

# Sperm Parameters: Paradigmatic Index of Good Health and Longevity

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## Key Words

Spermatozoa parameters · Longevity · Oxidative stress · Low testosterone

## Abstract

Since the discovery of spermatozoon by Anton van Leeuwenhoek in 1677, there has been an ever increasing understanding of its role in reproduction. Many factors adversely affect sperm quality, including varicocele, accessory gland infection, immunological factors, congenital abnormalities, and iatrogenic systemic and endocrine causes, such as diabetes mellitus, obesity, metabolic syndrome, and smoking. The mechanisms responsible for the association between poor sperm parameters and ill health may include oxidative stress, low-grade inflammation, low testosterone, and low sex-hormone-binding globulin. Oxidative stress in the testicular microenvironment may result in decreased spermatogenesis and sperm DNA damage, loss of sperm motility, and abnormal sperm morphology. Low testosterone caused by advanced age, visceral obesity, and inflammation is associated with the development of cardiovascular disease. Hence, semen analysis has an important role in the routine evaluation of idiopathic male infertility, usually manifested as low sperm counts, impaired sperm motility, or absence of sperm, and remains the most common single diagnostic tool. Several studies have shown an inverse relationship between semen quality and medical disorders. This review elu-

cidates the effect of medical disorders and social habits on sperm quality, the mechanisms that are involved in the impairment of sperm quality, and whether or not sperm quality can be used as an index of good health and longevity in a man.

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## Introduction

In 1677, Antonie van Leeuwenhoek discovered spermatozoa in a semen sample using a single-lens microscope that could magnify objects up to  $\times 200$  [1, 2], far more powerful than the magnification of  $\times 20$ – $30$  of compound microscopes of the late 14th century. With the aid of this microscope, he discovered ‘animalcules’, small motile elements in semen, which aid fertilization. The major breakthrough, however, came in 1875, when Oscar Hertig, using sea urchins, demonstrated that the sperm head actually fused with the female germ cells to form the nucleus of a new being [3]. From 1920 to 1950, John Macleod [4], working in New York, USA, made two important observations: that semen analysis can be used as an index of human fertility through sperm concentration, motility, and morphology, and that oxygen metabolism has a role in causing altered sperm quality. The World Health Organization (WHO) standardized the procedures for semen analysis by producing a guidance manu-

al for semen analysis, which is updated every 10 years [5]. These sperm parameters are now used to identify males with subfertility and sterility [6].

Spermatogenesis is a process that lasts for about 70 days of transformation from spermatogonia through primary spermatocytes, secondary spermatocytes, and spermatids to spermatozoa, which mature in the epididymis [7, 8]. There are large terminal deletions of the long arm of the Y chromosome (Yq) in men with azoospermia, suggesting that azoospermia factors essential for spermatogenesis reside within the euchromatic region of Yq [9, 10]. Spermatogenesis is regulated by testosterone and follicle-stimulating hormone (FSH), released by the pituitary gland. The FSH stimulates primary spermatocytes to undergo the first meiotic division. Testosterone, secreted and released by the Leydig cells of the testes under the control of luteinizing hormone, stimulates the development of secondary spermatocytes into mature spermatozoa [11]. The production, maturation, and longevity of spermatozoa are affected early in the pathogenesis of many medical conditions. Reports suggest that sperm parameters can indicate the health status of a man [12, 13].

Health, defined in its broader sense, is 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' [14, 15]. Prolonged psychological stress is a factor in cognitive impairment with aging, depressive illness, and expression of disease [16]. Apart from accident, homicide, and suicide, the main causes of death worldwide include cancer, cardiovascular disorders, diabetes mellitus, infection, and hypertension [17].

### **Biomarkers for Monitoring Health**

A biomarker, or biological marker, is in general a substance used as an indicator of a biological state. It is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [18, 19]. Biomarkers can therefore be substances in the body that may indicate risk or the presence of disease [20, 21]. In a comparative study of couples attending a combined infertility clinic, malondialdehyde, a marker of oxidative stress, was strongly associated with obesity and poor semen parameters [22]. Various biomarkers have been used in the diagnosis, monitoring, and treatment of medical disorders, in the blood, urine, and other body fluids. A widely used biomarker for diagnosis and assessment of anemia is the level of hemoglobin. Sim-

ilarly, kidney function is assessed with the level of creatinine in the blood, on its own or as the glomerular filtration rate, and with blood urea nitrogen [23]. Diabetes mellitus is marked by a high fasting glucose level in the blood [24]. Several tumor markers have been associated with several types of cancers, including breast, colon, liver, ovarian, prostate, testicular, and pancreatic cancers [25–28]. The seminal concentration, motility, and morphology of spermatozoa have been used as biomarkers of male fertility potential since the middle of the 20th century [4]. With the recent advances in sperm proteins, proteomic techniques will have an important role in the diagnosis of sperm dysfunction [29].

### **Relevance of Semen Analysis**

Semen analysis has an important role in the routine evaluation of idiopathic male infertility as a result of ductal obstruction from congenital abnormal development or infection, or testicular damage. According to the WHO, a normal sperm count is a concentration of 15 million spermatozoa/ml, with a total semen volume of at least 2 ml. The total number of spermatozoa in the ejaculate should be at least 40 million: 75% viable, 30% of normal shape and form, 50% swimming forward however sluggishly, and 25% swimming with a rapid forward movement [5]. Common causes of abnormal sperm parameters are varicocele, accessory gland infection, immunological factors, congenital abnormalities, obstructive azoospermia, and iatrogenic, systemic, and endocrine disorders [30]. The most common manifestation of male infertility is a low sperm count [31].

