin resistance[93]. Human resistin is expressed by the *RETN* gene, located at position 19 of chromosome 19p13.3. The relationship between serum resistin and insulin resistance, T2DM, and obesity in humans is controversial. Some studies have found no changes in circulating resistin levels in obesity, insulin resistance, or T2DM,

while others reported a significant increase of circulating levels of resistin during these conditions[105,106]. The mechanisms by which resistin exerts biological effects are not fully understood. Scientists have shown that the binding of resistin to Toll-like receptor 4 in the hypothalamus activates proinflammatory pathways in that organ[104]. This leads to the molecular mechanism involved in the inflammation and insulin resistance induced by resistin. In addition to the effects of resistin on insulin resistance, it has also been implicated in a variety of autoimmune diseases,[103]. Lower levels of resistin are found in metabolically healthy patients compared to those diagnosed with metabolic syndrome[107].

In humans, resistin is mainly produced by macrophages and monocytes[108] and transcription of the resistin gene (RETN) is induced by proinflammatory cytokines, like IL-1, IL-6 and TNF58 etc.[109,110]. Besides, resistin directly counters the anti-inflammatory effects of adiponectin on vascular endothelial cells by promoting the expression of the pro-inflammatory adhesion molecules vascular cell adhesion molecule 1 (vCAm1), intercellular adhesion molecule 1 (ICAm1) and pentraxin 3 in these cells, thereby enhancing leukocyte adhesion[111,112].

Visfatin or NAMPT.

Visfatin, or Nicotinamide phosphoribosyl transferase (NAMPT) is also known as pre-B cell colony enhancing factor and was originally identified as a modulator of B cell differentiation expressed in lymphocytes, bone marrow, muscle and liver[93]. Later on it was reported to be mainly expressed and secreted by adipose tissues through a non-classical secretory pathway[113]. It is a 52–55-kD protein produced primarily by perivascular adipose tissue and activate immune cells like lymphocytes and neutrophils[4]. Visfatin induces the production of cytokines such as IL-1, TNF-α, and IL-6 by leukocytes and thus can be regarded as a pro-inflammatory adipocytokine [114,115]. Patients with obesity and type 2 diabetes are known to have high circulating levels of NAMPT/ visfatin[116,117]. and its expression positively correlates with serum levels of IL-6 and CRP[118].

NAMPT/ visfatin is thought to function in the NAD biosynthetic pathway and to have an important role in insulin secretion by pancreatic β-cells[127]. It stimulates the p38 mitogen-activated protein kinase (p38 mAPK) and extracellular signal-regulated kinase (ERK) pathways and results in the production of IL-1β, TNF and IL-6. These factors enhance the human monocyte chemotactic activity; thus it is evident that NAMPT has a proinflammatory function.

Lipocalin-2

Lipocalin-2 (LCN2; also known as neutrophil gelatinase associated lipocalin, 24p3, p25, migration-stimulating factor inhibitor, human neutrophil lipocalin, α-1- icroglobulin related protein, siderocalin or uterocalin) is a glycoprotein encoded by a gene located at the chromosome locus 9q34.11[119]. WAT is the chief source of Lipocalin-2, but is also expressed in immune cells, liver, spleen and chondrocytes[119]. It belongs to the lipocalin protein superfamily, which also includes RbP4[120,121].

Lipocalin 2 expression is induced by inflammatory stimuli through activation of nuclear factor-κb (NF-κb)[122] and is highly expressed in adipose tissues of obese individuals[123,124] . Serum concentrations of lipocalin 2 are known to be positively associated with adiposity, hyperglycemia, insulin resistance and CRP levels[123].

The members of the lipocalin family contain a hydrophobic ligand binding pocket, which is known to induce apoptosis in haematopoietic cells, modulate inflammation and metabolic homeostasis[119]. There are various scientific reports suggesting the contributory role of LCN2 to obesity-related disorders, ~~such as~~

Considering the role of LCN2 in the modulation of inflammatory and immune response, future studies are required to identify the therapeutic potential of LCN2 in inflammatory/immune system disorders.

Chemerin

Chemerin is an inflammatory adipokines with autocrine, paracrine and endocrine function in vivo[125]. It is encoded by the gene retinoic acid receptor responder 2 (Rarres2), also known as tazaroteneinduced gene 2 (TIG2). Chemerin is highly expressed in white adipose tissue (WAT), liver and lung while its receptor CMKLR1 is predominantly expressed in adipocyte and immune cells[126]. In mammalian cells, chemerin is initially synthesized as a 163 amino acid (aa) proprecursor. The activation of chemerin is achieved by proteolytic cleavage at its C-terminus by plasmin, elastase and cathepsin G and generates various isoforms (chemerin-K158, -S157 and -F156) with different affinity to CMKLR1 (Chemerin chemokine like receptor 1). Further cleavage of bioactive chemerin by chymase produces chemerin-F154 and then its activity is terminated[127]. These events serve as a key regulatory mechanism to determine the local and systemic concentration of active chemerin.

In healthy humans, the inert chemerin precursor is the dominant isoform in plasma, but under inflammatory conditions various chemerin isoforms like chemerin-A155, -S157 and -K158 in human have been detected[128]. Mass spectrometric analysis indicates that bioactive chemerin is generated at early stages of inflammation[129]. Minimal levels of chemerin precursor and significant levels of bioactive chemerin-S157 are detected in the adipose tissue of patients with obesity.[130]

Chemerin has been shown to display various roles in the pathogenesis of inflammatory and metabolic disease in multiple organs such as adipose tissue, lung, skin, cardiovascular system, reproductive tract, digestive tract, skeleton and joints. There are controversies regarding the biological function of chemerin as pro- or anti-inflammatory modulators. At the onset of inflammatory reaction, polymorphonuclear cells are firstly recruited to the damaged sites, where they generate bioactive chemerin by releasing proteases including elastase and cathepsin G[129]. Subsequently, the chemotaxis of immature dendritic cells and macrophages increases and immune response is initiated. In contrast, chemerin treatment reduces the recruitment of neutrophil and macrophages to the inflammatory sites and the expression of proinflammatory cytokine is decreased[131]. These studies suggest that chemerin acts as either a proinflammatory or anti-inflammatory modulator depending on the biological system

Several studies have reported increased chemerin levels with increased body weight indicating a link between a long-term proinflammatory effect to insulin resistance in obesity. Scientific reports have revealed that visceral fat tissue is the primary source

for circulating chemerin. The chemerin secreted from white adipose tissue (WAT) affect adipose tissue homeostasis, adipocyte metabolism and inflammation in fat tissue[132].

Initially, studies in humans indicated that chemerin gene expression and its level in circulation are positively correlated with increased BMI and obesity-related biomarkers[126]. but other studies on mice have reported contradictory results. Thus, it is unclear whether raised chemerin levels promote obesity; more studies are needed to provide a definite answer. Similarly, roles played by this adipokine in human semen also needs to be further investigated.

RBP4

Serum RbP4 is a factor is known to responsible for the transport of retinol (vitamin A) throughout the body[93] and is currently secerted by both adipocytes[33] and macrophages[/134]. RbP4 released by adipocytes inhibits insulin-induced phosphorylation of insulin receptor substrate 1 (IRs1) in an autocrine or paracrine manner[135]. These data indicate that RbP4 is an adipokine that is important for the regulation of glucose homeostasis in type 2 diabetes. Supporting studies in human populations have also revealed that serum RbP4 levels were found to associate with features of the metabolic syndrome, including high blood pressure, low levels of high-density lipoprotein, high levels of cholesterol and triglycerides, and increased body mass index[136].

RbP4 is preferentially produced by visceral adipose tissues and it is known to be a marker of intra-abdominal adipose tissue expansion[137] and subclinical inflammation[138]. Thus treatment of insulin resistance can be done by taking approaches that lower the levels of RbP4[139].

Vaspin

Vaspin (visceral adipose tissue-derived serpin, serpinA12) is a member of the serine protease inhibitor family of serpins, and is known to be a pro-inflammatory adipokines[140]. The structure of Vaspin is made up by three β-sheets, nine α-helix and an exposed flexible reactive central loop (RCL)[141]. Human vaspin protein is a 47 KD protein[131] consisting of 414 amino acids and has a 40% homology with α1-antitrypsin[142]. In humans, vaspin is encoded by the SERPINA12 gene. In humans, vaspin is detected in 23% of the visceral and in 15% of the subcutaneous adipose tissue[143].

Some scientific studies have reported that serum vaspin concentration correlated positively with the markers for degree of obesity[144,145] whereas some other studies did not find any such correlations[146]. The discrepancies in the relationship between vaspin serum concentrations and body fat parameters among the reported studies suggest that it may be dependent on other variables, such as gender, age, physical activity, hormonal metabolism or drugs administered [147].

Currently, very little is known with regard to the expression and secretory profile of vaspin in humans and more scientific research on its functional role needs to be explored.

ANGPTL2

ANGPTL2 is a proinflammatory adipokine that promotes insulin resistance[148]. In humans, circulating ANGPTL2 levels are positively associated with adiposity, markers of insulin resistance and CRP levels. Overexpression of ANGPTL2 in adipose tissue leads to exacerbation of adipose tissue inflammation and insulin resistance. Moreover, ANGPTL2 activates inflammatory responses by endothelial cells, monocytes and macrophages through the activation of integrin signalling.[185/148]

Other proinflammatory cytokines related to obesity

TNF (Tumor necrosis factor)

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine that is mainly produced by monocytes and macrophages and has a central role in inflammatory and autoimmune diseases[93]. TNF is synthesized as a 26 kDa transmembrane monomer (TNFm), which after proteolytic cleavage by the TNF-converting enzyme results in soluble 17 kDa TNF (TNFs) molecules. TNFm functions through autocrine and paracrine actions, while TNFs mediates endocrine responses[149]. TNF is able to bind to two structurally related transmembrane receptors: TNFR1 and TNFR2. The TNF–TNFR complex undergoes a proteolytic cleavage, releasing its soluble forms sTNFR1 and sTNFR2 in the circulation[150]. TNF is derived from adipose tissue and is known to have an association between obesity, inflammation, and diabetes.

Scientific reports have revealed that high levels of TNF are detected in individuals with metabolic syndrome[151]. whereas individuals with MHO are known to have lower levels of TNF and a reduced proinflammatory profile[152]. It is suggested that inhibition of TNF might be effective at improving insulin resistance under inflammatory conditions. Although the exact mechanisms by which TNF and other inflammatory cytokines contribute to insulin resistance are not yet fully known, several downstream mediators like protein kinases (c-Jun N-terminal kinase, IκB kinase, and MAPK), are known to be involved in inflammatory and metabolic diseases[153]. In addition, TNF is also involved in the synthesis of proinflammatory cytokines, such as IL-6, CCL2, and TNF itself, through NFκB activation[18].

Scientists have shown that the semen of males suffering from inflammation related infertility shows increased levels of TNF-α[32]. Scientific report has revealed a negative correlation between TFN-γ and sperm concentration, motility, and morphology[32]. TNF-α levels are known to increase in the seminal plasma of oligozoospermic and asthenospermic patients compared to control patients. A polymorphism in the TNF-α 308 gene is known to be associated with a significant decrease of sperm count, sperm motility, normal sperm morphology, and acrosin activity[154].

