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LETTERS

Impact of altered Energy metabolism and Immune regulation in reproductive health of Aged Men

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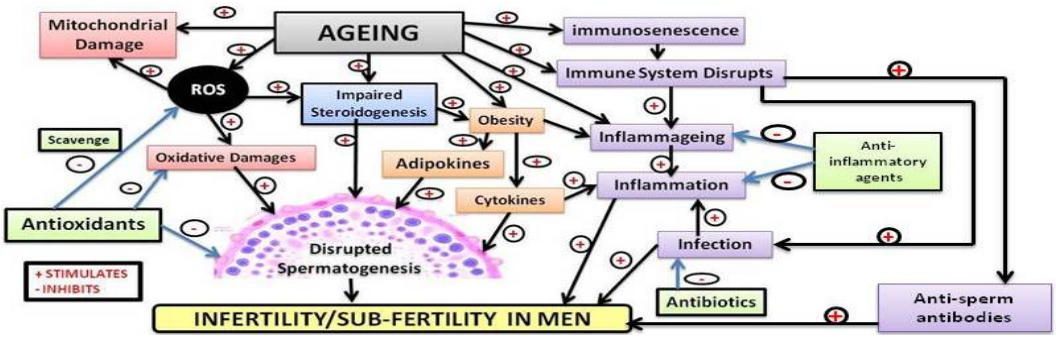
Review Article

ABSTRACT



The age of having a first child has increased all around the world. With advancing age, the reproductive system encounters several complications in both males and females. With increasing age in men, increased mitochondrial damage increases, oxidative stress, leading to disruption of immune system. All these are closely associated with one another, and together contribute to age-induced reproductive dysfunctions in men. Changes associated with ageing in men adversely affect steroidogenesis and spermatogenesis. Immunosenescence causes the altered immunoregulation and accounts for diminished quality and quantity of sperms in men. Various factors like the interaction of sex hormones with environment and genetic factors are the determinants of immune status in an individual. With ageing increased inflammation of the male urogenital tract is also known to account for infertility in men. Further, cytokines and adipokines in age induced obesity adversely effects fertility in men. Thus, there exists an axis connecting age, energy metabolism, sex hormones, immunity and reproductive health. The aim of this review article is to brief the role of various immunoregulatory factors associated with ageing and the impact of age-induced changes in energy metabolism on male reproductive health. Administration of antioxidants or anti-inflammatory agents separately or in combination may be beneficial in treating or mitigating age induced infertility in men.

Keywords: Energy metabolism, hormones, immune regulation, reproductive health, sperm

INTRODUCTION

Ageing causes several changes in the physiological system.[1,2] Besides its impact on the cardiovascular system, respiratory system, nervous system, digestive system etc., ageing also has a significant impact on the reproductive system in both males and females.[3,4] Increased age of marriage and childbearing has come up with issues of difficulties in having a healthy child and infertility.[5, 6] The impairment of reproductive health and its effect on infertility and child health is well known but age mediated impairment of male reproductive health is now yet well established. There have been some studies related to male reproductive health impairment with ageing and studies around the world are in progress. Certain interesting and useful information have been revealed with those studies. With ageing, the occurrence of reduced sperm chromatin quality and damaged DNA in sperm etc. are reported. Studies reveal that ageing causes significant detrimental changes in male reproductive health which includes changes in semen, altered testicular morphology and function, reduced sperm count, hormonal changes, damages in sperm DNA etc.[7] Changes in semen quality due to ageing include improper spermatogenesis, reduced sperm motility and reduced sperm viability.[8,9] On the other hand, remarkable changes in the testis are also noticed with ageing. Testicular volume is reduced, testicular vascularization is altered adversely, changes in Sertoli cells and Leydig cells are also reported to be associated with ageing in men. Ageing is known to have a normal physiological decay of reproductive tissues and organs and thus

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causes an overall effect on the reproductive health.[3,4] Aged men are also known to have prostate disorders and erectile dysfunctions.[10]

The underlying story of all those changes in male reproductive health with ageing is associated with age mediated altered energy metabolism and changed immune regulation due to ageing. In this context, mitochondria are the key player. Mitochondria are considered to be the centre of cellular events that leads to ageing. Mitochondrial energy metabolism is reported to be one of the most important factors influencing male reproductive health.[11] Studies reveal that with ageing levels of Nicotinamide Adenine Dinucleotide (NAD) declines in body and this is considered to be responsible for reduced metabolism in the body. This in turn may be the reason for altered energy metabolism, reduced hormonal synthesis in ageing men leading to reduced testicular volume and low-quality sperm production.[11,12] The volume of testis decreases from 60 years of age in men. It is reported that in males more than 75 years of age, the testicular volume decreases almost 70% compared to that in young men.[12]