### **Limitations of Semen Analysis and Advances in Sperm Testing**

Semen analysis deals with numbers and averages. Furthermore, having a sperm count below 15 million spermatozoa/ml [5, 6] does not indicate that a man will be unable to father a child; likewise, having a higher sperm count does not guarantee that a man will be able to do so. Moreover, there are no reliable tests of sperm function. Investigations for a more precise cause of infertility have continued in the modern era of assisted reproductive technology. One such investigation is sperm proteomics, which is the identification and functional study of sperm proteins with mass spectrometry [32–34]. In a recent study, Lazaros et al. [35] examined the prognostic value

**Table 1.** Sociodemographic and clinical characteristics of the patients

Characteristics	n	%
Mean age ( $\pm$ SD), years	34.6 $\pm$ 8.4	
$\leq$ 20	24	1.1
21–30	673	29.9
31–40	1,039	46.2
41–50	359	15.9
51–60	105	4.7
$<$ 60	51	2.3
Mean duration of infertility ( $\pm$ SD), years	7.4 $\pm$ 4.8	
Primary infertility	1,526	67.8
Secondary infertility	725	32.2
Second marriage	545	24.2
Mean BMI ( $\pm$ SD)	28.4 $\pm$ 3.8	
Underweight (BMI $<$ 18.5)	54	2.4
Normal weight (BMI 18.5–25)	688	30.6
Overweight (BMI 25–29.9)	626	27.8
Obesity 1 (BMI 30–34.9)	599	26.6
Obesity 2 (35–39.9)	221	9.8
Obesity 3 (morbid, BMI $\geq$ 40)	63	2.8
Sperm parameters		
Polyzoospermia	48	2.1
Normozoospermia	1,094	48.6
Oligozoospermia	925	41.1
Azoospermia	184	8.2
Asthenozoospermia	368	20.9
Teratozoospermia	346	15.4
Leukocytospermia	688	30.6
Genital disorders		
Genital injuries	234	10.4
Hernia/herniorrhaphy	87	3.9
Hydrocelectomy	21	0.9
Varicocele/vasectomy	86	3.8
Cryptorchidism/orchidopexy	24	1.1
Testicular sports injury	16	0.7
Chromosomal		
Klinefelter syndrome	5	0.22
Cystic fibrosis/CFTR	3	0.13
Y microdeletion	2	0.09
XX male	1	0.04
Endocrine		
Hypogonadotropic/hypogonadism	3	0.13
Hyperprolactinemia	18	0.80
Infection	134	6.0
Sexually transmitted	38	1.70
Mumps	22	1.00
Other	74	3.30
Malignancies	25	1.1

of semen flow cytometry on the successful outcome of intrauterine insemination (IUI). The authors concluded that semen flow cytometry could be used to evaluate semen samples before IUI and potentially prognosticate the outcome. Sperm DNA fragmentation and Y-chromosome microdeletion are common among patients with oligozoospermia and have a major effect on the management of obstetric and neonatal outcomes. Hence, monitoring with sperm chromatin structural assay (SCSA) for sperm DNA fragmentation has been increasingly used to improve treatment outcomes [36] and guide couples to make informed reproductive decisions, including the decision to seek donor insemination [37] or adoption.

### Decline in Sperm Quality

In 1992, in a publication that generated tremendous controversy, Carlsen et al. [38] drew attention to a 50-year decline in sperm parameters from 1938 to 1990 that appeared to have been supported by two other subsequent publications [39, 40]. The biological significance of these changes is emphasized by a concomitant increase in the incidence of genitourinary abnormalities such as testicular cancer, cryptorchidism, and hypospadias, suggesting a growing impact of factors with serious effects on male gonadal function [41]. Consequently, a search for attributable factors such as the environment, endocrine disruption, estrogens, and phthalates [42] became an urgent necessity. In addition to these factors, behavioral changes such as smoking and sexually transmitted diseases may have intrauterine effects on the growing fetus that may manifest as chronic medical conditions in adult life [43, 44]. In a recent study [45], male rats exposed in utero to certain phthalate esters administered to their mothers exhibited a high frequency of cryptorchidism, hypospadias, and abnormal testes associated with suppression of testosterone levels in the fetal testis, which may also impair sperm production and motility.

