Cytokines and adipokines in the regulation of spermatogenesis and semen quality

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ABSTRACT

Male reproductive tract inflammation/infection possibly has a direct association with the occurrence of male infertility. Semen quality has been reported to be markedly reduced in conditions of male reproductive tract inflammation owing to functional or anatomical alterations in the reproductive tract such as accessory glands dysfunctions, obstructions in sperm transport, or spermatogenic disruptions by the inflammatory microenvironment. The severity of the inflammatory process and the level of impairment in male reproductive functions are associated with the roles played by individual inflammatory mediators, prominently the cytokines, adipokines and the reactive oxygen species (ROS). The mutual interactions of these biologically active substances originating mostly from the activated seminal leukocytes adversely affect testicular functions and deteriorate semen quality. However, several aspects regarding the association of inflammation, pro-inflammatory mediators and male infertility need to be clarified. Thus, the current review aims to present the roles of cytokines and adipokines in the context of understanding the mechanisms of inflammation-induced alterations in semen quality.

Keywords: adipokines; cytokines; inflammation; male infertility; reactive oxygen species; semen quality

INTRODUCTION

Male reproductive system inflammation has closely been associated with the occurrence of male infertility.1-5 Inflammatory processes in the male reproductive tract may lead to deterioration of semen quality via impairment in secretory functions of the male accessory glands, obstruction in the passage of sperm transfer and via induction of an overall inflammatory environment that eventually disrupts normal spermatogenesis.5-6 Studies on inflammation of the genitourinary tract have put forth that a possible mechanism by which semen infection can be linked to reduced semen quality, is an imbalance in seminal redox potential.7-9 It has been hypothesized when ROS in the seminal plasma overwhelms the antioxidant capacity to maintain their physiological level, it leads to induction of oxidative stress (OS).10-13 This condition is associated with inflammatory progressions that may be initiated by pathogen-induced male reproductive tract infections.14

Male reproductive tract infection has been suggested to follow a simplistic model consisting of several distinct phases.15 Invading and colonization of pathological bacteria in the reproductive tract and seminal infiltration of leukocytes represent the initial elements of inflammation.16 This is
generally followed by elicited seminal levels of ROS mainly originating from the infiltrated leukocytes and these lead to redox imbalance and onset of leukocyte-mediated phagocytosis.17 In the next stages, appropriate receptors are activated to stimulate various intracellular inflammatory signaling cascades which induce the production of inflammatory mediators, such as the proinflammatory cytokines.15 These in turn regulate the functions of pro-oxidative and anti-oxidative systems resulting in further ROS burst. The next phase is characterized by ROS-mediated oxidative damage in the spermatozoa. It is suggested that the seminal remnants of OS responses remain even after the eradication of infectious agent and these factors are responsible for further sperm dysfunctions.14

The tentative hypothesis of the association of male reproductive tract inflammation with deteriorated semen quality18-22, highlights the importance of knowing the exact mechanism how individual inflammatory mediators are involved in the process of impairment of male reproductive functions. Thus, this review article presents a concise update on the roles of cytokines and adipokines in inflammation-induced disruption of spermatogenesis and semen quality.

**MALE REPRODUCTIVE TRACT INFECTIONS: LEUCOCYTES, CYTOKINES AND ADIPOKINES**

Cytokines are cellular messengers that play key roles in many biological conditions such as immune defense and reproduction. In recent years analysis of seminal cytokines has begun to increase interest in various pathologies.23 Current studies are yet to show direct links between cytokines and male infertility. However, cytokines may be useful markers for diagnosis and monitoring therapy in patients with urogenital infection/inflammation.24 Extensive studies are needed to clarify whether a single cytokine or a combination of different cytokines is required to elicit different pathologies.