Immune regulation is also known to alter with ageing and to influence reproductive health in aged men. Interestingly, change in energy metabolism is correlated with altered immune regulation associated with ageing. Studies show that an immune tolerant microenvironment for spermatozoa is maintained in the male reproductive tract by the blood-testis barrier and the biomolecules present in semen. The biomolecules present in semen are necessary also for maintaining the same immune tolerant microenvironment for sperm cells when they travel in the female reproductive tract. The immune tolerant microenvironment of the testis can be affected and altered by exposure to environmental contaminants, toxic pollutants, infections and inflammatory conditions. This may affect fertility adversely and significantly.[13] Loss of germ cells in testis with ageing is observed and it is considered to occur due to decreased formation of the proteins which maintain the blood-testis barrier (BTB) junction. Seminiferous epithelial and germ cells are joined together by the cell junctions and thus help in the formation of the BTB. This BTB protects the germ cells. Age mediated decrease in expression of proteins leads to the gradual collapse of BTB allowing immune cells and harmful biomolecules to cross the BTB which results in disruption of spermatogenesis and may also be responsible for damage of germ cells.[14] Also, certain biomolecules have been recognized to be associated with the immune tolerance of spermatozoa.[15]

Alterations in testicular structure and function with increasing age under the influence of reduced sex hormones and altered energy metabolism is known but the exact mechanism involved in the changes in fertility in ageing men are yet to be understood completely. In this review we are trying to connect the links and pave a clear pathway connecting energy metabolism, immune regulation and reproductive health in aged men.

Altered Energy Metabolism and Reproduction in Aged Men

With ageing, loss of gonadal function and several physiological changes are reported in both women and men.[16] This is termed late-onset hypogonadism (LOH).[17] LOH comprises several symptoms of including loss of libido, loss of erectile function, loss of testicular function, increased visceral fat, increasing depression, anemia, loss of muscle and bone mass, sweating, hot flushes etc.[17] Ageing significantly alters energy metabolism in both males and females. Changes in energy metabolism are considered directly or indirectly responsible for the LOH.[17, 18] NAD, mitochondria and changes in ROS production and intracellular antioxidant status work all together to bring about the alterations of energy metabolism in ageing men. This altered energy metabolism with advanced age in man adversely affects his reproductive health and causes infertility and other associated problems.

Mitochondria and reproductive health of ageing men

Mitochondria play an important role in maintaining a healthy male reproductive system. Age mediated decline in mitochondrial function is also an important contributor to decreased fertility with ageing.[19] Studies show that oxidative stress-mediated damages in the mitochondria causes alteration in energy metabolism in mitochondria. But oxidative stress-related changes in the ageing mitochondria are not the only factors responsible for altered mitochondrial energy metabolism and subsequently reduced fertility in ageing male individuals, rather other factors like changes in mitochondrial DNA leading to changes in production of mitochondrial testosterone plays significant role in declining reproductive health in ageing men[14,19] (Figure 1).