### Sperm Parameters and Health Disorders

During a 16-year period from January 1, 1995, to December 31, 2011, semen analysis was carried out according to WHO guidelines [5] on 2,251 men who presented with inability to achieve conception despite cohabitation with their spouses without the use of contraception for more than 12 months. The sociodemographic and clinical characteristics of the patients are shown in table 1. The

**Table 2.** Effects of medical disorders on sperm parameters

	Total number (%)	Azoo-spermia (n = 184)	OligoZP (n = 925)	NormoZP (n = 1,094)	AsthZP (n = 1,121)	Norm. Mot. (n = 1,130)	Sperm morphology		Leuko-cyto-spermia (n = 688)
							<30%	≥30%	
Smoking	810 (36)	68 (37)	538 (58.2)	204 (18.7)	601 (53.6)	209 (18.5)	371 (43.8)	439 (31.3)	313 (45.5)
Diabetes mellitus	189 (8.4)	21 (11.4)	120 (12.9)	48 (4.4)	125 (11.2)	70 (6.2)	79 (9.3)	120 (8.6)	98 (14.2)
Hypertension	212 (9.4)	34 (18.5)	78 (8.4)	104 (9.1)	84 (7.5)	94 (8.3)	75 (8.9)	103 (7.4)	82 (11.9)
Metabolic syndrome	146 (6.2)	12 (6.5)	83 (9.0)	45 (4.1)	86 (7.7)	42 (3.7)	58 (6.9)	70 (5.0)	68 (9.9)
Herniorrhaphy	87 (3.9)	52 (28.3)	31 (3.4)	4 (0.3)	29 (2.6)	6 (0.5)	28 (3.3)	7 (0.5)	35 (5.1)
Obesity									
BMI ≥30	890 (39.5)	100 (54.4)	498 (53.8)	272 (24.9)	586 (52.2)	314 (27.8)	365 (43.1)	375 (26.7)	101 (14.7)
Varicocele	86 (3.9)	14 (7.6)	50 (5.4)	22 (2.0)	57 (5.1)	15 (1.3)	28 (3.3)	44 (3.1)	32 (4.7)
Malignancies									
Seminoma, leukemia	25 (1.1)	3 (1.6)	15 (1.6)	7 (0.6)	18 (1.6)	4 (0.35)	9 (1.1)	13 (0.9)	8 (1.2)
Genital infection	134 (6.0)	15 (8.1)	86 (9.3)	33 (3.0)	88 (7.9)	31 (2.7)	75 (8.9)	44 (3.1)	82 (11.9)
Appendectomy	16 (0.7)	2 (1.1)	6 (0.6)	8 (0.7)	9 (0.8)	5 (0.4)	5 (0.6)	9 (0.6)	5 (0.7)
Others	34 (1.5)	8 (5.7)	16 (1.7)	12 (1.1)	15 (1.3)	13 (1.2)	9 (1.1)	19 (1.4)	11 (1.6)

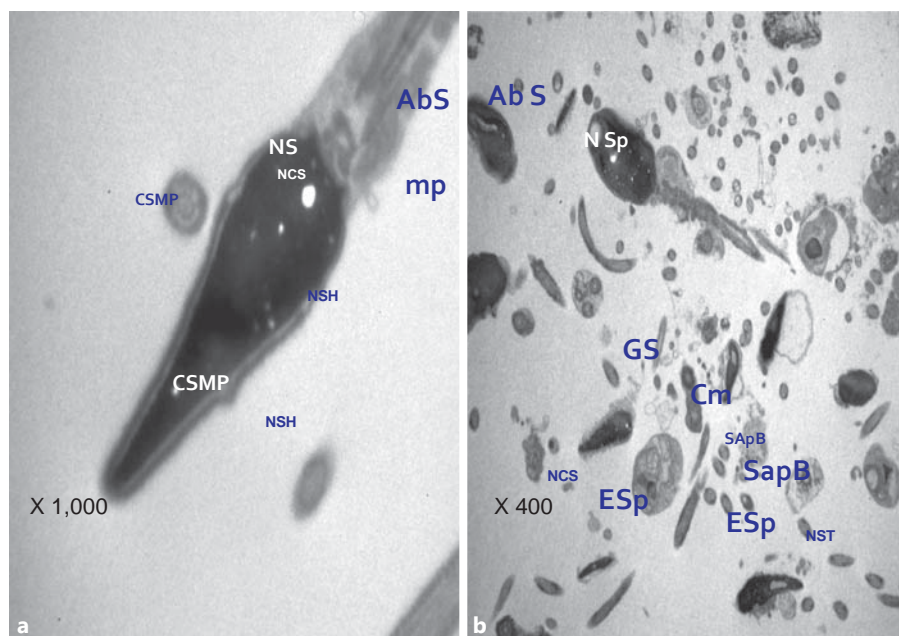
Values are presented as numbers (%). Smoking, diabetes mellitus, metabolic syndrome, obesity, and genital infection are more common with oligozoospermia, asthenozoospermia, and teratozoospermia ( $p < 0.05$  to  $0.001$ ). Herniorrhaphy, hypertension, and obesity are associated with azoospermia ( $p < 0.05$  to  $0.01$ ). OligoZP = Oligozoospermia; NormoZP = normozoospermia; AsthZP = asthenozoospermia; Norm. Mot. = normal motility.

mean age was  $34 \pm 8$  years (range 18–78) and 156 (7%) of the men were above 50 years of age. Primary infertility was more common than secondary infertility, i.e.  $n = 1,526$  (67.8%) versus  $n = 750$  (32.2%) ( $p < 0.05$ ). Using the body mass index (BMI), 54 (2.4%) were determined to be underweight and 883 (39.5%) were obese, with 63 (2.8%) being grossly obese [46]. Polyzoospermia, defined as a sperm concentration of more than 250 million/ml, occurred in 48 (2.1%) of the men, whereas azoospermia occurred in 184 (8.2%). About 234 (10.1%) of the men had had some form of genital operation, and cryptorchidism occurred in 24 (1.1%), while 134 (6.0%) had genital infection. The effects of chronic medical disorders and social habits on semen quality are summarized in table 2. Health disorders among the men included diabetes mellitus, obesity, hypertension, and genital operations such as herniorrhaphy and orchidopexy. Abnormalities such as azoospermia, oligozoospermia, asthenozoospermia, teratozoospermia, and leukocytospermia were more common with these disorders by 1.5- to 3.5-fold. Similarly, FSH increased in an inverse relation with testicular volume, determined by comparative bead orchidometry ( $r = -0.634$ ), and low testosterone was strongly associated with genital operations [46]. Medical disorders and social habits had differential effects on sperm parameters as discussed below.