In subfertile males, negative correlations of seminal plasma leucocyte count with sperm concentration, motility, and morphology have been reported.15 Negative associations of number of neutrophilic granulocytes, sperm DNA integrity and basic sperm parameters have also been recorded.25 Similarly, an association between granulocyte elastase and cytokines was found in ejaculate and sperm DNA fragmentation.26-28 In addition to reduced sperm motility, due to infection and inflammation of the male genital tract, it also may have other adverse effects on important sperm functions.29 Oxidative damage in sperm, including DNA fragmentation caused by elevated levels of ROS in the ejaculate, may be caused by the leukocyte concentration which is far below the World Health Organization (WHO) threshold.29 Besides the leucocytes, the tissue macrophages contribute as a major source of proinflammatory cytokines.30

The role of infections and obesity in infertility has been reported times and over.31-33 Inflammatory cytokines are key immunoregulators in male genital canal infections, and in the process, affect the HPG axis. Infertility may occur as a result of modulation of the HPG axis regulation over testicular functions. However, the endocrine mechanism for infection-induced male infertility requires to clarify the issue with new studies. On the other hand, adipose tissue secretes various pro- and anti-inflammatory factors.34 In summary, these include leptin, adiponectin, resistin and visfatin as well as cytokines and chemokines, tumor necrosis factor-alpha (TNF- α), IL-6, monocyte chemoattractant protein-1.35 Increased proinflammatory molecules associated with obesity improve insulin resistance and increase the risk of cardiovascular disease.31,36 It is necessary to clarify the pathophysiology of changing adipokine levels in infection.

**CYTOKINES, ADIPOKINES AND SPERMATOGENESIS**

Fertility in men depends on the proper production of sperm cells, via spermatogenesis, which is very complex and involves the synchronization of many factors. The presence of proinflammatory cytokines, TNF- α, interleukin (IL)-1α and IL-1β in the male reproductive system, specifically in testes, epididymis and spermatozoa, have several significant physiological functions involving immunoregulation in the male reproductive tract.37 Both Sertoli and Leydig cells produce large amounts of the immunoregulatory cytokine, IL-6, driven by IL-1. Both these cytokines regulate Sertoli cell and germ cell development.38 Testicular germ cells can produce TNF which has a dual role as a signaling molecule, to regulate Sertoli cell function, in response to toxic insults, and its receptor-mediated functions.39 A number of the transforming growth factor β (TGFβ) superfamily members regulate testicular development which is critical for sperm development.40 Colony-stimulating factor-1 (CSF1) and macrophage migration inhibitory factor (MIF) are most significantly connected to macrophage and Leydig cell development within the testis.41 Interferons (IFN-α, β, and γ) are produced by numerous testicular cells, specifically during viral infections. While these are implicated in protecting the testis from virus infection, there is evidence that they regulate Sertoli cell and Leydig cell function as well.42 The seminiferous epithelium continues the process of spermatogenesis in the coordination with a diverse group of signaling molecules including these immunoregulatory cytokines.9 Detection of these molecules in distinct seminiferous tubule cross-sections implicates their significant role in sperm production and development. Studies also specify that they serve key roles in inter-compartmental intercellular communication, regulation of steroidogenesis, and immunoregulation.43-45

In addition to immunoregulatory cytokines, adipokines are also known to be involved in the regulation of spermatogenesis.46 Adipokines, produced by white adipose tissue, regulate the lipid and glucose metabolism and the inflammatory system. Leptin, a widely studied adipokine was shown to regulate reproductive functions by synchronizing the hypothalamus-pituitary-gonadal (HPG) axis at both the central and peripheral levels. Other adipokines such as adiponectin, obestatin, resistin, visfatin and the growth hormone secretagogue (GHS), peptic hormone ghrelin affect spermatogenesis.1, 47, 48
However, when the levels of these cytokines are higher than normal, as seen in the conditions of inflammation, it is damaging to sperm production. In addition, inflammation is also associated with oxidative stress (OS) and the latter is well known to impair sperm function. Epidemiological studies of male infertility have revealed that an increasing number of infertile men suffer from acute or chronic inflammation of the genitourinary system, which are usually asymptomatic. Inflammatory reactions in the male genital system are inevitably linked to OS. OS, specifically in sperm, is harmful because it damages sperm DNA and causes apoptosis of developing spermatozoa.