IL6

IL-6 is a pro-inflammatory cytokine that is also involved in obesity-related insulin resistance. Besides its role in inflammation and host defense, IL-6 is involved in the regulation of insulin signaling, and lipid metabolism in peripheral tissues[18]. Increased levels of IL-6 are observed in obese subjects indicating the positive correlation between plasma IL-6 levels and adiposity in human populations[93]. It is estimated that approximately one-third of total circulating IL-6 is produced by adipose tissues[93], and the production of IL-6 is three times higher in visceral adipose tissue in comparison to subcutaneous adipose tissue, and provides a link between visceral fat and insulin resistance, as well as visceral fat and inflammation[155].

The mechanisms associated with insulin resistance induced by IL6 are similar to that found for TNF[18] . IL-6 first binds to the specific membrane receptor IL-6R. and the IL-6–IL-6R complex

then associates with the signal transducer receptor gp130[18]. The hypertrophy in adipocyte as well as stimuli for inflammation such as production of TNF, favors the increase of IL-6. The signaling pathways for IL6 differ markedly between myocytes and macrophages. The intramuscular expression of IL-6 is regulated by a cascade of signaling that includes Ca^{2+}/NF of activated T cells and glycogen/p38 MAPK pathways while in macrophages; IL-6 signaling is dependent on the activation of NFκB. Therefore, IL-6 in monocytes/macrophages induces a proinflammatory response, while in muscle it induces a TNF- and NFκB-independent respons[156].

IL18

IL-18 is a pro-inflammatory cytokine, produced by adipose tissues[157]. Serum levels of IL-18 are increased in obese individuals, and they decline during weight loss[93]. IL-18 seems to have complex roles in coordinating inflammation and metabolism.

Chemokine ligand 2

CCL2/monocyte chemotactic protein 1 is a chemokine with the C–C motif that participates in inflammation by recruiting monocytes toward the inflammatory site[159]. It is produced principally by macrophages and endothelial cells and the receptor for CCL2 is chemokine receptor 2 (CCR2)[160]. The chemotactic activity of CCL2 is regulated by binding of CCL2 to the receptor which induces chemoattraction, activation, and transmigration of the monocyte[161]. Elevated CCL2 plasma levels and its overexpression in adipose tissue have been found in insulin-resistant obese individuals[162]. It is expressed more in visceral adipose tissue in comparison to subcutaneous adipose tissue[18]. Kanda and his colleagues[163] have reported that increased CCL2 expression is positively associated with macrophage infiltration in adipose tissue in mice

Metabolically healthy obese (MHO) individuals display a reduced inflammatory profile, with lower numbers of infiltrating adipose-tissue macrophages and reduced serum levels of CCL2[152]. These results suggest that by inducing inflammatory response on adipose tissue the CCL2–CCR2 axis plays an important role in the development of insulin resistance, and also in the pathogenesis of metabolic syndrome.

C-X-C motif chemokine ligand 5

CXCL5, a protein encoded by the *CXCL5* gene in humans, is secreted by macrophages and is involved in adipose tissue inflammation and insulin resistance[93,164]. Circulating levels of CXCL5 are higher in insulin-resistant obese individuals than in insulin sensitive obese individuals. CXCL5 interferes with insulin signaling in muscles by activating the JAK–STAT pathway through its receptor CXC-chemokine receptor 2 (CXCR2). The expression of CXCL5 is controlled through TNF signaling by direct promoter activation, associated with increased occupancy of the CXCL5 promoter by NF-κb[164]. CXCL5 is well known to have chemotactic and activating functions on neutrophil, mainly during acute inflammatory responses.

Transforming growth factor-β

TGFβ is a member of the growth-factor family[165]. and almost all cells in rodents and humans can produce and respond to TGFβ[166]. TGFβ is recognized as a critical cytokine in the regulation of immune responses[166] as well as a potent neutralizer of macrophage activation, and exerts an inhibitory effect on growth and activation of immune cells.

The TGFβ level on adipose tissue is strongly associated with class III obesity[162]. The exact role of TGFβ in adipogenesis and obesity remains unclear, and needs further study.

IL1 β

IL-1β, is the proinflammatory cytokine produced by macrophages infiltrating the adipose tissue of obese patients. The main functions of IL-1β, is to impair insulin signaling and increase lipolysis[18]

IL-1RA is an antagonist of IL-1β that binds to IL-1β receptors without inducing cellular response, thus antagonizing the inflammatory action of IL1β. In obese patients with hyperleptinemia, circulating IL-RA levels are seven times higher than in nonobese patients[18]. In humans, the secretion of IL-RA in adipose tissue is induced by interferon and IL-1β through an autocrine and paracrine regulatory response[18].

Antiinflammatory adipokines

In addition to the numerous pro-inflammatory adipokines described above, adipose tissues also secrete a smaller number of anti-inflammatory factors which has been the subject of intense investigation.

Adiponectin

Adiponectin (also known as GBP28, apM1, Acrp30 or AdipoQ) is a 30 kDa protein encoded by the *ADIPOQ* gene, which is located on chromosome 3q27[18]. It is a 244 amino acid residue protein with structural homology to collagen type VIII and X, and complement factor C1q[3,18] . It has four different domains: a carboxy-terminal globular chain of 137- amino acids, an amino-terminal with 18 amino acids, a hypervariable chain with 23 amino acids and an acid collagen domain with 66 amino acids where 22 are repeat motif variables[167]. It is mainly synthesized in adipose tissue and unlike other adipokines, adiponectin is mostly expressed in subcutaneous adipose tissue[18]. Although the *ADIPOQ* gene is expressed primarily in adipocytes, scientific studies have shown that adiponectin can be expressed in other cells too[168]. It is found in several configurations: the globular adiponectin (gAPN), the full-length adiponectin (fAPN), the low MW (LMW) adiponectin, the medium MW(MMW) adiponectin, the high MW (HMW) adiponectin, and the serum albumin bonded LMW form (Alb-LMW)[169]. It has been suggested that the high-molecular-weight form of adiponectin is the main and most active form of adipokine[/168]. In morbidly obese patients, circulating adiponectin levels tend to be low, which increases with weight loss[169]

The two receptors of adiponectin are **Adipo1 receptor** predominantly found in skeletal muscle and **the Adipo2 receptor**, mainly present in the liver. Signaling pathways from the Adipo receptors lead to activation of **AMP-activated protein kinase (AMPK)**, peroxisome proliferator-activated receptor (PPAR-α, and PPAR-γ)[169]. AMPK activation by adiponectin helps in insulin-sensitizing activity in liver and muscles, while the regulation of glucose and fatty acid metabolism by adiponectin are performed through AMPK, Ca^{2+} and PPAR-α. The actions of adiponectin are also mediated by Ceramide and MAPK signaling pathways[169]. The action of adiponectin occurs through binding of its receptors AdipoR1 and -2 to APPL1 (adaptor protein, phosphotyrosine

interaction, PH domain, and leucine zipper-containing protein 1)[18], - an adaptor protein identified as a facilitator of adiponectin signaling.

The primary functions performed by adiponectin in adipose tissue are to improve insulin sensitivity, to perform fatty acid oxidation, to reduce the secretion of glucose from liver, to increase glucose uptake, and adipogenesis[170]. Adiponectin also suppresses the migration of monocytes/macrophages and their transformation into foam cells in the vascular wall. In vitro studies have shown that adiponectin may reduce the inflammatory response of endothelial cells through inhibition of TNF-α induced nuclear factor-kappa β (NF-κβ) activation.[18]

Adiponectin has been recognized as a key regulator of the immune system and has significant role in the progression of inflammatory and metabolic disorders[171]. This adipokine downregulates pro-inflammatory cytokines (TNF-α, CCL2 and IL-6), suppresses the differentiation and activation of M1 macrophages. On the other hand, it promotes proliferation of the M2 macrophage and expression of anti-inflammatory M2 markers (**arginase-1**, Mgl-1, and IL-10)[171]. Adiponectin is also known to modulate the activity of eosinophils, neutrophils, NK cells and DCs[213]. The anti-inflammatory effects of adiponectin are party due to the altered activity of TNFα. In vitro studies have shown that TNFα downregulates expression of the adiponectin gene via suppression of adiponectin-induced nuclear factor NFκB[172]. Studies in humans have revealed that adipose tissue with high adiponectin mRNA reduced secretion of TNFα, whereas growing insulin resistance and increased body fat mass upregulate the expression of TNFα resulting in reduced adiponectin levels[173]. Adiponectin also directly increases IL10 production by macrophages and decrease production of proinflammatory cytokines TNFα and IL6[15].

In the adaptive immune system, adiponectin activates plasma B cells and stimulates the secretion of the B cell derived peptide PEPITEM. This inhibits the migration of memory T cells[174]. In T cells, Adipo receptors are up-regulated after its activation and adiponectin *via* enhancement of T cell apoptosis decreased antigen-specific T cell proliferation and cytokine production[3]. Adiponectin also enhances differentiation of the Th1 and DCs treated with adiponectin significantly induced both Th1 and Th17 responses in allogenic T cells, contributing to enhanced pro-inflammatory responses.[3]

There are increasing evidence regarding the importance of adiponectin in inflammation-related ~~(RA)~~[169], probably due to its modulatory role, as well as B and T cells.[171]

A greater knowledge of adiponectin's effects on B and T cells and its mechanism of action will be important for developing new therapeutic strategies aimed at the adiponectin system.

Omentin

Omentin is a 38–40 kDa adipokine predominantly produced by the stromal-vascular fraction of visceral adipose tissue, but not by mature adipocytes[175]. Omentin is also produced by subcutaneous adipose tissue but in extremely low quantity.[175]

The two omentin genes, omentin-1 and omentin-2 are located adjacent to each other on the 1q22–q23 chromosomal region[176]. In humans, omentin-1 is the predominant isoform in plasma and adipose tissue.[177]

Several pathological situations, such as obesity and insulin resistance are known to modify the production and expression of omentin 1. Omentin-1 expression is also altered in inflammatory states[175]. It is reported that concentration of serum omentin-1 as well as expression of visceral adipose tissue omentin were significantly lower in overweight and obese subjects than in lean ones[218]. Scientists have proposed that as both adiponectin and omentin 1 concentration has an inverse relationship with obesity, the regulatory mechanisms of both the adipokines might be similar in nature. Researchers have also reported that omentin may improve insulin sensitivity.[175]

SFRP5

SFRP5 is an anti-inflammatory adipokine having beneficial effects on metabolic dysfunction[82]. SFRP5 is expressed at high levels in the visceral adipose tissue of obese individuals with adipose tissue inflammation and insulin resistance. sFRPs act as a soluble modulator sequester WNT proteins and prevent them from binding to their receptors. WNT5a is known to be implicated in a variety of inflammatory disorders and is antagonized by sFRP5.

In adipose tissues sFRP5 deficiency induced metabolic dysfunction is associated with increased accumulation of macrophages and enhanced production of pro-inflammatory cytokines (including TNF and IL-6). Various experiments revealed that overexpression of SFRP5 inhibits WNT5a stimulated phosphorylation of JNK1 in adipocytes, and similarly blocks the activation of WNT5a-induced JNK1 and the subsequent production of pro-inflammatory cytokine in macrophages.[93]

It is evident that the balance between SFRP5 and wNT5a in adipose tissue has an important role in the regulation of JNK1 activity in adipocytes and adipose tissue macrophages, thereby modulating inflammation and metabolic function. Thus, SFRP5 in adipose tissue can be a potential target for the control of obesity-linked abnormalities in glucose homeostasis.