### Effect of Obesity on Sperm Parameters

The relationship between increased BMI and sperm parameters has been evaluated in several studies [47–58]. All of these studies that collectively evaluated over 125,000 men with infertility showed that an increased BMI was associated with reduced testicular volume, a low sperm count, impaired sperm motility, increased sperm DNA fragmentation, increased infertility, a low serum testosterone level, reduced libido, and erectile dysfunction. Obesity is now an epidemic in both men and women worldwide, resulting in compromised physical and psychological well-being [48]. Much is known about the negative impact of obesity on pubertal sexual maturation resulting in hypogonadism [50]. Obesity is also a risk factor for stress urinary incontinence [51] and type 2 diabetes mellitus and the hormone profile is described as hyperestrogenic hypogonadotropic hypogonadism due to overactivity of aromatase [48]. Underweight or overweight may lead to a low sperm count and infertility [47, 52–54], and overweight men generally have less sex than do non-overweight men [55–57]. A National Institute of Environmental Health Sciences (NIEHS) study showed that a 3-point increase in BMI increased the risk of infertility by 10% in men [47].

There are several ways that obesity may impair fertility in men. Obesity is associated with a change in hor-



**Fig. 1.** Effects of diabetes mellitus on sperm quality. **a** Transmission electron microscopy of a nondiabetic patient with a normal sperm head (NH) mid-piece with abundant mitochondria and a normal tail (NT) and a normal cross section with 9-2n fibrils. **b** Sperm of ejaculated semen of an insulin-dependent diabetic man with infertility showing a globular head (GH), a cytoplasmic mid-piece with scanty mitochondria, elongated spermatide (ESp) and round spermatids (RSp), and a secondary spermatocyte and apoptotic body (Ap).

monal environment characterized by elevated estrogen and reduced testosterone levels. As sperm production is highly dependent on testosterone, low levels of this hormone are likely to impair sperm production [51, 58]. Obesity gives rise to sleep apnea, insulin resistance, and cardiovascular disorders which give rise to erectile dysfunction and collectively result in hypoandrogenism and impaired spermatogenesis. A recent study by Bakos et al. [59] using mice showed that both sperm parameters and embryonic development were significantly reduced when the male partner was obese. Obesity induces adipose cell enlargement and the adipose secretion of adipokines such as interleukin (IL)-1 $\beta$ , IL-6, IL-8, C-reactive protein (CRP), and tumor necrosis factor (TNF)- $\alpha$ . In addition, obesity is associated with overactivity of aromatase that results in hyperestrogenism and consequent suppression of the hypothalamic-pituitary-gonadal axis. This causes hypoandrogenism and subsequent impaired spermatogenesis [59].

### Diabetes Mellitus

In a case-control study of 31 diabetic men with infertility [60], the mean glycosylated hemoglobin (HbA1c) value in diabetic patients was  $8.8 \pm 4.1\%$  compared to  $4.6\%$  in the nondiabetic controls ( $p < 0.05$ ). Poor diabetic con-

trol (HbA1c  $\geq 7\%$ ) was significantly associated with impaired sperm motility (reduced progressive motility and asthenozoospermia) and sperm defects (abnormal morphology such as double head, round and elongated spermatids and cytoplasmic mid- and tail pieces) ( $p < 0.05$ ) as shown in figure 1. Similarly, poor diabetic control was associated with an abnormal lipid profile: high cholesterol, triglycerides, LDL, and VLDL and lower HDL. Leukocytospermia was also more common in diabetic men with poor diabetic control. There were positive correlations between serum glucose level and HbA1c, and the sperm DNA fragmentation index (DFI), and an inverse relationship with butyrylcholinesterase (BuChE) and total antioxidant capacity [60]. In a similar study of 27 diabetic men with infertility, Agbaje et al. [61] found that diabetes was associated with increased nuclear and mitochondrial DNA (mtDNA) sperm damage.

### Metabolic Syndrome

Metabolic syndrome is a complex disorder consisting of multiple interrelated factors including insulin resistance, central adiposity, dyslipidemia, endothelial dysfunction, atherosclerotic disease, and low-grade inflammation. Obesity is associated with the development of metabolic syndrome, which has its own plethora of del-

eterious effects on the sperm [62–64]. Metabolic syndrome plays a central role in obesity in the development of a chronic low-grade inflammatory state that leads to insulin resistance and endothelial and microvascular dysfunction. The subsequent increase in cytokine production recruits immune cells in the extracellular environment, inducing an overall systemic inflammation, which is the link between obesity and metabolic syndrome [65]. Similarly, it is associated with biomarkers such as C-RP, IL-6, and TNF- $\alpha$  that give rise to insulin resistance. Ultimately, this may lead to a low sperm count, impaired motility, and abnormality of sperm morphology [66–68]. On the other hand, metabolic syndrome poses a threat for the development of coronary heart disease and adiposity [69]. A recent study showed that IL-8 was significantly elevated in heart failure patients with metabolic syndrome compared to controls [70]. High IL-8 levels have also been noted in patients with T2DM with a direct correlation with hemoglobin A1C levels.