Inflammation and gland infections in the male genitourinary tract are regulated by inflammatory cytokines, which are also produced in the testes by Leydig and Sertoli cells and play a regulating role at the blood-testis barrier. Inflammatory cytokines also regulate spermatogenesis and affect testosterone production, acting at various levels of the HPG axis. Any imbalance in their production may result in infertility. Testicular macrophages, Sertoli and Leydig cells are thought to produce some cytokines. In studies, it is recommended that cytokine differences in fertile and infertile males be determined by identifying cytokines in leukocytospermia and revealing clinical markers.

Proinflammatory cytokines such as TNF-α and interferon-gamma (IFN-γ) have been described to be directly associated with disrupted spermatogenesis as they directly impair the seminiferous epithelium by damaging the expression and assembly of the junctional proteins leading to an impairment of the blood-testis barrier.

**EFFECT OF SEMINAL PLASMA CYTOKINES ON SEMEN QUALITY**

Various studies have demonstrated that cytokine levels increase in the seminal plasma of infertile males. Semen TNF-α and IFN-γ levels rise in males with inflammation were linked to infertility. Haney et al. reported no direct effect of TNF-α, IL1α, and IFN-γ on sperm motility in vitro. They have demonstrated the presence of IL2 and TNF-α in the ejaculate, however, they did not report any relation of these cytokines with sperm parameters. In addition, they have reported that IL2 concentrations in seminal fluids with identified bacterial agents were lower than in the control group, whereas TNF-α concentrations were not significantly different from the controls. Hill et al. reported significant antimotility effects when spermatozoa were incubated with IFN-γ and TNF-α. A negative correlation between IFN-γ and sperm concentration, motility, and morphology has been shown by Paradisi et al. Also, TNF-α levels were increased in the seminal plasma of oligozoospermic and asthenospermic patients.

A significant decline in sperm count, sperm motility, normal sperm morphology, and acrosin activity have been reported to be associated with TNF-α 308 gene polymorphism. The occurrence of A allele was significantly increased in infertile patients compared to fertile controls. An AA genotype of TNF-α corresponds more to a lowering sperm concentraion, motility, but with normal morphology. Moreover, TNFR1 36G allele has been found to be associated with oligozoospermia.

Anna Havrylyuk et al. and colleagues investigated blood and semen cytokines in infertile men. They evaluated pro and anti-inflammatory cytokine levels in 82 patients in subfertile and control groups. They concluded that IL-1B, IL-10, IL-18, TGF-B1, IFN-g should be investigated in serum and TGF-B1 should be investigated in specific types of male infertility in semen. The regulatory role of cytokines in the male genital system and its importance in infertility are still on the agenda as a research topic. There are many studies on the effects of seminal cytokines on human sperm function. The production of cytokines is increasing in the presence of foreign antigens in relation to pathogens and infections. In immunological defense mechanisms, proinflammatory

![Figure 1. Cytokine and adipokine-mediated male reproductive disruptions. GnRH, gonadotropin releasing hormone; LH, lutenizing hormone; FSH, follicle stimulating hormone](image-url)
cytokines, especially IL-1, IL-6 and TNF-α develop with primary or secondary signals. Lampiao and Du Plessis study, TNF-α and IL-6 increases Nitric oxide production in sperm and has a negative effect on progressive motility. IL-1 levels in semen have been shown to correlate with sperm membrane lipid peroxidation. Human sperm produce reactive oxygen derivatives against chemoattractant substances and also stimulate ROS production by leukocytes. The negative effects of reactive oxygen species on sperm function in humans have been shown in many studies.

Fedder and colleagues examined the effects of cytokines on sperm motility and ionophore stimulated acrosome reaction and found inhibition on sperm progressive motility. Researchers showed inhibitory effects on sperm motility in 5 out of 8 donors at high concentrations of recombinant cytokine, interferon. In the same study, they showed that reactive oxygen derivatives had similar effects but that this effect was not observed in the acrosomal reaction parameter.

