Minireview

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Interplay between male gonadal function and overall male health

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Abstract: The process-of-male reproduction is intricate, and various medical conditions-have the potential to disrupt spermatogenesis. Moreover, infertility in males can serve as an indicator of-potential future health issue. Numerous conditions with systemic implications have been identified, encompassing genetic factors (such as Klinefelter Syndrome), obesity, psychological stress, environmental factors, and others. Consequently, infertility assessment-presents an opportunity for comprehensive health counseling, extending-beyond discussions about reproductive goals. Furthermore, male infertility has been suggested as a harbinger of future health problems, as poor semen quality and a diagnosis of-male infertility are associated with an increased risk of hypogonadism, cardiometabolic disorders, cancer, and even mortality. This review explores the existing-literature on the relationship between systemic illnesses and male fertility, impacting both clinical-outcomes and semen parameters. The majority of the literature analyzed, which compared gonadal function with genetic, chronic, infectious or tumoral diseases, confirm the association between overall male health and infertility.

Keywords: gonadal function; infertility; male

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Introduction

Male fertility is influenced by different factors that play together. Evaluation of male fertility could be an opportunity to improve a man's overall health beyond his immediate reproductive goals serving as a surrogate biomarker for overall health [1–4]. The aim of this review is to-shed light-on the potential-link between male infertility and-health problems. This way, correct-counseling provides the opportunity to treat some diseases in advance before their onset (Figure 1).

Materials and methods

Male fertility is influenced by a myriad of factors spanning genetic, environmental, and lifestyle domains. The intricate interplay of these factors underscores the complexity of male reproductive health. We conduct a research on pubmed of all the existing literature (mostly review articles) on male fertility and his influence on overall men's health, using as key words 'male infertility' 'hypogonadism', 'overall health biomarkers'.

Genetic factors

Genetic factors play a significant role, out of the 25,000 genes found in the human genome, about 10 % are associated with reproduction [5]. Nonetheless, these genes likely intersect with pathways in various cell types and organ systems, potentially explaining why many genetic defects result in clinical phenotypes encompassing infertility among other symptoms. Klinefelter syndrome stands as the most prevalent chromosomal anomaly in males, characterized by well-defined clinical manifestations which bring to gonadal dysfunction [6–8].

Another group of recognized genetic causes of gonadal disfunction overall azoospermia and severe oligozoospermia involves Y chromosome microdeletions, particularly those within the azoospermia factor (AZF) region [9].