### Effects of Hypertension on Sperm Parameters

Few studies have evaluated the effects of the treatment of hypertension with calcium ion channel blockers [71] and hypertension itself [72] on sperm parameters. It is known that hypertension can cause problems with erection, either directly or as a side effect of medication. Calcium channel blockers like nifedipine have a direct adverse effect on spermatogenesis, motility, and sperm longevity [73]. Muciaccia et al. [72], in a recent evaluation of 25 hypertensive men and 25 normotensive controls, showed high levels of clusterin, a biomarker of hypertension. The sperm DFI was higher in hypertensive men than in controls, with a significant correlation between high levels of clusterin immunolabeling and the presence of sperm DNA damage. They also reported reduced forward sperm motility and lower sperm vitality in the hypertensive men.

### Seminal Infection

In a comparative study of 50 men with seminal infection, those with infection had a 3-fold lower sperm count than those without [74]. *Chlamydia trachomatis* infection was associated with poor semen quality in young men with prostatitis [75–77] and a high prevalence of *C. trachomatis* in males was associated with a low sperm count in Kuwait [76, 77] and Nigeria [78]. A recent study

assessed the effect of human immunodeficiency virus (HIV) and hepatitis C (HCV) and B (HBV) virus infection on semen parameters from 27 HCV, 34 HIV, 30 HBV, and 41 HCV-HIV-seropositive patients and compared with those of a control population of healthy seronegative subjects. Tests for detection of HIV, HCV, and HBV were performed on seminal samples. The sperm concentration, mean sperm motility, and sperm viability were significantly decreased in HCV- and HBV- and HCV-HIV-seropositive males compared to controls ( $p < 0.001$ ) [79].

### Smoking and Sperm Parameters

Studies evaluating the effect of smoking on sperm parameters have produced controversial results [80–82]. Marinelli et al. [80] reported that smoking has a limited effect on sperm parameters. However, other studies have shown a strong association between smoking and reduced semen quality [81, 82]. In a study of heavy smokers, a zinc-deficient diet was associated with high cadmium testicular accumulation, comparable to diets supplemented with cadmium. The serum concentration of cadmium had a linear correlation with TNF- $\alpha$  and IFN- $\gamma$ , but not with IL-4 [83], with consequent poor sperm parameters [84]. Fawzy et al. [85] reported that both sheesha and cigarette smoking adversely affected semen quality. Sheesha smoking was more significantly associated with a decrease in sperm with a normal morphology and lower testosterone levels relative to cigarette smoking [85]. In two studies where the men were followed for up to 12 months after smoking cessation, both studies reported a marked improvement in semen quality [86, 87]. It is of great clinical interest to draw a parallel to other devastating effects of smoking. Smoking has a dose-dependent association with lung cancer and other epithelial malignancies [88, 89].

### Genital Operations

Cryptorchidism is generally associated with impairment of germ cell maturation and subsequent infertility in adulthood [90]. In a recent study, out of 21 men who had cryptorchidism and subsequent orchidopexy, 6 men (28.6%) who had had orchidopexy before 5 years of age had normal sperm parameters as adults, and 9 (42.9%) had moderate-to-severe oligozoospermia [91]. The remaining 6 (28.6%) had testicular atrophy, nonobstructive azoospermia, and low testosterone levels. In a review by

Murphy et al. [92], in unilateral ectopic and emergent testes, the fertility outcome was good as long as the surgery was carried out in early childhood. However, men who underwent bilateral orchidopexy in their childhood had an appreciably poorer prognosis for fertility compared to men who underwent a unilateral procedure. In another study, men who underwent unilateral orchidopexy in childhood before the age of 8 years had a better prognosis for fertility compared to those who had surgery later. Early diagnosis of cryptorchidism and orchidopexy in early childhood is advocated in order to sustain fertility in adulthood [93]. Secondly, it may be a sign of testicular dysgenesis syndrome [94]. Very few studies have evaluated fertility after herniorrhaphy [95]. In one study, more than half of all men who underwent inguinal repair as children had serum antisperm antibodies and low sperm counts, and both conditions were associated with decreased fertility [96]. In a series of 87 men with a history of herniorrhaphy, 49 (56.3%) had testicular atrophy and low serum testosterone of less than 5 nmol/l, 52 (59.8%) had azoospermia, and another 31 (35.6%) had severe oligozoospermia [91]. The introduction of minimally invasive techniques like laparoscopy in the last 15 years [97, 98] has improved the postoperative outcome. In a comparative study of laparoscopic versus open hernia repair by Bingener et al. [99], major morbidities in the open surgery group were 15 versus 7% in the laparoscopic group ( $p = 0.01$ ). Postoperative inpatient admission was more frequent after the open procedure than after the laparoscopic procedure (28 vs. 16%,  $p < 0.05$ ), thus encouraging a preference for laparoscopic hernia repair. Fertility potential was, however, not evaluated.