MAJOR EFFECTS OF INFLAMMATORY CYTOKINES ON MALE REPRODUCTIVE FUNCTIONS

During male reproductive tract inflammation, cytokines play both pleiotropic and redundant roles in mediating the immune responses. For example, the initial inflammatory responses are stimulated by the actions of IL-6 and TNFα. Leukocytes are infiltrated in the seminal plasma and activated by IL-6 and as the number of seminal leukocytes increases, they lead to toxicity via induction of higher generation of ROS causing oxidative stress. TNFα is responsible for the induction of chemokine expression and germ cell apoptosis, thereby impairing spermatogenesis and sperm development. Neutrophil chemoattraction and infiltration into male reproductive tissues are also mediated by IL-8. Activated neutrophils initiate the process of phagocytosis. Several other essential roles of cytokines on male fertility parameters are reported. These include restructuring of blood–testis barrier by IL-1; association of IL-2 and IL-6 with dyspermia cases as it is found to negatively correlate with testosterone production by the Leydig cells, while it may amplify the negative feedback of testosterone over luteinizing hormone production by the anterior pituitary; increase in IL-4 in unexplained male infertility cases; negative correlation of IL-17 and IL-18 with sperm concentration and motility; association of IL-21 with sperm auto-antibodies production; and the role of interferons in unexplained male infertility cases.

ADIPOKINES FOUND TO BE EFFECTIVE IN THE REPRODUCTIVE SYSTEM

Leptin

Leptin, an adipokine mainly secreted by adipose tissue is widely studied in animals and humans. Leptin is present in testis and particularly in seminiferous tubules. Human seminal plasma leptin levels are positively correlated with serum leptin levels, but inversely with serum testosterone and sperm parameters. Elevated leptin level may negatively affect testosterone synthesis as it inhibits conversion of 17α-hydroxy progesterone into testosterone. In obese men high leptin levels correspond to male infertility mediated by leptin resistance or insufficiency at hypothalamus and modulation of testicular physiology. Mice and humans lacking leptin receptor have hypothalamic hypogonadism, which leads to delayed pubertal development and infertility.

Although different studies showed contradicting results, leptin affects sperm motility. Studies in which seminal plasma had high concentrations of leptin showed a negative correlation with sperm motility showed a negative correlation between seminal leptin and progressive and straight motility in 64 males. In this study, mean concentrations of seminal leptin were 1.5 ng/mL and 3.19 ng/mL in the ‘normozoospermic’ and ‘pathozoospermic’ groups respectively. Two other studies have shown a negative correlation between leptin concentrations in seminal plasma and progressive motility. Guo et al. found that seminal plasma leptin levels were higher in men with asthenospermia compared to controls. Ni et al. reported higher seminal plasma leptin levels in infertile patients with varicocele compared to control men. These data suggest deleterious effects of high seminal leptin concentrations which are often associated with spermatic pathologies.

In two other studies, in which patients had relatively low leptin concentrations there was no correlation between seminal plasma leptin levels and sperm motility. Leisegang K et al. found no correlation between seminal leptin and sperm motility. However, in this study, seminal leptin levels were higher in the obese group (12.5 ng/mL in the obese group, 5 ng/mL in the nonobese group), and sperm motility was significantly lower than the nonobese group. Thus, it may be suggested that, at high concentrations, leptin in seminal plasma is associated with a decrease in sperm motility, whereas at lower/ physiological concentrations, leptin may either have a beneficial effect on motility or have no effect.