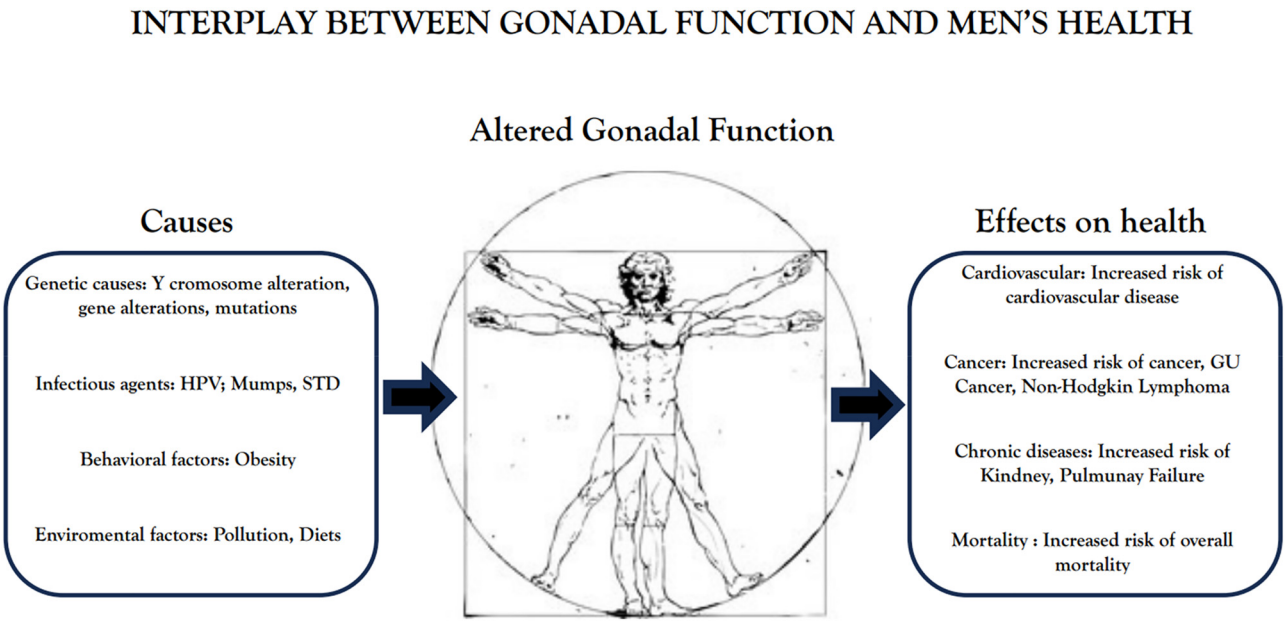

Figure 1: Interplay between male gonadal function and overall male health.

The influence of genetics continues to expand. DNA mismatch repair (MMR) mechanisms are crucial for preserving spermatozoa DNA integrity and are pivotal in spermatogenesis [10]. Mutations in MMR-related genes such as MLH1, MLH3, PMS2, MSH4, and MSH5 have discernible impacts in humans, leading to severe oligozoospermia or non-obstructive azoospermia [11]. MMR mutations have also been identified in individuals with Lynch syndrome [12], although they are not currently part of the standard assessment for infertile males. As our understanding of the genetic foundations of spermatogenesis advances, it may broaden the scope of genetic screening for men presenting with infertility.

Infactious factors

Infectious agents also pose a significant threat to male fertility: Infectious causes of male infertility vary from testicular injuries to systemic infectious disease that damage the testis, with injury mechanisms ranging from inflammation to vasculitis, endocrine disruption, or direct tissue damage. Additionally, systemic infections can induce febrile illness, directly impairing spermatogenesis. Infections may manifest at the testicular site or distally in the spermatic tract, such as the prostate or urethra. Sexually transmitted infections (STIs) may be asymptomatic in men but are acknowledged to cause infertility.

Mumps orchitis is a classic infectious cause of male infertility, which was more prevalent prior to the availability of a vaccine in 1988. The virus, an RNA virus of the paramyxovirus genus, spreads from human reservoirs through direct contact and airborne droplets [13].

Human papillomavirus (HPV), among the most common STIs in both genders, is linked with male infertility, with an estimated prevalence of HPV DNA within the semen of infertile men at approximately 16 % [14]. Infertile men harboring HPV DNA in semen exhibited reduced motility, abnormal morphology, and elevated DNA fragmentation indexes [15, 16]. Women inseminated with spermatozoa containing HPV DNA experienced a four-fold decrease in clinical pregnancies compared to those inseminated with HPV-negative spermatozoa [17].

The implications of other infections are less elucidated. *Chlamydia trachomatis*, an STI symptomatic in only up to 50 % of men, has been detected in fresh testicular biopsy samples from infertile men, indicating a possible role in disrupting spermatogenesis [18].

Obesity

As behavioral factor influencing the gonadal function there is the obesity. The obesity epidemic has garnered recognition as a public health crisis and is linked with various chronic diseases, including coronary artery disease, diabetes, and non-alcoholic fatty liver disease [19]. The mechanism through which obesity and heightened adiposity contribute to these conditions is intricate and not entirely clear, with proposed pathways primarily involving insulin resistance, chronic inflammation, and neurohormonal activation [20]. Meta-analyses investigating the correlation between body mass index (BMI) and semen parameters have revealed an inverse relationship between BMI and semen volume, total sperm count, and sperm concentration [21, 22]. Moreover, obesity has been associated with azoospermia, with an odds ratio of 2.04 (95 % confidence interval [CI] 1.59–2.62) [22]. Obesity play a role in lowering testosterone causing biochemical androgen deficiency [23, 24]. On the other hand increasing daily steps count shows to elevates serum testosterone levels [25]. Unfortunately, bariatric surgery in obese men has not demonstrated significant improvements in semen parameters even after 24 months of follow-up [26].