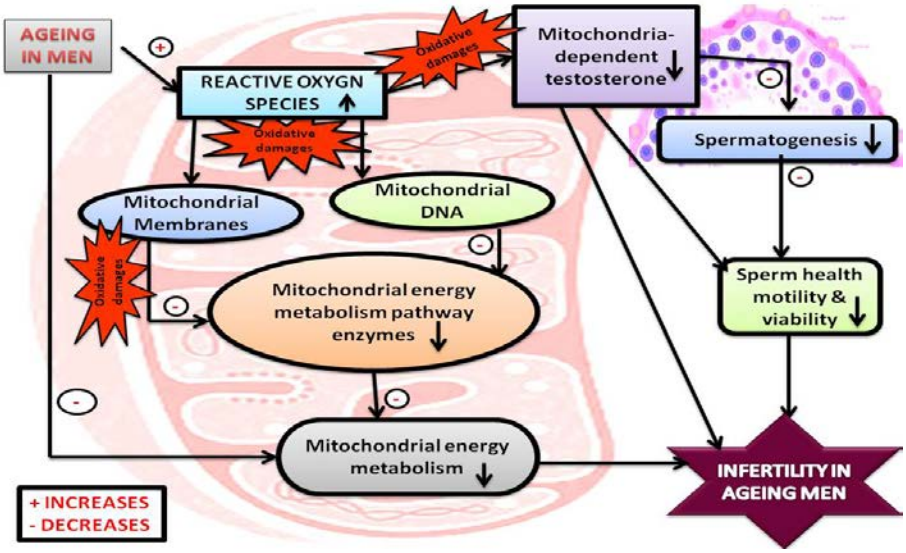

Figure 1. The mechanism of reduced mitochondrial function-mediated infertility in aging men.

Mitochondrial energy metabolism is associated with sperm motility. ATP is found to be extremely important for the motility of sperm. Those ATPs are generated by mitochondrial oxidative phosphorylation.

With ageing ATP generation is diminished and impacts sperm motility. Studies show that transport of metabolites to and from mitochondria is affected by ageing. Also, mitochondrial DNA being near the electron transport chain (ETC), the Reactive Oxygen Species generated and leaked from ETC easily damages mitochondrial DNA.[20,21] With ageing ROS generation is increased and as a result, ROS mediated damage to mitochondrial DNA, membranes of the chambers of mitochondria etc., increases with ageing (Figure 1). The overall outcome is that mitochondrial ATP production decreases with advanced ageing.

During spermatogenesis a significant change that occurs in the metabolism of germ cells. The germ cell of an adult testis depends on glycolysis and oxidative phosphorylation that occurs in the mitochondria. Numerous mitochondria are observed to be present in testicular germ cells revealing their significance in testicular metabolism. Studies show that spermatogonia, mature sperm and somatic Sertoli cells have high glycolytic activity. On the other hand, the major source of energy in spermatids and spermatocyte is oxidative phosphorylation.

Mitochondria dependent testosterone production is adversely affected with increasing age in men. Significant changes in the Leydig cells are observed with ageing. Some of those age-induced changes in Leydig cells include changes in the delivery of cholesterol into the mitochondria. Within Leydig cells, mitochondria play an important role in regulating steroidogenesis, which involve StAR (steroidogenic acute regulatory protein)-mediated delivery of free cholesterol to the inner membrane of mitochondria where cholesterol is converted to testosterone through series of biochemical conversions.[14, 19] Thus, mitochondria-dependent testosterone synthesis is involved in age associated deteriorative changes in man's reproductive health.[23, 24]

ROS leaks from mitochondrial chambers during that oxidative phosphorylation and are related to oxidative stress-mediated ageing of cells. Oxidative damage to sperm mitochondria and sperm membrane is also reported and leads to male infertility.[25] Thus, energy metabolism plays a significant role in relation to reproductive health in ageing men[20] (Figure 1).

Mitochondria, estrogen and infertility in ageing men

Changes in Leydig cells in ageing males includes the fact that with ageing in men, reduced transfer of cholesterol which is a precursor for hormone synthesis occurs. Thus, testosterone production decreases which simultaneously reduces level of estrogen which is actually synthesized from testosterone. Physiological level of estrogen in the male reproductive tract is known to have a protective effect on male reproductive health and reduces inflammation. Thus, reduced estrogen results in reduced protection of testis and leads to eventual testicular atrophy in ageing men.[27, 28] This reduced testosterone can actually cause impaired and reduced spermatogenesis in ageing men. Also, increased ROS generation in ageing men imposes risk for oxidative damage to cellular DNA in Leydig cells responsible for the synthesis of the aromatase enzyme in men. Also, ROS may cause direct damage to the enzyme aromatase in ageing men. Thus, defective production or damaged aromatase may impair steroidogenesis and lead to reduced or impaired spermatogenesis and infertility in ageing men.[28] Those changes occur in Leydig cells naturally as a part of the ageing process in men and those together contribute to age induced infertility in men.[28]

NAD and its impact on reproductive health of ageing men

With ageing, NAD decreases and that causes alteration in testicular volume. NAD occurs in various forms inside cells. Those various forms of NAD are NAD, NADH, NADP+, NADPH etc. These act as coenzymes of various important enzymes of metabolic pathways including TCA, ETC etc. Thus, NAD is associated with energy metabolism regulation in our body. Also, NAD is the substrate for certain enzymes like CD38, SARM1, sirtuins and enzymes of the poly(ADP-ribose) polymerase (PARP) family.[29-31] With ageing, the oxidized form of NAD (NAD+) is decreased significantly compared to that of the reduced form of NAD (NADH). This causes an imbalance in the redox potential of cells.[31, 32]