### Effects of Age on Sperm Parameters

There are several studies suggesting that an increase in age is associated with a decline in semen parameters [100, 101]. Paulson et al. [102] identified an inverse association between age and total sperm count. In a study involving 97 healthy nonsmoking men aged 22–80 years, Eskenazi et al. [103] showed that as the men aged, sperm parameters declined with a continuous reduction in sperm motility and semen volume. In a comparative study on the effects of advancing male age on multiple genomic defects in the human sperm DFI, chromatin integrity, gene mutations, and numerical chromosomal abnormalities, Wyrobek et al. [104] demonstrated a consistent decline in semen quality and increased sperm DNA damage, chromatin integrity, and gene mutations.

### Sperm Parameters and Male Health

There are two lines of evidence that link sperm parameters to male health. Two Norwegian studies and a linkage study from England and Wales have shown that fertile couples live longer, especially if they have children, but it has not been determined whether this is due to biologic and/or social factors [105–107]. Epidemiological evaluation of the health disorders and sperm quality of 2,251 patients over a 16-year period showed that most health disorders have a deleterious effect on sperm parameters [46]. There is a rich body of literature on the effects of lifestyle habits such as substance abuse, cocaine or marijuana, and smoking on sperm quality [108–110]. Deficiencies in certain nutrients such as vitamins C and E, folate, selenium, and zinc may lead to low sperm counts [111, 112].

### Sperm Parameters and the Longevity of Men

A sperm concentration of 40 million/ml or more has been found to increase the probability of conception [6]. A higher mortality rate was found for infertile men without any specific comorbidity. This assertion has given credence to the assumption that disorders of spermatogenesis may be an indicator of exposure of the male organs to noxious agents within or outside the body environment. At the Third European Congress of Andrology and the 16th Congress of the German Society of Andrology, Groos et al. [13] demonstrated that men with normal sperm quality survived longer than men with poor sperm quality. The main criticism of this study was that it did not take the age of the participants and the duration of follow-up into consideration. These defects were corrected in a much larger Danish study from 1963 to 2001 [12]. All men who were referred to the Copenhagen Sperm Analysis Laboratory were included in the study. They were all linked to the Danish Cancer Registry, the National Register, and Statistics Denmark. Among 43,277 men without azoospermia referred for infertility problems, mortality decreased as the sperm concentration increased up to a threshold of 40 million/ml. As the percentage of motile and morphologically normal spermatozoa and semen volume increased, mortality decreased in a dose-response manner due to a decrease in many diseases like infectious diseases (including tuberculosis), cancer, and cardiovascular, respiratory, digestive, and urogenital and endocrine diseases like diabetes mellitus. This was observed among men with and with-

out children [12]. This study strongly demonstrated that semen quality may be a fundamental biomarker of overall male health.

### **Mechanisms of Association between Sperm Parameters and Male Health**

#### *Primary Mechanisms*

There is increasing evidence that male reproductive disorders have become more prevalent during the last 50 years, with an increase in the incidence of testicular cancer and a decline in sperm counts [113, 114]. Simultaneously, the incidence of congenital malformations of the male reproductive tract such as cryptorchidism and hypospadias has also increased [115]. Testicular cancer is associated with maldescent of the testis [116], reduced semen quality, and decreased fertility before cancer is diagnosed [117]. Against this background, Skakkebaek [118] proposed that these conditions are all symptoms of one underlying entity designated testicular dysgenesis syndrome, with a common origin in fetal life, in tacit support of the 'fetal origins hypothesis' proposed earlier by Barker [119]. According to this hypothesis, the fetal environment has been suggested to influence later health. Fetal malnutrition in utero and early life increases the risk of common adult diseases, such as cardiovascular disease and diabetes mellitus, and environmental factors, particularly nutrition, act in early life to potentiate the risks for adverse health outcomes in adult life. The mechanisms by which early life conditions are associated with male reproductive disorders and major late-life diseases are still not well understood. In a review, McMillen and Robinson [120] suggested critical windows during which perturbations of the intrauterine environment have major effects, and that epigenetic, structural, and functional adaptive responses result in a permanent programming of cardiovascular and metabolic disorders.