Environmental factors

Moreover, environmental factors can also influence male fertility through exposure to pollutants. Air pollution may be linked to elevated concentrations of carbon monoxide, sulfur dioxide, ozone, and particulate matter. Of particular concern is particulate matter in the air due to the presence of trace elements and potential endocrine disruptors. Ambient air pollution has been associated with various conditions, ranging from chronic cardiopulmonary diseases to mortality [27]. Not surprisingly, exposure to air pollution has been correlated with impairments in semen parameters as well. Hammoud and colleagues analyzed 1699 semen analyses of men seeking artificial insemination and correlated the results with particulate air pollution levels over a 5-year period. They observed that elevated indices of air pollution levels were associated with decreased sperm motility 2–3 months post-exposure, suggesting a detrimental impact on spermatogenesis [28]. A study of Czech Republic citizens residing in areas with higher concentrations of sulfur coal usage for industrial and home heating purposes found a significant increase in sperm DNA damage during periods of peak air pollution levels [29]. Interestingly, neither study identified a significant difference in sperm counts.

Bisphenol A (BPA) is a potent endocrine disruptor extensively used as a raw material for manufacturing consumer products, ranging from canned goods to plastic containers [30].

Phthalates are a class of synthetic chemical additives commonly used as plasticizers in consumer products, including food packaging materials and personal hygiene products like shampoos [31]. Most of the human exposure is associated with dietary ingestion from contaminated food and beverage products. Phthalate exposure is widespread: a 2004 NHANES study analyzing 2540 urine samples from the 1999–2000 cycle detected phthalate metabolites in over 75 % of samples [32]. Phthalates have also been found in human blood, sweat, and breast milk, highlighting the ubiquity of exposure [33].

Phthalates and their metabolites have demonstrated hormone-disrupting properties and are linked with increased serum estradiol concentrations [34].

Pesticides can infiltrate the body via direct skin contact or inhalation, particularly among those in the agricultural sector, or through dietary intake, which is the predominant route for the majority of individuals. Historically, the pesticide most extensively associated with male infertility is 1,2-dibromo-3-chloropropane (DBCP), a soil fumigant and nematocidal agent utilized in the USA from 1955 until 1977, following which its use was halted in the USA due to health apprehensions [35]. An initial study conducted in 1977 on DBCP factory workers unveiled that among 25 men, 14 exhibited azoospermia or oligozoospermia, a phenomenon observed solely in individuals employed at the factory for more than 3 months [36]. Additional pesticides like ethylene dibromide, malathion, and paraquat have also been linked to diminished sperm counts among exposed workers [37, 38].

Moreover, cannabis can negatively influence the levels of testosterone [39, 40].

Understanding the multifactorial nature of male infertility is crucial for developing effective prevention and treatment strategies. The intricate relationship between male infertility and diverse health outcomes has been extensively explored across numerous epidemiological studies. This comprehensive investigation tries to shed light on the multifaceted nature of male infertility, revealing its potential as a significant predictor and marker for various health conditions beyond its immediate reproductive implications.

Male infertility and cardiovascular disorders

In many men, serum testosterone levels gradually decrease with age, and several studies have shown that decreasing testosterone levels increase cardiovascular risk [41, 42]. Subclinical hypogonadism may also lead to an increased cardiovascular risk and mortality related to cardiovascular events [43, 44]. Many authors have also highlighted that male infertility can be a marker for future cardiovascular risks. It is noteworthy that varicocele represents a risk factor for infertility and occurs in about 15 % of healthy men and is associated with about 35 % of infertility. In an observational study, the authors demonstrated that the presence of varicocele was associated with a higher cardiovascular risk compared to the control group. Two other studies have shown that infertility is associated with a higher number of cardiovascular events [45].

Male infertility and cancer risk

While it has been well established that the treatment of many types of cancer has a negative impact on male fertility, male infertility may be associated with certain types of cancer. The mechanisms behind this process are still not fully understood. For example, one cause of male infertility is associated with the malfunctioning of the MLH1 gene, and mutations in this gene are associated with Lynch syndrome [8, 11]. However, the mechanism linking infertility to potential cancer development remains unclear. Eisenberg et al. 2013 analyzed the impact of infertility on cancer risk and demonstrated that infertile men have a higher risk of developing cancer. And azoospermic men have a higher risk