Cardiotrophin 1

Cardiotrophin-1 (CT-1) is a protein consisting of 203 amino acids having a molecular weight of 21.5 kDa[123], Human CT-1 gene is located on chromosomal region 16p11.1–16p11.2[121] and the coding region of exon 1, 2 and 3 shows a homology of 96%, 84% and 81% respectively between human and mouse.[122]

In adult humans, CT-1 is highly expressed in heart, skeletal muscle, liver, lungs, kidney and adipose tissue.[175] Lower levels of CT-1 expression are also seen in testis and brain.[121] CT1 act as an adipokine[178] and acts through both paracrine and endocrine manner.[175] The structure of CT-1 is very similar to the interleukin-6 (IL)-6 family of cytokines, and is considered as a member of this family.[120]

Like other members of IL6family, CT1 also induces its physiological actions by activating the gp130 receptor and require interaction with two gp130 or one gp130 and another related signal transducing receptor subunit[175]. Heterodimerization of gp130 and LIF receptor (LIFR) is required to induce signal transduction by CT1[179]. Several families of intermediary molecules, including the PI3K/AKT system, the Janus kinase/transducer and activator of transcription (JAK/STAT) signal system, the mitogen activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) system and the nuclear factor κB (NF-κB) system are reported to be

involved in the initiation of intracellular signaling due to phosphorylation of gp130.[175]

CT 1 has the ability to modulate the production of adipokines, in vitro and in vivo, and this suggests that the regulation of the secretory function of adipocytes is linked to the metabolic actions of this cytokine.

Progranulin

Progranulin (PGRN; also known as granulin-epithelin precursor (GEP), proepithelin, GP88, PC-cell-derived growth factor or acrogranin) is a cysteine-rich, 68–88 kDa secreted glycoprotein encoded by the *GRN* gene, located on chromosome 17q21.32[180]. It is a 593-amino acid long growth. PGRN contains 7½ repeats of a cysteine-rich motif (CX5–6CX5CCX8CCX6CCXDX2HCCPX4CX5–6C) in the order, P–G–F–B–A–C–D–E, where A–G are full repeats, and P is the one-half motif[181]. This protein can undergo enzymatic proteolysis by many proteinases, including matrix metalloproteinase 9, 12, and 14, elastase, and proteinase 3[182] into small homologous subunits – granulins or epithelins[183]. PGRN is highly expressed macrophages[181] and is also expressed in a broad range of other tissues and cell types, including, adipose tissue, and immune cells, including T cells and DCs.[184-186]

Progranulin is having multiple physiological functions. It plays significant role in many types of diseases, including autoimmune disorders, cancer, and neurodegenerative diseases. Macrophage-derived PGRN is a key regulatory factor in the processes of inflammation and wound healing[181]. It has been considered as a therapeutic target and biomarker in inflammatory diseases.[180] PGRN directly interacts with TNF receptors (possessing higher affinity for **TNFR2** than TNF-α, especially), and consequently act as an antagonist of TNF/TNFR proinflammatory signalling pathway[230/183]. It is thus considered to be a key regulator of inflammation. PGRN also binds to **death receptor 3**, which is involved in various inflammatory disorders[186]. Furthermore, scientific studies have revealed that PGRN suppresses the production of two chemokines, **CXCL9** and **CXCL10**, through the **TNFR1** pathway, and induces production of the T_{reg} populations and IL-10.[183,186]

PGRN being a key regulator in the inflammatory processes, it recruits itself into the sites of inflammation and competes with the inflammatory mediators. Although PGRN is one of the major anti-inflammatory molecules, the exact function of PGRN may vary depending on the stage and components involved in inflammation[181] . It also up-regulation of IL-6 expression[185] . PGRN mainly plays an antiinflammatory role in both acute and chronic inflammatory processes. The acute inflammatory cascade involves the complex interplay and recruitment of humoral and cell-mediated, immunological components to combat with the foreign antigens.

In contrast to its anti-inflammatory role, PGRN is also known to play proinflammatory function in obesity and insulin-resistant diabetes mellitus.[187] A scientific study has reported that PGRN levels, as well as macrophages in omental adipose tissue, omental adipocyte size, and serum CRP, are significantly higher in insulin-resistant obesity than in insulin-sensitive obesity[181]. Moreover, a significant correlation was observed between PGRN gene expression with BMI, visceral fat, MAPK, and AKT gene expression. Consequently, PGRN was found to be a major adipokine to mediate high-fat-induced insulin resistance[185].

OBESITY, INSULIN RESISTANCE AND MALE INFERTILITY

Insulin resistance is defined as the reduced sensitivity of cells to insulin effects in normal or elevated blood glucose levels. As a consequence, the pancreas secretes higher amounts of insulin, and this results in a state of hyperinsulinemia[188]. Visceral adipose tissue has been shown to strongly correlate with insulin resistance. Visceral obesity increases production of adipokines and inflammatory mediators which significantly influences insulin signaling in insulin-responsive tissues, promoting systemic insulin resistance and hyperinsulinemia. Insulin stimulates HPG axis activity both at central (hypothalamus and pituitary) and peripheral (testis) levels. Insulin resistance may also affect hypothalamic neurons and consequently hamper GnRH secretion. In obese patients, hyperinsulinemia decreases SHBG (serum sex hormone-binding globulin) secretion by the liver, resulting in more estrogen activity[189]. Since estrogens are more biologically active than testosterone, the increased levels of estrogens can inhibit the HPG axis, suppressing the activity of the kisspeptin neurons, further reducing testosterone production[190]. Thus excess insulin has a detrimental effect on testicular function and androgenic status in obese adult men, giving rise to a “metabolic” form of male hypogonadism. Hypogonadism levels further deteriorate insulin sensitivity and promote adipocyte proliferation and increase in body fat.[191] Consequently, low testosterone levels can worsen obesity and promote the development of metabolic diseases in overweight and obese patients.[192]

Hyperinsulinemia also has an inhibitory effect on spermatogenesis, increasing nuclear and mitochondrial DNA damage[188]. The pro-inflammatory cytokines and adipokines secreted from the adipose tissue are known to inhibit testosterone production.

The state of systemic inflammation plays a pivotal role in sperm damage in obese males among several other mechanisms. Obesity is a clinical example of systemic oxidative stress and is associated with the increased production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor-necrosis factor α (TNFα), leading to a low chronic inflammatory state[193]. Reactive oxygen species (ROS) are products of normal cellular metabolism and are essential for physiological processes. At physiological levels, ROS stimulates capacitation and the acrosome reaction and at high concentrations, they can oxidize, and in turn, damage DNA, proteins, and lipids[194]. Antioxidants present in human seminal fluid counteract the negative effects of ROS. However, an imbalance between production of oxidants and antioxidant capacity increases oxidative stress which can directly damage sperm DNA. Spermatozoa are unable to repair DNA due to the lack of the cytoplasmic enzyme systems that are involved in the molecular mechanisms for DNA repair.[188]

ADIPOKINES AND THEIR MOLECULAR FUNCTIONS RELATING OBESITY WITH INFLAMMATION MEDIATED MALE INFERTILITY

The incidence of male infertility is shown to be increasing with passing decades[195,196]. The association of male infertility with obesity has recently received a lot of attention and the adipokines

are known to play key role in the underlying mechanisms that lead to obesity-related male infertility[197].

The molecular mechanisms through which obesity impairs male reproduction, include obesity-associated hypogonadism and its effects on spermatogenesis, chronic inflammation, and oxidative stress. Obesity negatively impacts sperm parameters, and it also induces epigenetic changes that can be inherited by the offspring. Moreover, obesity-related diseases are linked to an imbalance of adipocyte function and inflammatory processes. The dysregulated adipokines significantly influence insulin signaling, and they may also have a detrimental effect on testicular function.

Adipose tissue being an active endocrine organ produces several hormones (adipokines) and immune molecules (cytokines and chemokines)[92] which contribute to the maintenance of body homeostasis and can modulate the activity of the immune system[58]. However, chronic low-grade inflammation is generated in obese people due to a dysregulation of the adipokine and cytokine pathways leading to the chronic complications of obesity. Hypertrophic adipocytes have pro-inflammatory potential and promote insulin resistance. These adipocytes in obese patients, produce non-esterified fatty acids (NEFA) and induce local macrophages to secrete high levels of TNFα. This, in turn, stimulates adipocytes to produce more NEFA, pro-inflammatory cytokines (interleukin 1ß (IL1β) and IL6), acute phase proteins, and chemokines [+(C-C motif chemokine ligand-2 (CCL2) or monocyte attractant protein-1 (MCP-1)), which attract more monocytes/macrophages within adipose tissue[188]. Thus a systematic state of low-grade inflammation is established[92].

Leptin

In the male reproductive system, Leptin is present in the seminiferous tubules of testis[198]. The presence of leptin in human sperm was recorded at different levels: mRNA expression, protein expression, and immunolocalization[32]. Among various studies on human sperm only Jope and his team[199] have reported that seminal plasma and sperm contain leptin receptor and the presence of leptin receptors on the tail of spermatozoa suggests a probable effect on motility[199]. Although different studies showed contrasting results, it is possible to consider a physiological involvement of leptin on sperm motility.

Glander and his colleagues[200] have shown a negative correlation between seminal leptin and progressive ($r = -0.53$, $p = 0.0004$) and straight ($r = -0.3$, $p = 0.029$) motility and at high concentrations, leptin in seminal plasma is associated with a decrease in sperm motility[90]. Two other studies have shown a negative correlation between leptin concentrations in seminal plasma and progressive motility[198,201]. On the contrary, other studies have concluded that there is no correlation between seminal leptin and sperm motility [32,202]. At lower or "physiological" concentrations, leptin may either have a physiological effect, beneficial to motility, or may have no effect. Similarly, patients with high seminal concentrations of leptin showed a negative correlation between this adipokine ($r = -0.187$, $p < 0.05$), and sperm concentration ($p = 0.0001$)[198,203]. For low concentrations of leptin (0.83–0.91 ng/mL), a positive correlation between seminal plasma leptin and sperm concentration ($r = 0.24$, $p < 0.05$)[90] was also reported. It is still undecided whether or not there is a link between seminal leptin and ejaculate volume[32]. On the other hand, various studies have revealed seminal leptin does not have any effect on sperm morphology[90, 202].

Obese men have increased leptin concentrations which may have serious link with male infertility. High leptin concentrations are known to lead to low serum testosterone concentrations[30]. This occurs due to inhibitory action for the conversion of 17(OH) progesterone into testosterone. Males have leptin receptor deficiency having hypothalamic hypogonadism which results in delayed pubertal development, atrophic testis and impaired spermatogenesis[204,205]. Furthermore, leptin stimulates the release of LH and FSH via the NO synthase activation in the gonadotropic cells[205] .hCG in a dose dependent manner is inhibited by increased concentrations of leptin and thus affect testosterone production by Leydig cells[30]. Thus leptin regulates male reproductive function by stimulating hypothalamus and pituitary and inhibiting the gonadal function.

Resistin

Resistin is expressed in interstitial Leydig cells and Sertoli cells of testis[206]. under control of the gonadotropins[207] Roumaud and his team pointed out that direct exposure of resistin in low concentration stimulates Leydig cell proliferation[208]. These data suggest that resistin can favorably control steroidogenesis in Leydig cells as well as its proliferation. Scientific reports recommend a potential function of resistin in the hypothalamo-pituitary axis[206]. Resistin has been known to operate via the AMPK and ERK1/2 signaling pathways in regulating the pituitary gonadotrophins secretion[206].