Due to ageing, the hypothalamus-pituitary-gonadal axis is changed. Studies reveal that NAD and sirtuins have a regulatory impact on hypothalamus. Reduced NAD in ageing men causes derogation of hypothalamus.[33] Leydig cells' ability is reduced with ageing. Thus, testosterone level decreases in the blood of ageing men while on the other hand this condition stimulates feedback loop and as a result level of follicle stimulating hormone (FSH) and luteinizing hormone (LH) increases in blood of aged men. Testosterone metabolites like estradiol and inhibin are observed to be lowered in such aged men's blood. Estradiol and inhibin are the factors involved in negative feedback loop control. Interestingly, studies show that lowered level of NAD with ageing is the prime contributor to dysregulation of the hypothalamus.[34] NAD is considered the main regulator of all biochemical processes in the human body.[35]

It is also observed that with ageing, the level of antioxidant endogenous enzymes namely superoxide dismutase, catalase gets decreased leading to a redox imbalance in those cells. Glutathione is a key player in maintaining our cellular redox balance. Glutathione occurs in reduced form (GSH) in cells which is an antioxidant and is capable of scavenging free radicals from the cellular environment and in turn, the glutathione gets oxidized[35]. A net balance is maintained between this oxidized form of glutathione (GSSG) and reduced glutathione (GSH) by the enzymes Glutathione Reductase (GR) and Glutathione Peroxidase. As an outcome GSH level is always maintained higher than that of GSSG. Glutathione Reductase is directly dependent on the levels of NADPH in cell. NADPH is formed from NAD. With ageing these NAD and NADH levels are reduced leading to reduced activity of Glutathione reductase and this leads to an increased level of GSSG compared to that of GSH in cell. This causes generation of Reactive Oxygen Species (ROS) in excess in cell and leads to oxidative stress mediated oxidative damage in testicular cells. Increased ROS damages DNA of germ cells impairs steroidogenesis and also damages germ cells.[36] Similarly, ROS mediated oxidative damage occurs

in spermatogonial cells at stages and affects spermatogenesis adversely in ageing men. Low level of testosterone also affects spermatogenesis. As a result of which low sperm concentration (oligospermia), poor sperm motility (asthenospermia) abnormal morphology of sperm (teratospermia) etc., are observed in aged men.[37] With ageing damage of DNA in sperm is also reported to be increased leading to altered morphology of spermatocytes.

IMMUNE REGULATION & REPRODUCTION IN AGED MEN

Infertility in men is related to certain immune components. Certain proteins which are allogenic spermatozoa specific proteins, affect sperm kinematics. This leads to immune infertility. About 18% of infertile males reported to have idiopathic infertility are known to carry anti-sperm antibodies.[38] Sperm specific antigens are immunogenic in men. All men do not produce antibodies to their own sperm.[29] Evolution of immune system has occurred to suppress this autoimmunity to own sperm. The tight junctions between adjacent Sertoli cells (which is a part of the BTB) prevent sperms from getting in contact with immune cells.[29] In some places, though the barrier is thin and may cause interaction of sperm and immune cells leading to the formation of anti-sperm antibodies. Studies reveal that there are some immune molecules that originate in the testis and travel in the seminal fluid up into the uterine cavity up to the fallopian tube and helps in fertilization and embryo formation.[38] Unlike in circulation in other parts of the body, CD8+ T suppressor/cytotoxic T lymphocytes are profuse in circulation in epididymis and vas deferens.[36]

Disruption of the immune system occurs with advancing age and this phenomenon is termed immunosenescence. This increases the chance of infection and inflammation in the male reproductive tract with increasing age. Reproductive tract infection has a direct relationship with diminished semen quality and infertility in men.[31] The inflammatory microenvironment in the male reproductive tract is known to cause functional and anatomical changes therein and ultimately leads to poor sperm quality. Poor sperm quality is often associated with inflammation in male reproductive tract. In this regard, the prime inflammatory mediators namely, adipokines, cytokines and ROS are considered accountable for determining the severity of inflammation in the male reproductive tract and are thus the key players responsible for inflammation induced infertility in men.[40] Studies reveal that during the inflammatory conditions, leucocyte count in the seminal fluid increases and is activated. This leads to leukocytospermia.[40, 41] Leukocyte induced ROS production leads to ROS-mediated increased level of lipid peroxidation in sperm cell membranes and disrupts the membrane integrity of sperm cells.[39] Similarly, Leukocyte induced ROS production also damages DNA and other cellular components of spermatocytes. All these taken together causes reduced semen quality in men and is the connecting link between leukocyte induced male infertility.[40] With immunosenescence in ageing men, risk and chances of inflammation and inflammation-induced increased production leukocyte increases and those factors can thus be directly considered to be responsible for age-induced reduced semen quality and infertility in men.[42-44]