of developing cancer [46]. Eisenberg also demonstrated in a 2015 study that infertile males have a higher risk of developing non-Hodgkin lymphoma [47]. The association between semen quality and cancer development remains uncertain due to the heterogeneity of studies in the literature. Hanson et al. demonstrated that only oligospermia was associated with all types of cancer, unlike men with azoospermia who did not have a significantly higher risk of developing cancer [48]. Some studies analyze an overall risk of cancer development while others focus on types of cancer related to the genitourinary tract. Regarding the development of tumors of the genitourinary tract, Hanson et al. demonstrated the relationship between male infertility and the development of testicular tumors. In the aforementioned study, the authors showed that infertile men had a high risk of developing testicular cancer compared to the control group [48]. Furthermore, several studies have shown that the condition of infertility itself can be a risk factor for the development of prostate cancer [49], and urological cancers in general [50–52], although further studies are needed due to the heterogeneity of the results.

Male infertility and chronic diseases

Chronic diseases are a heterogeneous group of diseases related to aging and lifestyle habits. It has been observed that lifestyle habits such as smoking, high BMI, alcohol or drug abuse are associated with various types of chronic diseases such as metabolic syndrome, liver, and chronic kidney failure. These same conditions are also associated with infertility and alteration of semen quality [4, 8]. A study conducted by Ventimiglia et al. showed that infertile patients have more comorbidities (cardiovascular, pulmonary, liver, DM disorders) than fertile men [53]. Although these studies indicate a potential correlation between infertility and the development of chronic diseases, the causal link of the condition has not yet been fully demonstrated, and further studies are therefore needed. Giovannone et al. shows a correlation between hyperhomocysteinemia (when levels exceed 15 μmol/L, in terms of disruption in the metabolism of homocysteine) and erectile function. Assuming that it could be considered as an early predictor of erectile dysfunction, this would demonstrate a link between male infertility and general metabolic health [54].

Male infertility and autoimmune disorders

A link between male infertility and autoimmune disorders is described by Glazer et al. who reported a higher incidence of multiple sclerosis in males with infertility [55]. A lower, but statistically significant link was also found between male hypogonadism and psoriasis, systemic lupus erythematosus, Grave disease and thyroiditis.

Male infertility and overall mortality

Although the data are partial and require further confirmation, some studies have shown a potential association between infertility and an increased risk of premature mortality [56–58]. A Danish study conducted by Jensen et al. evaluated a large cohort of patients who underwent infertility analysis, the study showed that the risk of mortality was inversely proportional to sperm concentration and quality, with a level of at least 40 million per mL associated with a higher risk of overall mortality [59]. An American study by Eisenberg MI et al. showed that men with sperm anomalies had a twofold risk of overall mortality compared to the control group represented by men without sperm anomalies [60]. Obviously, further studies are needed to draw more statistically relevant conclusions, but these studies, in their simplicity, represent the first evidence associating infertility with an increased risk of mortality.

Conclusions

This small review of existing literature suggests that there is an association between male infertility and overall somatic health. In fact, much of the literature associate infertility with an increased cardiovascular risk, and similarly, infertile men appear to have a higher risk of chronic diseases despite sociodemographic factors. However, the association between infertility and cancer varies depending on the type of cancer examined, leading to results that at least seemingly appear to be in contrast. In any case, the general literature agrees that overall testicular function is an indicator of general health. This condition also allows us to follow men who develop infertility early to ensure proper counseling for the development of future pathologies. This assertion is of critical importance as infertile men represent a rather young population for whom preventive programs for the development of chronic pathologies can be implemented.

Discussion

The correlation between male infertility and male malignancies, as well as chronic cardiovascular conditions and overall-mortality, suggests promising findings. However,

these results remain exploratory, indicating the necessity for further prospective studies with extended follow-up periods and additional clinical data. This underscores the importance of understanding the underlying mechanisms-linking-male infertility and this health conditions, including genetic, epigenetic, developmental, and lifestyle factors.