From the study of Moretti and his team, it is evident that there is a negative correlation between the concentrations of seminal resistin and sperm motility and vitality[209] but due to low number of studies available, it is difficult to conclude on the role of resistin, on spermatozoa and thus male fertility. However, it has been shown that resistin is associated with markers of inflammation in seminal plasma. The concentrations of seminal resistin correlate positively with those of proinflammatory mediators such as elastase, interleukin-6 (IL-6)[210], and tumor necrosis factor- α (TNF-α)[209]. The concentrations of cytokines and ROS increase during inflammation, and this may have a negative impact on the male reproductive function[211]. An increase in ROS could induce a decrease in sperm concentration, motility, and sperm count[212]. In patients with leukocytospermia having the habit of smoking, the seminal concentrations of resistin is found to be significantly higher[209], associated with a significant increase in TNF-α and IL-6, as well as a sharp decrease in spermatic motility and the number of sperm with normal morphology. All these results suggest that resistin could be considered as a marker of inflammation, and in patients with leukocytospermia, the presence of resistin can be related to an alteration of sperm parameters.

Visfatin

In the male genital tract, visfatin has been detected in Leydig cells, spermatocytes, and spermatozoa[92]. Visfatin levels are a hundred times higher in seminal plasma than in blood which suggests the probability of local production of visfatin in the male genital tract[90,92]. Visfatin concentrations causes increased concentration of serum testosterone, increased body and testis

weight, and is negatively correlated with blood glucose concentrations.[30,213]

Visfatin is actually produced by immature human spermatozoa[206]. An in-vitro study has revealed that Visfatin can enhance testosterone synthesis in Leydig cells[214]. No consistent information regarding its exact functions in male reproductive pathologies has been obtained yet. In a current research in obese and diabetic rats, it was reported that plasma visfatin was negatively associated with semen quality, testosterone, and levels of LH and positively linked to degenerative changes in the testis, suggesting that this adipokine might play a role in the metabolic syndrome-induced male infertility[215].

Chemerin

Chemerin expression is evident in male reproductive tissues, and besides being involved in metabolism and inflammation, it has been found to inversely correlate with Leydig cell functions, testosterone levels, as well as sperm functions[216,217]. Chemerin and its receptors (CMKLR1, GPR1, and CCRL2) are expressed in the male reproductive tract specifically on Leydig cells and in very poor quantity in germ cells[92] of different species, including humans, mice, and rats, having an endocrine and/or paracrine function in testicular activity[218]. Till date only few studies have been done on the involvement of chemerin in regulating male reproductive functions in human and a scientific study has reported about the presence of chemerin in the seminal plasma of human with no spermatogenic abnormalities. It was also shown that this adipokine correlated negatively with sperm motility and positively with sperm concentration in individuals with no spermatogenic problem[90,197]. The association of chemerin with sperm functions is independent of either body weight or reproductive hormones, and this adipokine may possess a unique role in male reproductive functions[219]. Chemerin negatively correlates with luteinizing hormone (LH), sex hormone binding globulin (SHBG) and estradiol[197]. The negative association of chemerin with SHBG suggests the association of obesity with compromised testicular functions. Scientific reports have indicated that chemerin has an inhibitory impact upon hCG-induced Leydig cell steroidogenesis[254]. Unlike seminal plasma chemerin, serum chemerin levels were not linked to sperm parameters.

Chemerin along with resistin and visfatin are thought to inhibit the development of sertoli cells leading to testis dysfunction and reproductive issues associated with obesity. *In vitro* studies have also demonstrated the inhibitory impact of chemerin upon steroidogenesis[220]. However, further investigations are needed to explore the exact role played by chemerin in human male reproduction..

Vaspin

In the male genital tract, Vaspin, is expressed in epididymal, retroperitoneal, and mesenteric adipose tissue and is related to the metabolic state[142]. It is evident that seminal plasma vaspin is negatively correlated with ejaculate volume ($r = -0.36$, $p < 0.001$) and positively correlated with sperm DNA fragmentation ($r = 0.22$, $p < 0.05$).[90] Due to insufficient data available, the exact role of vaspin in regulating male infertility cannot be inferred.

Adiponectin

Various authors have reported about the existence of adiponectin in different parts of the male genital tract as well as their role in various male reproductive functions. The mRNA for Adiponectin is detected in Leydig cells and spermatocytes[32] of testis, whereas the adiponectin receptors, AdipoR1 and AdipoR2 are present ~~in~~ specifically in Sertoli cells, Leydig cells, and germ cells in testis[32, 220] of rats. Semen or seminal fluid have been reported to contain adiponectin at concentrations of about 66- and 180-folds less than its concentration in serum in men and bulls, respectively[90,221].

Expression of adiponectin and its receptors, AdipoR1 and AdipoR2 has been reported in the human hypothalamus and pituitary indicating its regulatory function of HPG axis[222] . Moreover, its deficiency has been suggested to have inhibitory effects over FSH and LH secretion thereby hampering reproductive functions.[223] *In vitro* studies have demonstrated that adiponectin inhibits hypothalamic GnRH secretions through activation of AMPK[224,] influencing the kisspeptins mediated GnRH inducing signal[167] as well as involving the proteins such as AMPK, peroxisome proliferator-activated receptor-alpha (PPARα) and mitogen-activated protein kinase (MAPK)[167]. This suggests the role of adiponectin in regulating the process of testosterone production. Another essential aspect of adiponectin action is its capability to sustain insulin sensitivity *via* induction of testicular glucose uptake[225] as it is well known that intratesticular glucose level is one of the major regulators of steroidogenesis[226].

It is suggested that adiponectin might have a role in sperm capacitation as they are expressed during pre- and post-capacitation of spermatozoa[227]. Thus, local actions of adiponectin in testis are involved in the production of sperm capable of fertilization[228]. Adiponectin levels in seminal plasma have been shown to be positively correlated with sperm concentration, sperm count, and percentage of typical sperm forms.

Antiinflammatory properties of Adiponectin protects the Leydig cells from inflammatory cytokines and chemokines-mediated cytotoxicity. Thus, adiponectin has a testicular defense mechanism to combat the impacts of pro- inflammatory mediators like macrophage-derived tumor necrosis factor-α, interleukin 1, and interferon-γ on steroidogenesis[229], The adiponectin signaling in male gonadal tissue seems to be essential for various testicular functions, but further clarifications are required to establish the exact level of contribution of the adiponectin mediated pathways on male reproduction.

Progranulin

Progranulin is increased in cases of obesity or metabolic syndrome and is known to contribute to the inflammatory mechanisms found in certain pathologies via recruitment of macrophages[230]. Thomas and his colleagues[90] studied this adipokine in the seminal plasma and it was found that Progranulin is positively correlated with sperm motility ($r = 0.32$, $p < 0.001$), sperm count ($r = 0.23$, $p < 0.05$), and sperm morphology ($r = 0.25$, $p < 0.01$). In vasectomized patients, seminal progranulin levels are significantly decreased ($p < 0.05$), indicating their probable local secretion. More studies are required for exploration of the exact role of the adipokine in regulating male infertility.

Cytokines, obesity and inflammation mediated male infertility

Inflammation in the male reproductive tract is an important factor that plays a significant role in male infertility[231] and involves an interplay between pro inflammatory ~~cytokines~~ and anti-inflammatory cytokines. Studies regarding male infertility have revealed presence of acute and chronic inflammation in the male genitourinary tract. The inflammatory reactions are immensely related with oxidative stress which in return is harmful to the sperm as it causes damage in the sperm DNA and finally cause apoptosis[232] . Cytokines are known to play a major role in the inflammatory response by regulating its nature, intensity and duration, and by modulating the communication between the different cells of the immune system.[213] During inflammation, the level of these cytokines and other inflammatory mediators become high and harmful for sperm production leading to male infertility[232]. Various cytokines are known to act in coordination with adipokines and play a significant role in inflammation mediated male infertility.

Obesity is a disorder that favors the development of chronic inflammation. Excess adipose tissue and hypertrophic adipocytes lead to high levels of CRP[233] and other acute phase proteins including (TNFα)[234], (IL6)[55,234] and interleukin 34 (IL34)[235] in the circulating blood. Increase in plasma pro-inflammatory cytokines induces vascular endothelial response causing enhanced production of adhesion molecules, which, along with adipokine-induced chemokines, stimulate macrophage recruitment into adipose tissue. This results in development of local inflammation promoting local insulin resistance[234]. A similar mechanism is seen peripherally, leading to systemic inflammation and subsequently to systemic insulin resistance[234,235]. C-reactive protein (CRP), is known to be a sensitive and reproducible marker of inflammation[233,234] and it is synthesized in the liver in response to the proinflammatory cytokines (TNFα, IL1 β and IL6)[235]. CRP levels rapidly increase in the process of inflammation, which enables its use as a marker of inflammatory conditions. Scientific studies conducted on 12 European countries revealed that CRP levels were positively correlated with BMI and glycated haemoglobin and negatively correlated with high HDL cholesterol levels.[233]

Inflammatory cytokines, such as IL-1, IL-2, IL-6, IL-10 and TNF-α, produced by Sertoli cells, leukocytes and germ cells are associated with autocrine/paracrine regulatory mechanism and the endocrine mechanism involves the gonadotropins- LH and FSH. IL-2 has negative correlation with the production of testosterone by the Leydig cells and amplifies negative feedback of testosterone on the production of LH by the pituitary gland.[30]

High levels of IL34 is detected in the serum of obese patients compared with metabolically healthy indivuals[236] having a positive correlation between insulin-resistance-related metabolic parameters (BMI, systolic BP, fasting plasma insulin, HOMA-IR, serum leptin, hsCRP, VAT and SAT) and IL34 level. VAT contains more IL34 than the WATs.

Numerous data indicate that TNFα levels increase along with the severity of obesity[237]. TNF-α can directly impair the seminiferous epithelium by damaging the expression and assembly of the junctional proteins leading to an impairment of the blood-testis barrier[247]. TNF-α and IFN-γ are known to rise in semen from males with an inflammation linked infertility having a negative correlation between IFN-γ and sperm concentration, motility, and morphology has been reported by a group of scientists[32]. TNF-α levels are increased in the seminal plasma of oligozoospermic and asthenospermic patients compared to control patients. A polymorphism in the TNF-α 308 gene was associated with a significant decrease of sperm count, sperm motility, normal sperm morphology, and acrosin activity[154].

IL-18 is a pro-inflammatory cytokine found in testicular tissue and elevated IL-18 concentrations have been associated with impaired spermatogenesis[30]. IL-18 has negative correlation with semen parameters like sperm concentration and motility whereas sperm motility decreases on increase of IL-17[213]. High concentration of IL-17 has been found to be associated with an elevated concentration of TNF-α, IL-6 and IL-8[30]. It has been reported that high levels of the proinflammatory cytokines TNFα, IL 1α and IL1ß are very harmful to sperm production[231].Figure I gives an overall idea of how adipokines and cytokines link obesity with inflammation mediated male infertility as well as other metabolic disorders and their probable immune regulatory mechanism.

IMMUNE MODULATORY ROLE OF ADIPOKINES

Modulation of the immune system that leads to any change in the immune response involving induction, expression, amplification or inhibition of any part or phase of the immune response is referred to as immunemodulation[238]. Thus, immunemodulators may be defined as a substance, biological of synthetic, which can stimulate, suppress or modulate any of the components of the immune system including both innate and adaptive arms of the immune response[49]. Based on their effects, there are generally two types of immunomodulators: immunosuppressants and immunostimulators. A group of therapies has been developed that alter immunologic function for the treatment of human disease. Basic immunobiologists have elucidated mechanisms of immunologic specificity, recognition, activation, regulation, and tolerance induction that depend on the interactions of many cell types and their products. These discoveries have led to the development of therapies that target components whose altered function results in more focused effects, which may permit selective modulation of immunologic balance without severe side effects. Immunomodulation also includes therapies that boost an individual's defenses by providing physiologic dosages of exogenous cytokines to treat chronic viral infections and malignancies.