NAD, Ageing, Immunity and Infertility in men

Studies reveal that with ageing immune system disrupts.[39] With ageing, decreased NAD mediated oxidative onslaught in the testis leads to damage of some of the various cellular components of the testis. This includes damage of Leydig cells and their organelles which leads to defective steroidogenesis and lower formation of testosterone and estrogen. This alteration in sex steroid concentration and also sex steroid receptor interactions, leads to dysregulation of the immune system in ageing men leading to dysregulation of the protective immunosuppressing mechanism in the male genital tract. This may actually destroy the immune suppressor adaptations in the male genital tract, testis and epididymis and cause the production of anti-sperm antibodies in ageing male leading to idiopathic infertility.[45] Also, oxidative damage of the BTB may cause sperm immune cell interactions leading to immune reactions and the formation of anti-sperm antibodies in aged men.

Hsps, gammasigma T cells and infertility in ageing men

Infection of the male genital tract or any of the male reproductive organs can cause inflammation and immunomodulation and lead to infection induced infertility.[35,36] With ageing immunity is reduced and hence chances of infection mediated inflammation induced male infertility increases in ageing men. Heat shock proteins (Hsps) are known to be associated with infection and the formation of anti-sperm antibodies. Hsps are found to be present in semen. Transcription of Hsps genes not only inhibits genes which code for proinflammatory cytokines but also activates gammasigma T cells. Activated gammasigma T cells induces transcription of HSPs genes in turn. T cells having gammasigma type of receptor antigens are known as gammasigma T cells. And these gammasigma T cells are found to be abundantly present in semen and male reproductive tract and they are found to be activated in men with reported sperm autoimmunity.[45] Probably with ageing there occurs a disruption in this balance of HSPs and gammasigma T cell activation which leads to enhanced sperm autoimmunity in ageing men which impacts fertility in them adversely. Studies also reveal cross reactivity of antigens on human sperm and antigens on T lymphocytes.[35]

Immune cell population and infertility in ageing men

Ageing is reported to alter the population of various immune cells in the reproductive tract of females.[46,47] Though there is no detailed report of such alteration in male reproductive tract but, changes in immune environment that occurs in the reproductive tract of ageing men suggests a possibility of changes in the population of immune cells in male reproductive tract. Damaged spermatocytes are devoured and removed regularly by phagocytic immune cells in the reproductive tract of men. Alteration in immune cell population in ageing men's reproductive tract may cause less and inefficient removal of defective spermatocytes and as a result, defective spermatocytes increase in the semen of ageing men[47] (Figure 2).

Studies reveal that with ageing the population of CD4+ and CD8+ cells decline in both men and women. Interestingly, the population of the NK cells and Tregs were found to be more in aged men were more than that in aged women.[47] Testosterone is

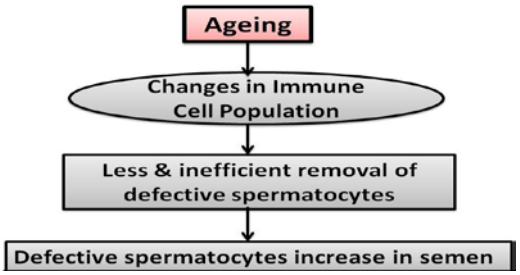

Figure 2. The age-induced immune cell population alteration mediated increase in defective spermatocyte in semen.

known to have an augmenting effect on Th1 response and activation of CD8 cells and a down-regulating effect on response of the NK cells and TNF-α. Testosterone also increases the production of anti-inflammatory IL-10.[48]

Leukocyte and monocyte subpopulations in aged males and females are reported to express different levels of receptors.[49, 50] Studies show more expression of CD38 in males. Testosterone is known to impose an immunosuppression impact on inflammatory cytokines production. Thus, a decrease in the level of testosterone with ageing increases chances of infection in male genital tract and is associated with an increase in serum soluble IL-6.[51]