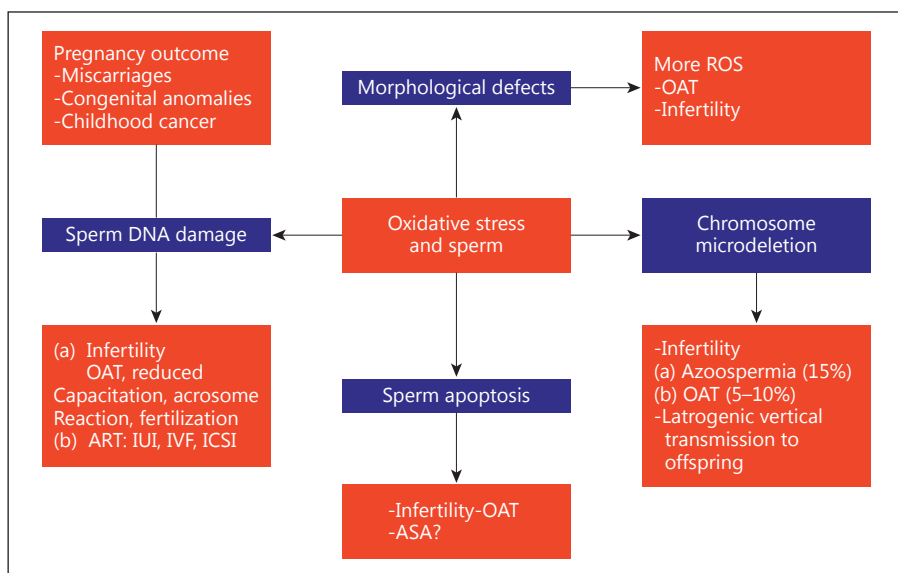
#### *Secondary Mechanisms*

Several mechanisms may account for the deleterious effects of obesity, diabetes mellitus, metabolic syndrome, smoking, genital injuries, and other health problems on sperm parameters. It has been suggested that insulin-dependent diabetes in men is associated with hypothalamo-pituitary derangement and impairment of semen quality [121] through low androgen levels. Sperm damage may be caused by oxidative stress, with adipose tissue acting as an endocrine organ, which produces adipokines, low-grade inflammation, and proinflammatory cytokines,

which results in insulin resistance and low testosterone [122–124]. In a recent review, Mammi et al. [125] showed that excessive adipose tissue is associated with impaired testosterone production. Spermatozoa were the first cell type reported to show a potential susceptibility to oxidative damage [4, 126, 127]. In a landmark paper published in 1943, MacLeod [4] confirmed a rapid loss of motility if spermatozoa were incubated in an oxygen-rich environment. Believing the loss of motility was due to an overproduction of oxidants arising from increased oxygen metabolism by sperm, he added the antioxidant catalase to the medium and restored motility, thereby successfully validating his hypothesis. The literature in andrology is replete with evidence of damage to sperm morphology and impairment of function by oxidative stress, with abundant production of free radicals from inflammation and abnormal sperm [128, 129], as shown in figure 2. The white adipose tissue produces adipokines such as leptin, adiponectin, IL-6, and TNF- $\alpha$  with proinflammatory properties which lead to the development of oxidative stress [130–132]. Consequently, protein cross-linking and lipid peroxidation cause impairment of sperm-oocyte interactions due to loss of membrane fluidity. The Y chromosome is particularly susceptible to gene deletions because of the inability of the haploid genome to deploy recombination repair in retrieving lost genetic information. Sperm DNA damage and fragmentation may occur as a result of aberrant recombination, defective chromatin packaging, abortive apoptosis, and oxidative stress [133]. Oxidative stress and sperm DNA damage are common features of human spermatozoa, with purported links to poor rates of conception, impaired embryonic development, an increased incidence of miscarriage, and chronic morbidity in the offspring including childhood cancers [132]. This is particularly of clinical significance in uncontrolled diabetes mellitus with chronic hyperglycemia [134]. Hyperglycemia leads to production of advanced glycation end products (AGE), harbingers of proinflammatory cytokine production of TNF- $\alpha$  and IL-6, which cause insulin resistance. This leads to a vicious cycle of further hyperglycemia and resultant impairment of the hypothalamo-pituitary-testicular axis, culminating in decreased testosterone production. This results in endothelial dysfunction [134] and is simultaneously associated with oligozoospermia, asthenozoospermia, and sperm DNA apoptosis [58, 59]. In another signaling pathway, hyperglycemia is associated with increased glycolysis and high pyruvate production with mitochondrial uncoupling and, consequently, production of sorbitol, AGE, and expression of AGE receptors (RAGE) [135], which



**Fig. 2.** Effects of oxidative stress on sperm parameters. Oxidative stress is associated with impaired spermatogenesis, sperm morphological defects, sperm chromosome microdeletion, sperm DNA damage (fragmentation), reduced sperm capacitation, acrosome reaction, and fertilization. All abnormalities lead to infertility and miscarriage, congenital anomalies, and childhood cancer. OAT = Oligo-asthenoteratozoospermia; ROS = reactive oxygen species; ART = assisted reproductive technology.



activate proinflammatory cytokine production and stress signaling [136].