Immune responses in humans are divided into two categories: innate and adaptive responses. Innate immune responses are the first line of defense against any external pathogen invasion because they are fast responding and nonspecific. Adaptive immune responses, on the other hand, come into play when innate immune responses are unable to completely defend or fail to respond to an external pathogen invasion because they are specific to the type of pathogen. Acute phase reactants (IL-1, TNF-α) and neutrophil-macrophage system (neutrophils, monocyte-macrophage system, natural killer cells), mononuclear or polymorphonuclear phagocytes (PMNs) are responsible for the majority of innate immune functions, whereas T-cells and B-cells are responsible for

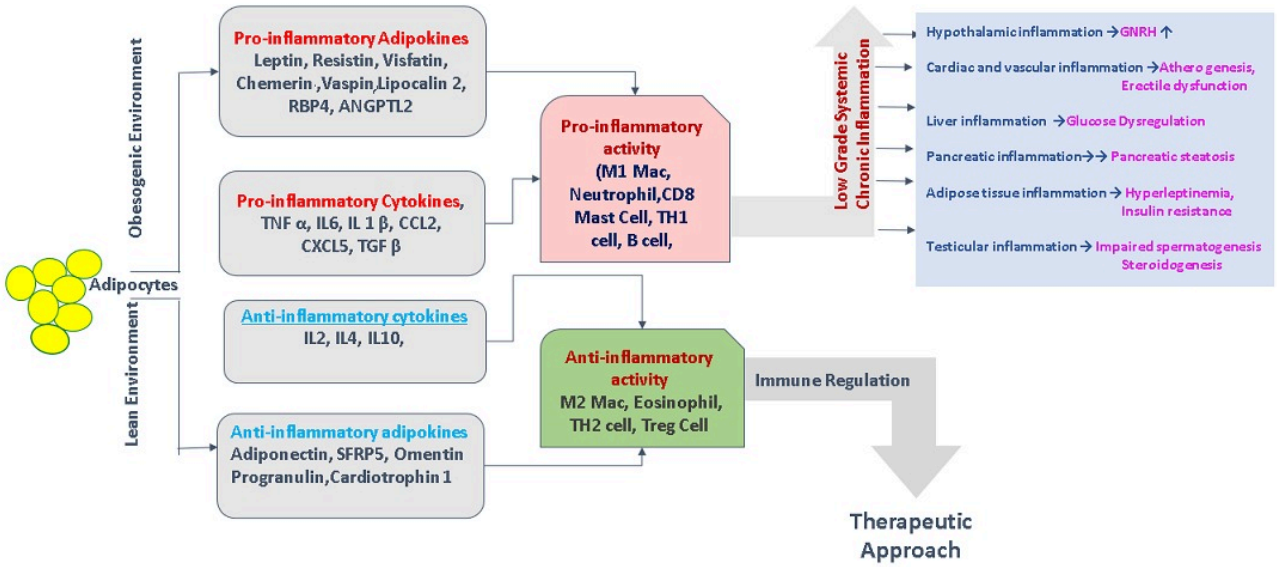

Figure I: Adipokines linking obesity, inflammation mediated male infertility and their probable immune regulatory approach.

the majority of adaptive immune responses. Once the adaptive arm has been activated toward a particular pathogen, however, it can respond rapidly in the future due to the persistence of memory lymphocytes, which form the basis of immunization.[239]

It is believed that the physiological responses to any type of stress are mediated by a complex interplay between stress hormones secreted by the hypothalamo-pituitary-adrenal axis, their effects on humoral and cellular immune responses, modulation of the activity of mediators of inflammation such as IL-1, IL-6 TNF-α and negative feedback on their own pro-inflammatory activities. The majority of lymphoid organs, including the bone marrow, thymus, and lymph nodes, are connected with adipose tissue in some way. Adipose tissue serves as a milieu in which adipokines, can communicate with one another, thereby maintaining immunological and metabolic balance.[28, 29]

Leptin

Leptin is an adipocyte-derived hormone/cytokine that links nutritional status with neuroendocrine and immune functions. Besides being an anti-obesity hormone, leptin also has a critical role as an immune modulator. Leptin acts on different immune cell types and can affect both the development and function of immune cells. Leptin receptor is expressed by most cells of the immune system and many immune cells have been shown to be leptin responsive to varying degrees. Increased systemic leptin levels in diet-induced obesity directly promote obesity-associated inflammation through this mechanism.[240]

Effect of Leptin on innate immune cells:

Leptin has distinct pro-inflammatory effect on each type of innate immune cells. Leptin acts specifically on **macrophages** via the leptin receptor to promote both phagocytosis and cytokine production[17]. In an in-vitro study, in response to leptin treatment primary human **monocytes** (PBMCs and THP-1 monocytes) from a human monocyte cell line -, have been shown to increase toll like receptor 2 (TLR2) expression[241]. By promoting TLR2 expression on monocytes, leptin is able to promote the innate immune response to pathogens such as *E. coli*. In human studies, leptin treatment of monocytes isolated from PBMCs increased the production of type 1 cytokines, including IL-1β, IL-6, and TNF, and resistin.[242]

Mast cells are known to play a role in adipose tissue remodeling in obesity, promoting the inflammatory phenotype of adipose tissue by secreting inflammatory molecules such as TNF and pro-angiogenic molecules such as chymase[243]. Scientific study has revealed that Leptin treatment of the **mast cells** lead to increased macrophage production of IFN-γ. Thus, Leptin production by mast cells may be important in promoting a pro-inflammatory macrophage phenotype.[244]

Dendritic cells (DCs) function at the interface of the innate and adaptive immune system by uptaking, processing, and presenting antigens to T cells. DCs express leptin receptor, both at the protein and mRNA level, which signals through STAT3 upon stimulation. Furthermore, by increasing expression of the anti-apoptotic proteins Bcl-2 and Bcl-xL, leptin is found to have an anti-apoptotic effect on DCs in vitro. Mature DCs are more capable of stimulating an appropriate and strong T cell response[245]. Leptin treatment of DCs increases production of IL-1β, IL-6, IL-12, TNF, and MIP-1α.[240]

Neutrophils are the best studied innate immune cells with regard to leptin response. Neutrophils only express the short form leptin receptor, which lacks JAK-STAT signaling[246]. Leptin acts as a survival factor for neutrophils by inhibiting apoptosis of the neutrophils[240]. Leptin primarily acts as a chemoattractant for neutrophils, particularly during infection. Similar to neutrophils, leptin has also been shown to act as a chemoattractant for both **basophils** and **eosinophils**. Basophils, on treatment with leptin increases type 2 cytokine production, including IL-4 and IL-13.[240]

Natural killer (NK) cells and **innate lymphoid cells (ILCs)** function at the interface between adaptive and innate immunity. These cells are able to respond to pathogens with rapid cytokine production. Leptin receptor is required for normal NK cell development.[240]

Effect of leptin on adaptive immune cells

Leptin has been shown to have a role in modulating **T cell** development, as well as their function and metabolism. Leptin deficiency has been shown to result in thymic atrophy and decrease in numbers of the circulating T cells[239,247]. CD4+ T cells express high levels of the long isoform of the leptin receptor and it is the only isoform that can signal through the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway[240] Leptin treatment of CD4+ T cells increased proinflammatory cytokine (namely T helper 1 (Th1) cytokines interferon gamma (IFN-γ) and IL-2) production, , while decrease production of the T helper 2 (Th2) cytokine IL-4. These data suggest that leptin promotes pro-inflammatory cytokine production in CD4+ T cells[240].

Leptin has also been shown to play a role in the differentiation of T cells into functional subsets. Leptin promotes the differentiation of effector T cells, but not Treg cells[247]. Treg cells express high amounts of leptin receptor, and have been shown to be capable of secreting leptin[248].Leptin is also known to promote differentiation of Th17 cells and leptin promoted transcription of RAR-related orphan receptor gamma (RORγt are the critical transcription factor for the fate of Th17. Leptin has also been shown to inhibit Treg cell proliferation in primary human cells, and blockade of leptin binding to Treg cells using anti-leptin antibodies leads to increased Treg cell proliferation[240].

Leptin is also known to promote B cell development[249] as well as B cell homeostasis by inhibiting apoptosis and promoting cell cycle entry[240] There might be a probable involvement of leptin on B cell survival[250] . Leptin is also known to promote cell cycle entry by increasing the transcription of genes that regulate cell cycle, particularly in the presence of co-stimulation[250]. Human B cells stimulated with leptin in vitro were shown to exhibit a more pro-inflammatory phenotype characterized by increased expression of inflammatory cytokines IL-6 and TNF, as well as toll-like receptor 4 (TLR4), a pattern recognition receptor that recognizes lipopolysaccharide (LPS) found on gram-negative bacteria[251]. These B cells also showed reduced class switching and IgG production in response to leptin. Another study has shown human peripheral blood B cells increase IL-6, TNF, and IL-10 production when treated with leptin in vitro. Leptin signaling in B cells activated JAK2, STAT3, ERK1/2, and p38 MAPK pathways[252].

While the etiology of obesity is complex, it is possible that increased leptin signaling promotes excessive inflammation and potentially cytokine storm. It is possible that targeting leptin or leptin signaling could be therapeutic for autoimmune disease or the low-grade, chronic inflammation associated with obesity and metabolic syndrome.

Resistin

Resistin is thought to be a critical mediator in the development of chronic inflammatory and autoimmune conditions[209]. A number of studies revealed that inflammatory stimuli can induce secretion of resistin. In human peripheral blood mononuclear cells (PBMCs), proinflammatory cytokines (IL-6, IL-1, and TNF-α) as well as bacterial virulent factors (such as the Lipopolysaccharides) have all been shown to increase the expression of resistin mRNA. In addition to activating cytokines, such as IL-6, IL-12, and TNF via NFκB pathway, resistin also activates SOCS-3, recognized by reducing insulin signaling in adipose tissue and other tissues. Lower levels of resistin were found in metabolically healthy patients compared to those diagnosed with metabolic syndrome[107]. Resistin also acts as a good marker for male genital tract inflammation and its elevated levels may indicate pathological conditions like leukocytospermia which again link with altered sperm parameters[253]. Binding of resistin to Toll-like receptor 4 in the hypothalamus activates proinflammatory pathways in that organ, contributing to the comprehension of molecular mechanisms involved in the inflammation and insulin resistance induced by resistin[18].

Visfatin

Visfatin is ~~more than~~ just an adipocyte-derived molecule ~~and is~~ involved in the process of differentiation of preadipocytes to adipocytes and acts as a stimulating factor for pre-beta lymphocyte colony.

Visfatin was originally identified as a modulator of B cell differentiation expressed in lymphocytes, bone marrow, muscle and liver[93]. Visfatin enhances the effects of interleukin-7 (IL-7) and stem cell factor during development of pre-B cell colonies. It stimulates the p38 mitogen-activated protein kinase (p38 mAPK) and extracellular signal-regulated kinase (ERK) pathways, leading to the production of IL-1β, TNF and IL-6, ~~the~~ expression of ~~the~~ CD80 (B7-1), CD40, and ~~also of~~ ICAM-1 and other co-stimulatory ligand that binds to LFA-1 (lymphocyte function-associated antigen-1). In this way, it promotes the activation of T cells[254] and thereby increase human monocyte chemotactic activity. Administration of recombinant visfatin has been shown to ~~have~~ induce of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1, while also upregulates some anti-inflammatory cytokines, such as IL-1 and IL-1 receptor antagonist, in human monocytes (and other cells). Numerous investigations have demonstrated that visfatin is released by neutrophils as part of an important inflammatory response and that it acts as an inhibitor of apoptosis through a caspase 3- and caspase 8-mediated mechanism[254].