Other immune changes associated with ageing & infertility

The immunocompromised state due to ageing in humans is related to the evolution of mankind. During reproductive years, the immune system remains sensitive which is necessary for maintaining good reproductive health. Whereas, with ageing the immune system gradually disrupts and becomes less responsive and sensitive compared to that of men of reproductive age.[43] Studies conducted on house mouse revealed that ageing causes increase in apoptosis in certain parts of the male genital tract. Induction of apoptosis was observed in epididymis and ventral prostate of ageing male experimental animals. [52] With ageing apoptosis is known to increase in testis also leading to damage of germ cells there and damage of Leydig cells leading to reduced production of testosterone and defective spermatogenesis. All these taken together are responsible for diminished fertility in ageing men.[53,54]

With a total immunocompromisation with ageing, chances of reproductive tract infection and inflammation increases which is turn is known to induce infertility in men.[32,33]

Interestingly some genes are reported to have shared effects on sperm and immunity in men. Effect of ageing on the expression of those pleiotropic genes are the inevitable cause of the correlation between the disruption of immunity in ageing men and production of non-viable, defective and reduced number of spermatocytes.[55]

Studies show that the immune system is related and dependent on energy metabolism. Studies conducted on humans showed that long term nutrients and calorie restriction and also intense physical exercise causes immune suppression.[56-58] Interestingly, supplementation of nutrients and calorie helps to prevent age related reduction in immunity.[59]

Obesity in Ageing Men, Infertility/Subfertility and Immune System

Obesity is known to be associated with infertility in men.[60-63] Various factors like endocrinopathy, sexual dysfunction, psychological and thermal effects, sleep apnea, leptin, minor toxins etc., are some of the factors responsible for obesity induced infertility in men.[64,65] Among these, inflammation and endocrine factors are the major contributors of infertility in obese men.[66-68] With ageing in men changes in energy intake and total energy expenditure causes obesity. Also reduced secretion of growth hormone (GH), LOH, altered insulin action, hormonal changes and changes in the adipokines leads to age induced obesity. Some of these adipokines are appetite related peptides play multiple roles in our body.[69] Several studies reveal that presence of immunomodulatory cytokines like TNF-α, interleukin (IL)-1α , IL-1β , IL-6 etc., in the male reproductive tract and some organs of the male reproductive system plays significant role in regulation of the complex process of spermatogenesis and maintaining the immune-microenvironment in male reproductive tract.[69] Also, Adipokines, which are produced by white adipose tissues is known to have a regulatory role in spermatogenesis. Adipokines regulate the inflammatory system and metabolism of lipid and glucose. Leptin which is an adipokine is known to synchronize the hypothalamus pituitary gonadal axis (HPG) at central and peripheral levels and thus controls the functions of the reproductive system.[65] Adiponectin, another well studied adipokine is reported to cause infertility in men.[70] Several other adipokines namely, resistin, visfatin, obestatin, the growth hormone secretagogue (GHS), ghrelin etc. are reported to affect spermatogenesis.[69]

The major reproductive hormones play important roles in regulation of infertility in ageing men.[71-73] Inflammatory cytokines are known to affect the Leydig cells and thus affect synthesis and secretion of testosterone, the prime regulatory hormone of spermatogenesis in men. Adipokines released from the adipocytes in obese men are known to affect and disrupt the HPG axis and cause infertility in men.[74] Also, estradiol has a critical role in regulation of metabolism in men. Studies reveal that in men with increasing obesity, activity of aromatase increases. Aromatase is the enzyme that irreversibly converts testosterone to estradiol.[75] Thus, with obesity the level of estrogen increases in men. Increased level of estrogen is known to disrupt the process of spermatogenesis in men and is thus responsible for production of defective and nonviable sperms and cause infertility in obese men.[75] With ageing, changes in metabolism and energy management increases accumulation of fat in adipocytes and the tendency of central obesity increases. Thus, obesity mediated estradiol induced infertility increases in men with increasing age. On the other hand, increased production of ROS by adipocytes causes germ cell apoptosis. ROS induced damage to various cellular and subcellular components of spermatocytes and germ cells leads to infertility in men.[76]