Ghrelin

Ghrelin is a 28-amino acid peptide, it is primarily expressed in the hypothalamus and has been found to affect growth hormone secretion. It has also been observed that it plays an important role in stimulating food intake and in the development of central neuroendocrine activity and adipose tissue. It has been found that ghrelin is an endocrine, paracrine and autocrine regulator in human testis and there is no study on its activity and direct effect on spermatogenesis. It is also a multifunctional peptide hormone that affects several biological functions including regulation of food intake, sleep, body weight, gastrointestinal motility, cardiovascular functions, cell proliferation, production of proinflammatory cytokines, and reproduction in many species. Ghrelin and its receptor GHS-R1a are expressed in both male and female reproductive organs. Besides adipokines, ghrelin is suggested to play a role in the regulation and control of reproduction. Ghrelin is also present in the human testis and particularly in Leydig and Sertoli cells but not in germ cells. In human testis, the expression of ghrelin by Leydig cells is inversely correlated with the serum testosterone levels in patients with normozoospermia, obstructive azoospermia, or varicocele suggesting that ghrelin
has an indirect effect on spermatogenesis. Gherelin has been shown to cause immature Leydig cell proliferation in vitro, but has an inhibitory effect at increased growth hormone concentrations. Studies remind Gherelin’s role as a regulator on spermatogenesis.

Adiponectin

Adiponectin seems to have a positive effect on sperm parameters. In a study investigating the relationship between seminal adiponectin concentrations and sperm parameters in humans, adiponectin levels in seminal plasma were positively correlated with sperm concentration, sperm count, and percentage of typical sperm forms. Adiponectin polymorphism has been not described in relation to male infertility. According to the study of Elfassy et al., Adipokines may be a link between metabolic syndrome (MS) and infertility. While the relationship between circulating adipokines and fertility in women has been extensively studied, although some adipokines can be detected in seminal plasma, this relationship has been less studied in men. The duration of infertility was higher in men without Metabolic Syndrome. Adipokine concentrations were higher in blood than seminal plasma, except for IL-6 and visfatin. The most striking result was the significant correlation between seminal IL-6 and spermatozooid concentration, progressive motility and sperm viability. In addition, men with MS exhibited lower adiponectinemia than expected, while SP showed 2.1 times higher levels of adiponectin than men without MS. Finally, logistic regression analysis showed that BMI, infertility time, and adiponectin serum/SP ratio were independently associated with MS.

Other adipokines such as resistin or chemerin would have a rather deleterious effect on spermatogenesis: when resistin and chemerin are increased sperm motility decreases.

Visfatin/NAMPT (nicotinamide phosphoribosyltransferase) was originally cloned from a human peripheral blood lymphocyte cDNA library in 1994 as a cytokine called pre-cell colony enhancing factor (PBEF). Although it is commonly expressed in human bone marrow, liver, and muscles in human PBEF, it has expression everywhere. In 2001, a study identified the nadV gene; Its presence allows independent growth of Haemophilus influenza and Actinobacillus pleuropneumoniae due to the presence of nicotinamide adenine dinucleotide (NAD). The authors found that NadV had significant sequence homology with PBEF, thereby suggesting a new role for PBEF in NAD biosynthesis. It has also been described as visfatin, cytokine hormone and an enzyme that plays a role in metabolic (obesity, type II diabetes) and immune disorders. Visfatin plasma concentrations in humans show positive correlation with obesity measurements. Protein expression of iNAMPT in mice is highest in brown adipose tissue (BAT) and in the liver and kidneys, moderate in the heart, white adipose tissue (WAT), and in the lungs, spleen, testicle and skeleton. Below detectable levels in muscle and pancreas and brain. Although the function of INAMPT is firmly constructed as an NAD biosynthetic enzyme and has an important role in circuim activation in mitochondria, the function of eNAMPT is controvertical. eNAMPT is released by a number of normal cell types, such as adipocytes, hepatocytes, myocytes, pancreatic cells, neurons, and immune cells. It has also been shown that eNAMPT is released by cancer cells under pathological conditions and can be used as a marker for cancer development.
Visfatin, also known as nicotinamide phosphoribosyltransferase (NAMPT) is involved in the regulation of human ovarian follicle and is shown to be involved in follicular growth, maturation of oocytes and ovulation in humans. It has also been found in Leydig cells, spermatoocytes, and spermatozoa. Seminal plasma blood level ratio of visfatin indicates local production in the male genital tract, however its role in spermatogenesis is not yet reported in humans.