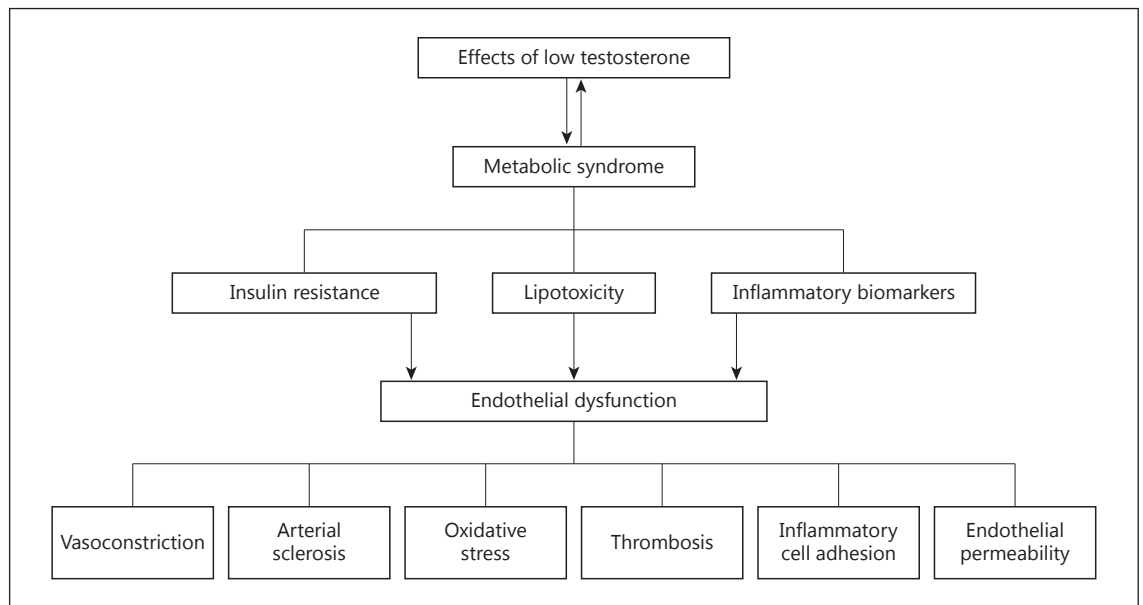
Most (98%) circulating testosterone is reversibly bound to albumin and sex-hormone-binding globulin (SHBG) [137]. SHBG is a protein manufactured in the liver that is responsible for the transportation of sex hormones testosterone, dihydrotestosterone, and estradiol. SHBG helps keep sex hormones in balance. Lower SHBG is more strongly associated with metabolic syndrome than is lower total testosterone in community-dwelling older men. SHBG may be the primary factor of these relationships, possibly reflecting its association with insulin sensitivity [138, 139]. Reduced circulating testosterone and SHBG are implicated as risk factors for metabolic syndrome [138] and may therefore be strongly associated with reduced sperm quality. Epidemiological observations suggest that low androgens, especially testosterone, and SHBG, are associated with high BMI [139], nonobese diabetes mellitus [59], hypertension [140], and metabolic syndrome [61, 141, 142].

As shown in figure 3, low testosterone levels in men may be associated with increased cardiovascular risk [143, 144]. A European prospective study among men aged 40–79 years showed that endogenous testosterone concentrations were inversely associated with all-cause mortality and cardiovascular mortality [145], in confirmation of an earlier report [116]. Several mechanisms have been implicated in the association between low testosterone levels and cardiovascular disease. Low testosterone has been linked to elevated triglyceride and low

high-density lipoprotein levels, central or visceral obesity, glucose intolerance, and diabetes mellitus [146, 147]. Reduced testosterone is associated with increased levels of several cytokines and growth factors such as TNF- $\alpha$ , IL-6, IL-1 $\beta$ , and CRP [147]. In a report by van Guilder et al. [148], an increased level of oxidative and inflammatory stress played an important role in the initiation and progression of atherosclerotic vascular disease. Furthermore, elevated proinflammatory cytokines, including TNF- $\alpha$ , IL-6, and IL-18, as well as CRP, are markers of systemic inflammation and strong determinants of future atherosclerotic events. In summary, while oxidative stress and low grade inflammation are associated with poor sperm parameters, they are also potential mechanisms underlying the increased cardiovascular and renal risks in obese adults with metabolic syndrome [60, 62, 63].

### Limitations of Utility of Association between Sperm Parameters and Male Health Status

A better understanding of the association between sperm parameters and general health could lead to possible pharmacological development and interventions that could delay, alter, or prevent the progression and development of medical complications and effects on sperm parameters. However, there is a need to exercise caution on two main fronts. While drugs like gentamycin, used for infections, may improve the general health of the patient, they may have directly adverse effects on spermatogenesis



**Fig. 3.** Effects of low testosterone on spermatogenesis and male health. Testosterone is essential for spermatogenesis. Low testosterone leads to reduced sperm counts and increased sperm morphological defects. There is a strong bilateral association between low testosterone and metabolic syndrome, insulin resistance, and diabetes mellitus. This may lead to production of biomarkers of inflammation and oxidative stress. Ultimately, this may cause endothelial dysfunction, which may give rise to atherosclerosis and coronary heart disease.

and sperm parameters [148]. Another difficulty in advocating sperm parameters as biomarkers of individual male health is the variation in semen quality from the effects of biological, environmental, and seasonal changes on spermatogenesis [149, 150], and the use of different parameters of assessment of sperm quality among laboratories [39, 151]. Lifestyle changes in the form of weight reduction, exercise, cessation of smoking, and a balanced diet may differentially improve sperm parameters and general health [52, 138]. In a recent study, combinations of adverse lifestyle factors had a detrimental impact on sperm in terms of motility and sperm count. This negative impact was shown to be compensated by a higher ejaculation frequency and a shorter period of sexual abstinence [152]. The compensation is most likely due to a shorter storage time in the male gonads, thus reducing the duration of sperms' exposure to reactive oxygen species [153].

## Conclusion

There are a number of difficulties in using semen parameters for screening to determine male health status. The physiological variation of spermatogenesis and the significant impact of individual lifestyle choices such as

exercise, diet, and health awareness are important variables. There is compelling evidence of an association between medical disorders, social habits, and sperm parameters. Through various mechanisms, sperm parameters are affected early in the pathogenesis of medical disorders. However, the use of sperm parameters for monitoring male health requires further evaluation for the role of age, environment, and congenital abnormalities of the genital tract. With advances in proteomics, personalized therapy for male infertility and medical disorders will be achievable.

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The author declares that no conflicts of interest exist.

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