Inflammation and infertility in aged men

Ageing is known to be associated with mild chronic proinflammatory conditions. This phenomenon is termed as ‘inflammaging’.[77, 78] Infections in the male reproductive tract are

reported to lead to male infertility. [25, 32] Prostatitis, epididymitis and orchitis are some of the infectious conditions of the male reproductive system that are known to be associated with infertility in men.[79] A matter of concern is that chronic inflammatory state in male urogenital tract may remain asymptomatic at times. With increasing age, chances of inflammation in male reproductive tract increases.[39] Inflammatory changes are observed commonly in male reproductive tract with advancing age in men. A strong relationship between inflammation in male urogenital tract and infertility in men is known.[79] Inflammaging is considered as an indicator of age-related pathogenesis and age-related development of diseases.[77,78] Incidence of inflammation in male reproductive tract is known to vary greatly among elderly men. Ageing thus being proinflammatory, causes mitochondrial deteriorative changes, oxidative stress mediated damages, endocrinosenescence and immunosenescence.[80,81] These changes associated with ageing causes impairment of spermatogenesis and damages sperms and accounts for infertility in ageing men[39]. Thus, inflammation is deeply associated with infertility in aged men.

Antioxidants / Anti-Inflammatory Agents and the Fertility of Aged Men

As it is evident, with advanced ageing, generation of ROS, oxidative stress mediated oxidative damages and inflammation in various parts of the male reproductive tract causes infertility in men. Administration of antioxidants, anti-inflammatory drugs and combination of antioxidants, antibiotics have been reported to be effective in treating various infections, inflammatory conditions, and inflammation related complications.[82-88] Use of antioxidants in combination with other nonhormonal drugs have been found to be beneficial in improving semen quality and treat infertility in men.[87,89]

In some infertility cases, supplementation of antioxidants, antibiotics, anti-inflammatory drugs and vitamins have been reported to be effective in improving certain fertility parameters. Antioxidants administered singly or in combination with other antioxidants have been reported to be effective in treating idiopathic infertility in men.[90-93]

Carotenoid, the precursor of Vitamin A is known to control spermatogenesis. Dietary deficiency of carotenoid which is known to have radical scavenging potential has been reported to be associated with impaired spermatogenesis.[92] Low sperm count and infertility in men. Supplementation of vitamins like antioxidant vitamins, namely, Vitamin E and vitamin C are reported to improve certain parameters of fertility in men.[90-92] Supplementation of various antioxidants has been reported to improve infertility in men. Various parameters like sperm concentration, sperm motility, vitality and morphology are known to be improved with antioxidant supplementation. Antibiotic supplementation helps to heal infection in male reproductive tract and thus ameliorates infection induced infertility in men. Anti-inflammatory drugs also help to improve inflammatory conditions in male reproductive tract and mitigates inflammation induced infertility in men. Combination of all these antioxidants, antibiotics and anti-inflammatory agents are expected to act synergistically and have better healing effect on infection/inflammation induced infertility in men. Antioxidants scavenge free radicals and thus mitigate oxidative damages[86]. Supplementation of antioxidants are known to ameliorate various age-induced ROS mediated oxidative damages in man. Antioxidants are also involved in redox modulation of inflammation.[93] Thus, we can consider antioxidants, antibiotics and anti-inflammatory agents combinatorial supplementation therapy[94] for treating age-induced ROS mediated infertility in ageing men.[95]

Conclusion

Male infertility is actually a multifactorial, heterogeneous condition and affects more than 30 million men around the globe. With advancing age, inhuman, the volume of semen declines. As semen volume is one of the determinants of fertility in men, reduction in semen quantity and quality is correlated with infertility in aged men. Ageing is considered a pro-inflammatory condition which is associated with several health issues including damage to mitochondrial, increased ROS generation and oxidative stress, immune-ageing and disruption of the immune system, endocrinosenescence etc., finally leading to deteriorating male reproductive health. There have been several studies on male infertility but there is still limited literature available on energy metabolism and immune regulation of fertility in ageing male. Detailed study and understanding of all the various factors associated with age-induced infertility in males is important for finding proper and affective solution to the current situation of troubles encountered by people trying to have their first child at an advanced age and also to eliminate idiopathic infertility in ageing men. In a nutshell, altered energy metabolism and changed immune regulation in ageing men leads to a cascade of physiological changes ultimately culminating in reduced fertility or infertility in ageing men.

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Conflict of Interest

The authors declare no conflict of interest

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