Two recently discovered adipokines are vaspin, a serine protease inhibitor with insulin sensitizing effects. It is found in the VAT of the OLETF (Otsuka Long-Evans Tokushima Fatty) rat, an animal model characterized by central obesity and T2DM. Both circulating and adipocyte vaspin levels were found to be significantly increased in OLETF rats at 30 weeks when obesity and insulin resistance peaked. While uncontrolled diabetes and weight loss reduced vaspin expression, administration of insulin sensitizers such as pioglitazone normalized expression and serum concentration. Recombinant vaspin administration in DIO (diet-induced obesity) mice significantly improved glucose tolerance and insulin sensitivity. This beneficial effect results in normalizing plasma glucose levels and altering the expression of genes involved in the pathogenesis of insulin resistance such as resistin, leptin, TNFα, glucose transporter-4, and adiponectin. Based on these data, it has been assumed that vaspin acts as an insulin sensitizer with anti-inflammatory effects and can act as a compensatory mechanism with target white adipose tissue (WAT), which is activated in response to decreased insulin sensitivity.

Vaspin is expressed in epididymal, retroperitoneal, and mesenteric adipose tissue and is related to the metabolic state. Thomas et al. showed that seminal plasma vaspin was negatively correlated with ejaculate volume and positively correlated with sperm DNA fragmentation.

Progranulin
Progranulin is increased in cases of obesity or metabolic syndrome and could contribute to the inflammatory mechanisms found in certain pathologies demonstrated that progranulin was positively correlated with sperm motility, sperm count and sperm morphology. In vasectomized patients, progranulin levels in semen were significantly decreased indicating probable local secretion. The presence of progranulin in the male reproductive tract was firstly described in guinea pig reproductive tract compared with peripheral blood and they suggested that it could affect sperm functionality. There is currently much unknown about omentin’s role in male infertility.

Ismail et al. demonstrated that the concentration of omentin-1 was significantly higher in seminal plasma than in serum. Semen and serum Omentin-1 positively correlated with sperm concentration and percentage of progressive motility and were negatively correlated with percentage of abnormal forms, DNA fragmentation index (DFI) and ROS. The mean serum level of omentin-1 was significantly decreased in patients with varicocele. Both serum and seminal omentin-1 levels were significantly lower in infertile patients than fertile men. In cases of leukocytospermia and smoking, seminal omentin-1 concentrations were decreased, suggesting that it may play a regulatory role in inflammation of the male reproductive system.

CONCLUSION
There are many unknowns in the relation of cytokines and adipokines with male reproductive tract infections and in the spermatogenesis process. In the process of spermatogenesis, proinflammatory cytokines secreted in the testis and epididymis (TNFα, IL-1α and IL-1β) have been produced. It regulates the development and physiology of sertoli and germ cells. In addition, TGF, CSF1, MIF, IFNα, IL-6, IL-10 and IL-12 contribute to the regulation of spermatogenesis. Adipokines play a role as a regulator in spermatogenesis process. However, they have a detrimental effect on spermatogenesis with increasing serum concentrations in infections. With the new studies, there are many issues to be clarified about the physiology and physiopathology of seminal, testicular cytokines and adipokines.

Conflict of Interest
The authors declare no conflict of interests.

REFERENCES
27. M. Panner Selvam, P. Sengupta, A. Agarwal. Sperm DNA
23. O. Theam, S. Dutta, P. Sengupta. Role of leukocytes in reproductive
25. A. Micillo, M. Vassallo, G. Cordeschi, S. D’andrea, S. Necozone, F.
Chemical Biology Letters
10.5534/wjmh.190145.


73. L.-F. An, X.-H. Zhang, X.-T. Sun, L.-H. Zhao, S. Li, W.-H. Wang. Unexplained infertility patients have increased serum IL-2, IL-4, IL-6, IL-8, IL-21, TNFα, IFNy and increased Th1/CD4 3 T cell ratio: Increased Th1 and IL-21 strongly correlate with presence of autoantibodies. Immunol. Invest. 2015, 44(2), 164-173.


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