Visfatin has been shown to be produced by human spermatozoa, particularly by immature ones, and its concentrations in seminal fluid are 100 times higher than those found in blood plasma[206]. No consistent information, on the other hand, has been acquired about its precise activities in male reproductive diseases. Plasma visfatin levels were found to be negatively connected with semen quality, testosterone levels, and LH levels. These findings imply that this adipokine may play a role in the metabolic syndrome-induced male infertility.

Progranulin

Progranulin is an adipokine which has its significant importance in cubic of immunity, infection, and inflammation. It is also considered to be a vital immunomodulator and it has a dual function in playing the pro- inflammatory and anti-inflammatory role in immune-mediated diseases. The immune system is intimately linked with the changes in inflammatory mechanisms. Among the cytokines released as a result of immune response and inflammation, TNF-α is known to have the highest inflammatory role. The TNF-α/TNFR signaling pathway is known to coordinate a large number of inflammatory processes, and is pivotal for the occurrence and development of inflammation-induced immune-

mediated diseases[255]. Progranulin (PGRN) is a unique ligand of TNF receptor (TNFR), which plays its anti-inflammatory action mainly through TNF Receptor 1 (TNFR1) and stimulus CD4+CD25+Foxp3+regulatory T cells (Treg) activity by binding to TNF Receptor 2 (TNFR2). In this way, it limits the role of TNF-α in some immune- mediated diseases, such as RA and IBD[256].

PGRN is highly expressed in $CD8^{+}CD28^{-}$ T cells[181] also called T-suppressor cells and maintain a regulatory function in many autoimmune diseases. This indicates the importance of PGRN in regulating the immune reaction. In an in- vitro condition of T cell differentiation, PGRN is found to induce naïve $CD4^{+}$ T cells to specifically differentiate into $CD4^{+}Foxp3^{+}$ Tregs. PGRN also protects Tregs from negative regulation by TNF-α[257]. These findings suggest the probable role of PGRN in enhancing the function of Tregs, which in turn, inhibits autoimmune diseases. PGRN influences Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway to reduce cell response of Th1 and Th17 and cytokines secretion both in vitro and in vivo conditions.[258]

PGRN is cleaved by elastase to yield discrete fragments named Granulin (GRN) in vitro. The GRN acts as an essential role in defense infection in the innate immunity. GRN assists in recruiting ~~of~~ CpG oligonucleotides (CpG-ODNs) in macrophages by binding to Toll-like receptor 9 (TLR9) and thus works against bacterial invasion[255]. TLRs are important components of the innate immune system, and are known to recognize structurally conserved molecules derived from microbes.[181] Binding of TLR9 to CpG-ODNs plays a role in intracellular delivery of CpG-ODNs to macrophages. All of these results show that PGRN is critical in innate immunity against micro-organisms.

PGRN is highly expressed in neutrophils, and it converts into GRNs by neutrophil-released elastase[181]. After cleavage, GRN B stimulates IL-8 expression in epithelial cells to recruit additional neutrophils to the site of inflammation.[181].

Currently, the inhibitory effect of PGRN on inflammation has received greater attention. The central anti-inflammatory role of PGRN is to mediate the TNF-α/TNFR signaling pathway through binding to the slender cysteine-rich domain 2 (CRD2) and CRD3 of TNFR1 and TNFR2 extracellular region[259]. PGRN binds to TNFR1 and activates extracellular regulated protein kinase 1 and 2 (ERK1/2) and phosphatidylinositol 3 kinases/protein kinase B (PI3K/AKT) pathways to competitively interfere with activation of TNF-α mediated nuclear factor of kappa (NF-κB) inflammatory pathway.[259] This promotes the release of pro-inflammatory cytokines, mainly IL-6; PGRN selectively inhibits expression and release of CXCL9 and CXCL10 induced by TNF-α in a TNFR1 dependent manner. Combination of PGRN and TNFR2 ameliorate chronic inflammatory disorders via production of IL-10 in a FOXO4–STAT3-dependent manner in Tregs[259]. These findings suggest the regulatory role of PGRN in inflammation and autoimmunity and is thought to serve as biomarkers. It also indicates a promising and novel therapeutic concept to treat diverse inflammatory immune- mediated diseases.

Chemerin

Chemerin is a multifunctional protein and is known primarily for its chemotactic and adipokine properties. Several immune cell subsets, such as **plasmacytoid dendritic cells (pDCs), macrophages and NK cells** express CMKLR1 and respond to chemerin either through chemotaxis or modulation of their defense function[218]. This protein is also known to inhibit bacterial growth[260].

Chemerin transcription is known an important part of local and systemic programs of gene expression that are crucial in immunity and metabolism. The production of chemerin can be regulated by immunomodulatory mediators (e.g. cytokines of acute or chronic inflammation and LPS)[260]. TNFα may promote chemerin production in adipocytes[261].

During expression of CMKLR1 by macrophages, DC subsets, and NK cells, in most cases these cells respond to chemerin with integrin activation, calcium signaling and chemotaxis[262]. CMKLR1+ leukocytes are multifunctional innate immune effector cells that can initiate pro-inflammatory or immune suppressive responses. In humans, the immunohistochemical detection of chemerin, CMKLR1 and leukocytes are known to express CMKLR1 in diseased tissues and this helps in recruitment of immune cells to inflammatory sites. Recruitment of Chemerin-dependent CMKLR1+ macrophage to adipose tissue may contribute to the chronic, low-grade systemic inflammation associated with obesity. Adipose tissue is one of the major sites of chemerin expression, and the secretion of chemerin from adipose tissue increases with adipocyte differentiation and obesity[260]. During obesity a significant increase in macrophage infiltration is observed in obese patients[77].

Adiponectin

The hormone adiponectin exerts its anti-inflammatory effects by reducing the activity of inflammatory immune cells. It protects testicular cells from the cytokines released by testicular immune cells during an inflammatory response. Recent evidence indicates that adiponectin can modulate immune functions in addition to their role in regulation of metabolic homeostasis within adipose tissue.

Effect of adiponectin on innate immune cells

There are evidences which suggest that adiponectin regulates energy expenditure and insulin sensitivity via innate immune response dependent mechanisms.[171]

Monocytes/macrophages

Adiponectin receptors AdipoR1 and AdipoR2, have critical roles in the modulation of inflammation, lipid and glucose metabolism, as well as in the development of OS[254] is evident that the AdipoR1, AdipoR2, and T-cadherin receptors are highly expressed in macrophages but their exact roles in the regulation of adiponectin's anti-inflammatory activity is not very clear[263]. AdipoR1 binds primarily to globular adiponectin (gAd) and suppresses the activation of the nuclear factor-kB (NF-kB) and the production of pro-inflammatory cytokines in monocytes and macrophages[264] . On the other hand AdipoR2 is required for complete M2 polarization to occur as a result of the adiponectin-mediated signalling[254]. According to recent research, microglial development and function appear to be regulated by adiponectin through a variety of intracellular signaling pathways. It is noted that TLR mediated NF-kB signaling, is critical for the regulation of M1 macrophage activities and its adiponectin mediated proliferation. Adiponectin also increases endotoxin tolerance in primary macrophages by activating the Erk signalling pathway.[254] Furthermore, adiponectin

stimulates the production of anti-inflammatory cytokines such as IL-10 by macrophages through cAMP-dependent pathways.[254] In addition to the NF-kB, Erk, and cAMP pathways, the Akt pathway, is involved in the stimulation of M2 macrophage proliferation induced by adiponectin.[265] Though adiponectin is known for its anti-inflammatory characteristics, some scientific reports have also revealed its pro-inflammatory qualities by activating the NF-kB and Erk pathways, which increase the production of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-8.[254]

Eosinophils

They are immune components ~~that are~~ responsible for allergen-induced inflammation and parasite infection, [96,97] and are known to migrate and infiltrate the adipose tissue, resulting in ~~atypical~~ macrophage activation as well as cold-stimulated adipose tissue browning[266]. Despite the fact that adiponectin receptors AdipoR1 and AdipoR2 are both expressed in human eosinophils, it is unclear whether adiponectin has an effect on eosinophil activity through an adiponectin receptor-mediated signaling pathway[254]. Furthermore, it is yet to be determined if adiponectin influences the activity of adipose-resident eosinophils, which are found in the fat tissue.

Neutrophils

Neutrophils are most important first-line defenses against pathogenic microbes, eliminating infectious agents through phagocytosis, secretion of cytokines, the formation of 'neutrophil extracellular traps' (NETs), and the production of reactive oxygen species (ROS). Adiponectin in its full length inhibits neutrophil phagocytosis by inhibiting NADPH oxidase and ROS generation in an AMPK-activated pathway, which is thought to be responsible for the suppression.[254] Adiponectin inhibits the synthesis of ceramide in the neutrophil membrane, and as a result, it prevents neutrophil mortality through the action of the AMPK protein[267]. Additionally, adiponectin therapy inhibits phagocytosis of *Escherichia coli* neutrophil via inhibiting the PI3K/PKB pathway and activating the Mac-1 transcription factor, respectively.[267] According to these findings, adiponectin has a negative influence on neutrophil activity.

Dendritic cells

In the immune system, dendritic cells (DCs) are specialized antigen-presenting cells (APCs) that are essential for the development of immunity and tolerance to antigens. There is evidence to suggest that adiponectin has some influence on DCs, although it is yet unclear whether it is a positive or negative effect on DC function. Scientific studies have shown that the adiponectin receptor is required for DC activation via the phospholipase C g/JNK/NF-kB pathway, culminating in the differentiation of T cells into Th1 and Th17[268]. It is possible that duration and dose of adiponectin treatment influences the resulting outcome Additional research is needed to determine the mechanism through which adiponectin regulates the function of DCs.

Adiponectin in adaptive immune cells

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 critical components of the immune system that can mediate both adaptive and innate immunity.

Lymphocytes

Innate-like lymphocytes, including NKT cells and ILC2, are found in adipose tissues which play important roles in both inflammation and metabolic processes[254]. It has been demonstrated that constant decrease of the density of ILC2s and NKT cells in adipose in human individuals causes constant increase in density of GdT cells, showing a relationship between obesity and these innate-like lymphocytes[269]. As a result, ILC2s, NKT cells, and gdT cells are considered as a possible novel treatment approach for patients suffering from metabolic diseases.

Recently, ILC2s are found to increase browning of adipose tissue and thereby prevent obesity.[254] Type-2 cytokines like as IL-5 and IL-13 are released by ILC2s, which enhance maturation and infiltration of eosinophil while also stimulating M2 macrophages. ILC2s stimulated by IL-33, on the other hand, release methionine-enkephalin peptides that are directed to white adipose tissue and enhance browning and thermogenesis in the fat cells[254]. This thereby increases the population of ILC2 in white adipose tissue. The ILC2 population and activity are both significantly reduced during chronic stress, indicating that the downstream consequences of chronic stress may be responsible for ILC2 suppression in adipose tissue[254]. Furthermore, these contradictory results highlight the need for additional research into the physiological roles of adiponectin in regulating immunity as well as energy expenditure in the body.