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References

1. Kasman AM, Del Giudice F, Eisenberg ML. New insights to guide patient care: the bidirectional relationship between male infertility and male health. Fertil Steril 2020;113:469–77.
2. Del Giudice F, Kasman AM, Ferro M, Sciarra A, De Berardinis E, Belladelli F, et al. Clinical correlation among male infertility and overall male health: a systematic review of the literature. Invest Clin Urol 2020; 61:355.
3. Chen T, Belladelli F, Del Giudice F, Eisenberg ML. Male fertility as a marker for health. Reprod Biomed Online 2022;44:131–44.
4. Del Giudice F, Kasman AM, De Berardinis E, Busetto GM, Belladelli F, Eisenberg ML. Association between male infertility and male-specific malignancies: systematic review and meta-analysis of population-based retrospective cohort studies. Fertil Steril 2020;114:984–96.
5. Matzuk MM, Lamb DJ. The biology of infertility: research advances and clinical challenges. Nat Med 2008;14:1197–213.
6. Salzano A, Marra AM, D'Assante R, Arcopinto M, Suzuki T, Bossone E, et al. Growth hormone therapy in heart failure. Heart Fail Clin 2018;14: 501–15.
7. Guerri G, Maniscalchi T, Barati S, Dhuli K, Busetto GM, Del Giudice F, et al. Syndromic infertility. Acta Biomed 2019;90:75.
8. Guerri G, Maniscalchi T, Barati S, Busetto GM, Del Giudice F, De Berardinis E, et al. Non-syndromic monogenic male infertility. Acta Biomed 2019;90:62.
9. Kuroda S, Usui K, Sanjo H, Takeshima T, Kawahara T, Uemura H, et al. Genetic disorders and male infertility. Reprod Med Biol 2020;19:314–22.
10. Feitsma H, Leal MC, Moens PB, Cuppen E, Schulz RW. Mlh1 deficiency in zebrafish results in male sterility and aneuploid as well as triploid progeny in females. Genetics 2007;175:1561–9.
11. Terribas E, Bonache S, García-Arévalo M, Sanchez J, Franco E, Bassas L, et al. Changes in the expression profile of the meiosis-involved mismatch repair genes in impaired human spermatogenesis. J Androl 2010;31:346–57.
12. Stupart D, Win AK, Winship IM, Jenkins M. Fertility after young-onset colorectal cancer: a study of subjects with Lynch syndrome. Colorectal Dis 2015;17:787–93.
13. Masarani M, Wazait H, Dinneen M. Mumps orchitis. J R Soc Med 2006; 99:573–5.
14. Laprise C, Trottier H, Monnier P, Coutlée F, Mayrand MH. Prevalence of human papillomaviruses in semen: a systematic review and meta-analysis. Hum Reprod 2014;29:640–51.
15. Boeri L, Capogrosso P, Ventimiglia E, Pederzoli F, Cazzaniga W, Chierigo F, et al. High-risk human papillomavirus in semen is associated with poor sperm progressive motility and a high sperm DNA fragmentation index in infertile men. Hum Reprod 2019;34:209–17.
16. Moghimi M, Zabihi-Mahmoodabadi S, Kheirkhah-Vakilabad A, Kargar Z. Significant correlation between high-risk HPV DNA in semen and impairment of sperm quality in infertile men. Int J Sertil Steril 2019; 12:306.
17. Depuydt CE, Donders GGG, Verstraete L, Broeck DV, Beert JFA, Salembier G, et al. Infectious human papillomavirus virions in semen reduce clinical pregnancy rates in women undergoing intrauterine insemination. Fertil Steril 2019;111:1135–44.
18. Bryan ER, Redgrove KA, Mooney AR, Mihalas BP, Sutherland JM, Carey AJ, et al. Chronic testicular Chlamydia muridarum infection impairs mouse fertility and offspring development. Biol Reprod 2020; 102:888–901.
19. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med 2017;376:254–66.
20. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. Ther. Adv. Cardiovasc. Dis. 2017;11:215–25.
21. Guo D, Wu W, Tang Q, Qiao S, Chen Y, Chen M, et al. The impact of BMI on sperm parameters and the metabolite changes of seminal plasma concomitantly. Oncotarget 2017;8:48619.
22. Sermondade N, Faure C, Fezeu L, Shayeb AG, Bonde JP, Jensen TK, et al. BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. Hum Reprod Update 2013;19: 221–31.
23. Kasman A, Del Giudice F, Shkolyar E, Porreca A, Busetto GM, Lu Y, et al. Modeling the contribution of the obesity epidemic to the temporal decline in sperm counts. Arch Ital Urol Androl 2020;92:49–57.
24. Busetto GM, Del Giudice F, Virmani A, Sciarra A, Maggi M, Ferro M, et al. Body mass index and age correlate with antioxidant supplementation effects on sperm quality: post hoc analyses from a double-blind placebo-controlled trial. Andrologia 2020;52:e13523.
25. Del Giudice F, Glover F, Belladelli F, De Berardinis E, Sciarra A, Salciccia S, et al. Association of daily step count and serum testosterone among men in the United States. Endocrine 2021;72:874–81.
26. Reis LO, Zani EL, Saad RD, Chaim EA, de Oliveira LC, Fregonesi A. Bariatric surgery does not interfere with sperm quality – a preliminary long-term study. Reprod Sci 2012;19:1057–62.
27. Pope CA III. Mortality effects of longer term exposures to fine particulate air pollution: review of recent epidemiological evidence. Inhal Toxicol 2007;19:33–8.
28. Hammoud SS, Purwar J, Pflueger C, Cairns BR, Carrell DT. Alterations in sperm DNA methylation patterns at imprinted loci in two classes of infertility. Fertil Steril 2010;94:1728–33.
29. Rubes J, Selevan SG, Evenson DP, Zudova D, Vozdova M, Zudova Z, et al. Episodic air pollution is associated with increased DNA fragmentation in human sperm without other changes in semen quality. Hum Reprod 2005;20:2776–83.
30. Huang YQ, Wong CKC, Zheng JS, Bouwman H, Barra R, Wahlström B, et al. Bisphenol A (BPA) in China: a review of sources, environmental levels, and potential human health impacts. Environ Int 2012;42:91–9.
31. Guo Y, Wang L, Kannan K. Phthalates and parabens in personal care products from China: concentrations and human exposure. Arch Environ Contam Toxicol 2014;66:113–9.