NKT cells, which can be found in adipose tissue of humans, play an important role in metabolic control. In humans with obesity, the NKT cells act as a protective barrier against metabolic syndrome-induced inflammatory conditions by secreting inflammatory cytokines (such as IL-4 and IL-10) and their numbers are known to decrease. Despite this, the total number of T cells in adipose tissue increases as obesity advances. Studies have shown that adiponectin aids in the mobilization of plasma B cells and the production of the 'B-cell-derived peptide PEPITEM,' which inhibits the migration of memory T cells, among other things. Furthermore, B-cells express the adiponectin receptors AdipoR1 and AdipoR2, which may be responsible for the inhibitory effect of adiponectin on B-cell-specific PEPITEM production and secretion.[254]

An adipose-resident innate-like lymphocyte namely the GdT cells, promote diet-induced inflammation and insulin resistance with the production of GdT cells a small proportion of total T-cells predominantly CD42 and CD82 positive cells. However, it is uncertain whether adiponectin has an effect on the activities of adiponectin-producing gdT cells.

A SPECIAL NOTE ON SOME OTHER PROTEINS IN OBESITY AND INFLAMMATION INDUCED MALE INFERTILITY

Recently scientists have reported about some other proteins having regulatory function in obesity. Among them some are also involved in connecting obesity with inflammation mediated male infertility.

Ghrelin

Ghrelin (GHRL) is a natural ligand for the growth hormone secretagogue, which is secreted primarily by endocrine cells of the oxyntic glands of the gastric fundus and to a lesser extent by the body of the stomach, the mucosa of the duodenum and jejunum, the

lungs, the urogenital organs, and the pituitary gland[270] and operates as an orexigenic stomach hormone in response to nutrient restriction[271]. It is a well-known orexigenic hormone that stimulates food intake in a dose-dependent manner. GHRL has two main molecular forms, namely acylated GHRL and unacylated GHRL. Apart from its regulatory role in GH secretion and energy metabolism[272], acylated GHRL also influences the immune system and metabolic process[273] Unacylated GHRL can control local inflammatory responses to bacterial infection[274] Among the most documented functions of ghrelin fine-tuning of cell proliferation, anti-inflammatory cytokines secretion, as well as male and female reproductive functions are of great importance[275]. The exact role of ghrelin in the pathophysiology of obesity is still under investigation.[270]

Many studies have shown that GHRL has a beneficial effect on spermatogenesis and the development and programming of reproductive organ[274]. It is shown that mature Leydig cells express both ghrelin and its functional receptor, but these cells have almost no proliferative activities. The expression of Ghrelin receptor in the seminiferous tubules suggests its potential actions upon seminiferous epithelium. It is also evident that ghrelin regulates spermatogenesis by its inhibitory effects on tubular stem cell factor gene expressions[275]. Scientific studies have reported that GHRL protects testes against oxidative stress-induced damage, by decreasing diameter of the seminiferous tubule and increasing apoptosis and spermatogenesis[276]. Similarly, GHRL relieves ionizing radiation induced injury of the differentiating spermatogonia by spermatogenic recovery and testosterone (T) secretion. The molecular mechanisms of these protective effects are associated with the enhancement of antioxidative stress ability of ghrelin and the inhibition of cell apoptosis[274]. Some studies have revealed that GHRL improves immunocyte reactions and the inflammatory environment, by inhibiting the production of various pro-inflammatory cytokines including TNF-a, IL1β, IL6, and IL8 in human endothelial cells, monocytes, and T cells. All these proinflammatory cytokines are known to be correlated with obesity induced male infertility[274]. Decreased ghrelin levels were associated with hypogonadism in male as compared with lean individuals. Ghrelin also have negative correlation with insulin resistance[275]. Further, decrease in ghrelin level due to obesity may also have deleterious proinflammatory effect on the sperms and may contribute to male infertility.

Orexins

Orexins or hypocretins (OX/HCRT) are hypothalamic neuropeptides, which exists in two forms: orexin-A (OXA) and orexin B (OXB) and are derived from a common precursor, pre-pro-orexin (PPO). Pre-pro-orexins (PPO) is 130 amino acids in length and gets cleaved enzymatically into two HCRT peptides: HCRT1/OXA (33 amino acid) and HCRT2/OXB (28 amino acid)[277] . Orexin receptors are also of two types, OX1R and OX2R, and mediate their functions via transmembrane G-protein coupled receptors[36]. OXA binds to OX1R with more specificity, whereas OX2R has a similar affinity for both OXA and OXB[277]. Orexin and its receptors are found in all the mammals with considerable amount of conserved sequence in them. Orexins, their receptors and HCRT-producing cell bodies are collectively known as OX/HACRT system[277]. OXA has been found to influence the activities of gonadotropin releasing hormone (GnRH) neurons and funvtions of the gonadotropin-secreting pituitary cells. ~~functions.~~ Orexins may play additional roles in the regulation of reproductive functions. There are scientific reports indicating that OX/HCRT modulates reproduction by interacting with the hypothalamic-pituitary-gonadal (HPG) axis in mammals.[36]

The word ‘orexin’ is adapted from the Greek word referring to ‘appetite’ (orexin and male reprod).

OXA plays a key function in energy balance and obesity. The role of OXA in inflammation has recently been discovered and thus OXA is implicated in immune system[278]. It has been reported that orexins have the ability to influence both innate and acquired immunity and are known to suppress NF-kB activation and expression of the pro-inflammatory cytokine in macrophages[279].

Obesity is known to have connections with several physiological disturbances, of which impairment in normal reproductive functions is of major concern[36]. It is a known fact that obesity positively associates with male infertility. Orexin receptors are immunolocalized in Sertoli cells, Leydig cells, resting spermatocytes, spermatogonia, round, oval, and elongated spermatids[274] OX1R and OX2R are expressed in the testicular cells, epididymis, seminal vesicle, and penis[280]. Orexin receptors, OXA and OX1R, have also been found in the testicular interstitium and tubular compartments during the postnatal period The high expression of OXA and OX1R in the testis suggest that orexins might be playing an important role in spermatogenesis and steroidogenesis. OXA has been shown to enhance basal testosterone production in both in-vitro and in-vivo studies.[274]

The HPG axis is the main endocrine axis for the control of reproductive functions. The immunoreactive fibers of orexinergic system are distributed in the CNS and are known to overlap with the GnRH neurons. This suggests that orexins can influence the secretion of pituitary luteinizing hormone (LH) by modulation of the GnRH release. A large proportion of GnRH cells are in close contact with orexin immunoreactive terminals, indicating that orexins play a key role in GnRH neuronal regulations. GnRH secretion can be suppressed by orexins indirectly via -endorphins (endogenous opioid peptides)[274]. The activation of the phospholipase C/inositol triphosphate cascade and the expression of functional orexin receptors in testicular peritubular myoid cells may enhance other testicular activities.

Since orexins mediate obesity resistance and possess anti-inflammatory properties, further research should be conducted to reveal whether orexins can be ameliorative in obesity or inflammation induced male infertility or subfertility.

Obestatin

Obestatin is a 23-amino acid peptide that is derived from the same prepropeptide –(117amino acid long residue) as ghrelin[281]. The amide group at the C-terminal end undergoes a post-translational modification, which is thought to be essential for stabilization of the peptide into its regular conformation[282]. A single gene code for the common precursor protein for ghrelin and obestatin is called the ghrelin-obestatin preproprotein[281]. The gene is located in the short arm of chromosome 3 (3p) in human[283] and comprises of 4 exons leading to a 117-amino acid preprohormone,

preproghrelin[284]. In humans, majority of obestatin is produced in the GI tract, predominantly in the stomach, ~~in comparison to the~~ duodenum, jejunum and ileum. Besides its endocrine actions it may also act as local autocrine or paracrine factor[285].

Obestatin, is an anorexic hormone[281] that positively influences glucose homeostasis by enhancing the pancreatic β-cell mass, decreasing insulin resistance and associated adipose tissue inflammation. Its expression in the Leydig cells of testes and upregulation of testosterone secretion indicate its relevance in testicular functions[285].

Obestatin is known to play dual roles mediating both energy homeostasis and testicular functions. It is also reported to significantly reverse diabetes mediated male fertility parameters, such as epididymal sperm count, sperm motility, testicular enzyme activities, and sperm morphology in rats[285]. Moreover, due to the antioxidant property of obestatin, it is known to have protective role against diabetes-induced testicular dysfunctions[286].

The effects of obestatin on reproductive functions are not well defined but it is presumed to improve testicular functions in obese subjects[286]. Both obestatin and ghrelin levels were found to be higher in semen than in serum, indicating a linear correlation between serum and semen levels of ghrelin and obestatin. Moretti and his colleagues[286] have also reported immunoreactivity for obestatin in the spermatozoa, seminal vesicles and prostate gland. Obestatin levels in semen are found to be positively correlated with essential semen parameters such as the sperm motility and sperm concentration[286]. In a scientific study, on administration of obestatin and L-carnitine, obesity-related parameters were decreased testosterone levels were increased[285]. Administration of obestatin also showed increase in primary and secondary spermatocytes, spermatids and Leydig cell populations[285]. The improvement of semen quality by Obestatin may be due to improved spermatogenesis and by inducing proliferation of Leydig cells, thereby increasing the possibility of higher rate of steroidogenesis. Moreover, its possible influence on the male accessory reproductive glands may suggest its contribution in the secretion of seminal plasma. These studies indicate that obestatin may be a potential modulator in the management of obesity-induced male infertility or subfertility. Further research is required in this regard.

Adropin

Adropin is a unique and novel peptide hormone which may have a role in energy balance as well as glucose and fatty acid metabolism regulation[287]. Adropin is a metabolic regulator, which can potentially regulate body weight and ameliorate various metabolic disorders. As Adropin lowers body adiposity and has anti-inflammatory and antioxidant effects, it may have a role in restoration of male fertility. Several investigations have reported about the immune reactive property of adropin in humans and animals[288]. The 'energy homeostasis-associated' (Enho) gene encodes this protein. The precursor protein of adropin is 76 amino acid residues long and its proteolytic cleavage produces adropin protein, which is made up of 43 amino acids. The amino acid sequence of Adropin is remarkably conserved across species, being similar in rats, mice, humans, and pigs.[288] Adropin acts by biologically communicating with the G protein-coupled receptor, GPR19[288]. Adropin is primarily synthesized in liver [289]

During obesity, the degree of adiposity has been shown to positively correlate with the number of macrophages and systemic inflammation. Modulation of PPAR-γ, driven by Adropin mediates its regulation of lipogenesis and thus attenuates inflammation. Adropin also enhances the proliferation of 3T3-L1 by modulating ERK1/2 and AKT hence inhibiting the differentiation of pre-adipocytes into mature adipocytes by decreasing lipid accumulation and downregulating adipogenic genes in 3T3-L1[287]. This impairs macrophage infiltration and improves inflammation. Although adropin is known to downregulate PPAR-1 α, it also parallely upregulates PPAR-γ expression. PPAR-γ reduces the expression and secretion of TNF-α, IL-6, and monocyte chemotactic protein-1 (MCP-1) which induce macrophage infiltration and inflammation[290]. The amount of Treg cells in adipose tissue is dramatically decreased during obesity, and this immune cell imbalance leads to inflammation. This reduction in adipose tissue Treg population may induce insulin resistance.[291]. During inflammatory condition after conversion of the macrophages from M2 to M1 state, the M1 macrophages employ aerobic glycolysis to supply energy for fast, transitory bactericidal effects or proinflammatory reactions, whereas the M2 macrophages rely on the energy given by fatty acid oxidation (FAO) to maintain anti-inflammatory actions over time[292]. More studies are required to confirm whether adropin can change the macrophage phenotype via altering cell metabolism.

The pathophysiology of metabolic syndrome-induced male infertility ~~also~~ involves the crosstalk among metabolic hormones in a neuroendocrine way[293]. These hormones crosstalk with the key male reproductive hormones to regulate the metabolism and overall male reproductive functions[294]. Disruption in GnRH secretion due to the interaction of the metabolic hormones in obesity and other conditions can impact on male reproductive functions, steroid hormone synthesis, sperm production and maturation which ultimately led to subfertility or infertility in men. There are inadequate number of studies correlating the role of adropin on male reproduction, but from the evidences found till date, it can be assumed that adropin by decreasing body adiposity, can decrease the systemic inflammation, overproduction of cytokines, their interactions with central neuroendocrine axis. It can also improve the fertility status of a male by minimizing oxidative stress by its antioxidizing property.

Adropin has significant role in regulating steroidogenesis.. In inflammatory conditions, proinflammatory factors such as prostaglandins E2 (PGE2), TNF-α, and IL-6 enhance the transcription of CYP19 gene leading to increased aromatase activity via activation of cAMP/PKA/CREB pathway and suppression of BRCA1[295]. Exogenous and endogenous adropin could suppress CYP19 gene expression and consequent aromatase level by reducing accumulation of these proinflammatory cytokines via upregulation of P13K/Akt and extracellular signal-regulated kinase (ERK) signaling[296] and downregulation of nuclear factor KB (NF-kB). This prevents the irreversible conversion of testosterone and androstenedione to oestrogen by aromatase leading to improved levels of androgens. Adropin also improves glucolipid

metabolism and increases insulin resistance, ensuring optimal energy balance and preventing oxidative and inflammatory testicular damage, thus, maintaining optimal testicular production of testosterone[292].

Adropin is also known to minimise hyperlipidaemia induced endoplasmic reticular (ER) stress and germ cell apoptosis via downregulations of binding immunoglobulin protein[297]. Adropin maintains energy homeostasis[292] reduces activation of inflammatory cytokines via upregulation of PPAR-γ maintains optimal sperm chromatin condensation and DNA integrity[298], thus maintains sperm quality. In addition, adropin is known to play an integral role in maintaining the epithelial tubular cells and blood-testis-barrier integrity. The integrity of the epithelial tubular cells and blood-testis-barrier can be breeched due to oxidative damage. Hence, upregulation of Nrf2 and antioxidants activities by adropin possibly eliminate generated ROS and prevent degradation of the epithelial tubular cells and blood-testis-barrier by ROS. This helps to prevents disruption of spermatogenesis.

Sirtuins

Among various mechanisms by which obesity impairs male gonadal function, sirtuins (SIRTs) are known to have an emerging role. SIRTs are highly conserved nicotinamide adenine dinucleotide (NAD+)-dependent deacetylases that play a role in gene regulation, metabolism, aging, and cancer[188]. They catalyze the deacetylation of proteins by breaking the bonds between NAD+ and niacinamide ribosomes, transferring the acetylated groups from proteins to adenosine-50-diphosphate(ADP)-ribose, then releasing the deacetylated products[299]. Depending on structures, cellular localizations, and tissue expressions, seven types of SIRTs (SIRTs 1-7) have been identified in mammals. Variants of SIRTs, their location and function are given in the following table (Table no. I) [300]

Table I. Types of Sirtuins, their location and functions.

Type	Location	Function
SIRT 1	Nucleus and in some cases in cytoplasm	regulation of energy metabolism, stress, inflammatory responses, DNA repair
SIRT2	cytoplasm	cell cycle control
SIRT3	Mitochondria	regulation of metabolic enzymes involved in glycolysis, fatty acid oxidation, ketone body synthesis, and amino acid catabolism; apoptosis; and oxidative stress pathways, and may also regulate cellular metabolism both at the transcriptional and post-transcriptional levels
SIRT4	Mitochondria	works as an ADP-ribosylase
SIRT5	Mitochondria	regulation of amino acid catabolism
SIRT6	Nucleus	regulation of energy metabolism, stress, inflammatory responses, DNA repair
SIRT7	Nucleus	rDNA transcription via modifications of transcription factors, cofactors, and histones

Despite variable lengths and sequences, all SIRTs have a highly conserved catalytic core region consisting of approximately 275 amino acids, forming a Rossmann-fold domain, (characteristic of NAD+/NADH binding proteins), and a zinc-binding domain, connected by several loops. Outside the catalytic core, SIRT enzymes have variable N- and C-terminal regions that drive their enzymatic activities, substrate bindings, and subcellular localizations.[300]

SIRTs are present in hypothalamus, liver, brain, heart, kidney, pancreatic islets, skeletal muscles, adipocytes, testicular tissue, and oocytes. They play an important role in the regulation of cellular homeostasis and in particular, metabolism, inflammation, oxidative stress, and senescence[301] by activating several pathways and enzymes.

Many studies in recent decades have revealed that SIRTs regulate secretion of insulin, sensitivity, and mobilization or oxidation of stored fat by interacting with several transcription factors and adipokines[302]. The roles of SIRTs in balancing between inflammation and the antioxidant level significantly contribute to the onset of insulin resistance, obesity, and other metabolic diseases. SIRT1 seems to contribute to the maintenance of a balance between oxidative and antioxidant systems, protecting cells from oxidative stress damage.

SIRTs are highly expressed in mammalian testicular tissue. There are only a few studies which have evaluated the relationship, showing the possible role of SIRTs on male reproductive function and from these studies it is revealed that Sirtuins appear to play an important role in maintaining spermatogenesis[303] SIRT1 acts at the hypothalamic-pituitary level to alter gonadal function. The inactivation of SIRT1 affect the maturation of the fetal Leydig cells but does not affect their development. Low levels of LH and FSH have also been described in SIRT1-deficient mice. As SIRT1-deficient mice showed a significantly elevated number of spermatozoa with single or double-strand DNA breaks, it is said that SIRT1 may also play a role in maintaining genomic integrity[300]. SIRT1 also protects against apoptosis. Increased levels of SIRT1 are correlated positively with sperm concentrations, motility, and normal morphology[304]. SIRT1 appears to be involved in the formation of the acrosome cap. Since SIRT1 is involved in the deacetylation of LC3, which is essential for the redistribution of LC3 in the cytoplasm, it could play a role in the biogenesis of acrosome during spermiogenesis by modulating autophagy.[304]

The role of SIRT2 in male infertility is completely unknown In vitro and in vivo studies reported the deacetylase activity of SIRT2 on α-tubulin[300]. It can be hypothesized that SIRT2, ~~also~~ by deacetylating α-tubulin, has an important function on sperm motility and, therefore, on male reproduction.

Several studies have shown the role of SIRT3 in controlling ATP levels and its antioxidant properties. In various stress conditions, lack of SIRT3, and the consequent reduction in ATP levels, could lead to important metabolic alterations in male germ cells. SIRT3 plays an important role in the caloric restriction-mediated prevention of oxidative damage by improving the mitochondrial glutathione antioxidant defense system.[305]

SIRT4 is a major factor in mitochondrial dynamics and redox homeostasis. Suppression of SIRT4 cause mitochondrial

dysfunction which affects Leydig cell functions by modulating steroidogenesis and apoptosis.[306]

Considering the large number of mitochondria present in the microtubules of the sperm tail and their important role in sperm motility, the mitochondrial homeostatic activity of SIRT5 may play a role in male fertility.[307]

It is found that SIRT6 stimulates repair of the double-strand break pathways in mammalian cells exposed to increased levels of oxidative stress. Although this study was not conducted on germ cells, it cannot be ruled out that sirtuin exerts similar effects on these cells and, consequently, on male reproductive function.[300]

Sirtuins can be possible molecular targets for the treatment of obesity-induced male infertility. There are strategies that attempt to improve the activity of SIRTs to counteract the harmful effects of metabolic disorders[376/300]. In parallel, these approaches could also be used to counteract infertility caused due to overweight in male patients. In this regard, several molecules have been studied as activators of SIRTs and, particularly, of SIRT1[308]. These include resveratrol (RSV), metformin, berberine, quercetin, SRT1460, SRT1720, and SRT2183. Very few studies clarify the role of SIRT activators in obesity-related male infertility. The search for strategies to improve male reproductive function in overweight/obese patients is a challenge and understanding the role of SIRTs and their activators may open new interesting scenarios in future.

CONCLUSION

It is evident from the above discussion that obesity induced enhanced production of adipokines can have significant impact on a variety of physiological functions, including hunger, energy homeostasis, insulin sensitivity, as well as modulation of immune responses, and resistance. Adipocytokine research nowadays is of great importance, as adipokines are known to play a significant role in integrating systemic metabolism and immune mechanisms. Immune mechanism and metabolism are two intimately connected phenomena and metabolic dysregulation is known to induce immune activation. Nowadays, metabolic syndrome and obesity are a worldwide growing public health concern due to its numerous physiological side effects and the association of male infertility with obesity has recently received a lot of attention. Obesity-related diseases are linked to an imbalance of adipocyte function and inflammatory processes. The dysregulated adipokines significantly influence insulin signaling, and they may also have a detrimental effect on testicular function . The immune role of various adipose tissue-derived cells and substances are evident from various scientific studies. Several obesity-induced chronic diseases caused by inflammation are known to have associations with leukocyte subsets found in adipose tissue. These leukocyte subsets have been demonstrated to play critical role in both the restoration of homeostasis and the development of the chronic diseases.

Inflammation in the male reproductive tract is an important factor that plays a significant role in male infertility and involves an interplay between pro- inflammatory and anti-inflammatory cytokines. Studies regarding male infertility have revealed presence of acute and chronic inflammation in the male genitourinary tract. It is not known if adipose tissue has a role in conventional immunological functions such as host defence against infections. Furthermore, it is uncertain whether obesity-associated expansion of immune cell populations in adipose tissue contributes to systemic disruptions in immune surveillance that have been related to an increased risk of certain infections in obese patients.

Obesity is known to adversely affect the fertility status of male by disrupting the hormonal chain of reactions, altering sperm parameters, inducing inflammatory mechanism and by increasing oxidative stress. The pathophysiology of metabolic syndrome-induced male infertility involves the neuroendocrine crosstalk among metabolic hormones. Obesity may trigger inflammatory responses, where adipokines modulate the HPG axis and male reproductive functions. It is therefore necessary to understand the molecular mechanisms connecting obesity and fertility impairment to find means for preventing and managing obesity and infertility. Adipokines are known to be the potential modulator in the management of obesity-induced male infertility or subfertility and strategies should be taken to counteract the harmful effect of metabolic disorders. The immune modulatory functions of adipokines and their molecular mechanism provide a therapeutic target so that the reproductive health of obese or overweight individuals may be improved. Adipokines can deeply influence male reproduction by inducing low-grade systemic inflammation. Adipokines can be possible molecular targets for the treatment of obesity-induced male infertility. It is imperative to discover the molecular mechanisms which impact almost all levels of the reproductive function and thus, a more extensive study needs to be performed to comprehend the molecular mechanisms linking obesity to infertility. Since weight reduction along with modification of lifestyle is often a challenge, developing therapeutics for reproductive dysfunction for the betterment of reproductive health in obese subjects is essential. Till date, not all the corners of adipocytokine study has been explored and number of scientific evidences available are also inadequate; thus the scientific community needs to undergo more research in this field in order to understand the immune-modulatory role of adipokines.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest (academic, financial or otherwise) for publication of this work.

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