32. Silva MJ, Barr DB, Reidy JA, Malek NA, Hodge CC, Caudill SP, et al. Urinary levels of seven phthalate metabolites in the US population from the National Health and Nutrition Examination Survey (NHANES) 1999–2000. Environ Health Perspect 2004;112:331–8.
33. Genuis SJ, Beesoon S, Birkholz D, Lobo RA. Human excretion of bisphenol A: blood, urine, and sweat (BUS) study. J Environ Public Health 2012;2012:34–44.
34. Fong JP, Lee FJ, Lu IS, Uang SN, Lee CC. Relationship between urinary concentrations of di (2-ethylhexyl) phthalate (DEHP) metabolites and reproductive hormones in polyvinyl chloride production workers. Occup Environ Med 2015;72:346–53.
35. Babich H, Davis DL, Stotzky G. Dibromochloropropane (DBCP): a review. Sci Total Environ 1981;17:207–21.
36. Whorton D, Krauss R, Marshall S, Milby T. Infertility in male pesticide workers. Lancet 1977;310:1259–61.
37. Hossain F, Ali O, D'souza UJ, Naing DKS. Effects of pesticide use on semen quality among farmers in rural areas of Sabah, Malaysia. J Occup Health 2010;52:353–60.
38. Ratcliffe JM, Schrader SM, Steenland K, Clapp DE, Turner T, Hornung RW. Semen quality in papaya workers with long term exposure to ethylene dibromide. Occup Environ Med 1987;44:317–26.
39. Belladelli F, Del Giudice F, Kasman A, Kold Jensen T, Jørgensen N, Salonia A, et al. The association between cannabis use and testicular function in men: a systematic review and meta-analysis. Andrology 2021;9:503–10.
40. Belladelli F, Chen T, Basran S, Greenberg DR, Del Giudice F, Mulloy E, et al. The association between monthly, yearly, and lifetime cannabis use, and semen parameters in Asian-American men. World J Men's Health 2023;41:623.
41. Kloner RA, Carson C, Dobs A, Kopecky S, Mohler ER. Testosterone and cardiovascular disease. J Am Coll Cardiol 2016;67:545–57.
42. Capogrosso P, Ventimiglia E, Boeri L, Capitanio U, Gandaglia G, Dehò F, et al. Sexual functioning mirrors overall men's health status, even irrespective of cardiovascular risk factors. Andrology 2017;5:63–9.
43. Ponce OJ, Spencer-Bonilla G, Alvarez-Villalobos N, Serrano V, Singh-Ospina N, Rodriguez-Gutierrez R, et al. The efficacy and adverse events of testosterone replacement therapy in hypogonadal men: a systematic review and meta-analysis of randomized, placebo-controlled trials. J Clin Endocrinol Metab 2018;103:1745–54.
44. Corona G, Rastrelli G, Di Pasquale G, Sforza A, Mannucci E, Maggi M. Endogenous testosterone levels and cardiovascular risk: meta-analysis of observational studies. J Sex Med 2018;15:1260–71.
45. Ferlin A, Selice R, Angelini S, Di Grazia M, Caretta N, Cavalieri F, et al. Endocrine and psychological aspects of sexual dysfunction in Klinefelter patients. Andrology 2018;6:414–9.
46. Eisenberg ML, Betts P, Herder D, Lamb DJ, Lipshultz LI. Increased risk of cancer among azoospermic men. Fertil Steril 2013;100:681–5.
47. Eisenberg ML, Li S, Brooks JD, Cullen MR, Baker LC. Increased risk of cancer in infertile men: analysis of US claims data. J Urol 2015;193:1596–601.
48. Hanson HA, Anderson RE, Aston KI, Carrell DT, Smith KR, Hotaling JM. Subfertility increases risk of testicular cancer: evidence from population-based semen samples. Fertil Steril 2016;105:322–8.
49. Al-Jebari Y, Elenkov A, Wirestrand E, Schütz I, Giwercman A, Giwercman YL. Risk of prostate cancer for men fathering through assisted reproduction: nationwide population based register study. BMJ 2019;366:446–661.
50. Ferro M, Chiujdea S, Musi G, Lucarelli G, Del Giudice F, Hurle R, et al. Impact of age on outcomes of patients with pure carcinoma in situ of the bladder: multi-institutional cohort analysis. Clin Genitourin Cancer 2022;20:e166–72.
51. Crocetto F, Buonerba C, Caputo V, Ferro M, Persico F, Trama F, et al. Urologic malignancies: advances in the analysis and interpretation of clinical findings. Fut Sci 2021;7:67–82.
52. Miro C, Di Giovanni A, Murolo M, Cicatiello AG, Nappi A, Sagliocchi S, et al. Thyroid hormone and androgen signals mutually interplay and enhance inflammation and tumorigenic activation of tumor microenvironment in prostate cancer. Cancer Lett 2022;532:215581.
53. Ventimiglia E, Capogrosso P, Boeri L, Serino A, Colicchia M, Ippolito S, et al. Infertility as a proxy of general male health: results of a cross-sectional survey. Fertil Steril 2015;104:48–55.
54. Giovannone R, Busetto GM, Antonini G, De Cobelli O, Ferro M, Tricarico S, et al. Hyperhomocysteinemia as an early predictor of erectile dysfunction: International Index of Erectile Function (IIEF) and penile Doppler ultrasound correlation with plasma levels of homocysteine. Medicine 2015;94:e1556.
55. Glazer CH, Tøttenborg SS, Giwercman A, Bräuner EV, Eisenberg ML, Vassard D, et al. Male factor infertility and risk of multiple sclerosis: a register-based cohort study. Mult Scler J 2018;24:1835–42.
56. Del Giudice F, Kasman AM, Chen T, De Berardinis E, Busetto GM, Sciarra A, et al. The association between mortality and male infertility: systematic review and meta-analysis. Urology 2021;154:148–57.
57. Belladelli F, Del Giudice F, Kasman A, Salonia A, Eisenberg ML. The association between testosterone, estradiol and their ratio and mortality among US men. Andrologia 2021;53:e13993.
58. Del Giudice F, Kasman AM, Li S, Belladelli F, Ferro M, de Cobelli O, et al. Increased mortality among men diagnosed with impaired fertility: analysis of US claims data. Urology 2021;147:143–9.
59. Jensen TK, Jacobsen R, Christensen K, Nielsen NC, Bostofte E. Good semen quality and life expectancy: a cohort study of 43,277 men. Am J Epidemiol 2009;170:559–65.
60. Eisenberg ML, Kim S, Chen Z, Sundaram R, Schisterman EF, Buck Louis GM. The relationship between male BMI and waist circumference on semen quality: data from the LIFE study. Hum Reprod 2014;29:193–200.