Nutrigenetic Influences on Male Reproductive Health and Fertility: A Comprehensive Review of Dietary Factors and Genetic Linkages

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Abstract

Almost half of all families globally struggle with fertility problems, and in 40% to 50% of instances, a masculine element is involved. While the precise processes underlying this influence remain unclear, it is widely known that dietary status affects the progression of reproduction, wellness, and performance. Nutrigenetic processes may influence conception when variation in genes impacts nutrition expenditure. The information currently known on the effects of a number of food ingredients on masculine reproductive wellness is compiled in this article. These include vitamins A, B12, C, D, E, folate, betaine, choline, calcium, iron, caffeine, Fiber, sugar, dietary fat, and gluten. The proof of associations between genes and nutrients is also analysed, with possible implications for fertility. The development of individualized, DNA-based dietary recommendations to improve the chances for conception of men patients experience infertility requires a consciousness of the link underlying variation in genetic makeup, dietary intake, and the reproductive health of men.

Keywords: *Fertility, Genetics, Infertility, Male reproductive wellness, Nutrition.*

Introduction

A rising percentage of the population suffers from infertility, which is defined as being unable to conceive while having frequent, maximum annual sexual encounters despite the use of contraception [1, 2]. As many as fifteen percent of couples globally, or over seventy million individuals who are of sexual maturity, are thought to struggle to conceive, with masculine infertility accounting for roughly half of these instances [3,4]. According to reports, thirty-five percent of instances of fertility problems are thought to include solely women, twentieth percent are believed to include both men and women, thirty percent to require issues with the male alone, and fifteen percent or greater. of sterility cases are thought to have remained unresolved [5,6]."A disease characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse" is how the World Health Organization defines infertility [7]. Both men and women's capacity to reproduce is impacted by health and lifestyle variables, even though the exact reasons of infertility are sometimes unclear and complex. In males, anomalies related to motility, morphology, and sperm count all affect the likelihood of successful fertilization [8]. Oxidative stress has also been linked to sperm quality and fertilization capability. Oxidative stress is defined as an imbalance between antioxidants and free radicals created from oxygen that causes cell damage [.9]The complicated and expensive issue of infertility has a major negative influence on a couple's quality of life. To improve the likelihood

of becoming fertile, it is important to identify strategies for lowering the prevalence of infertility and changing one's lifestyle [10]. A strong correlation has been seen between the ability for reproduction in males and females and their diet, as evidenced by several studies [11]. As a result, a growing number of original research papers and review articles about the impact of diet on the male reproductive system have been published by scientists [12]. In their research, a number of scientists hypothesized that, in comparison to the Western diet pattern, the Mediterranean diet was better for the male reproductive system and semen quality. The reproductive health of men is greatly impacted by environmental factors such as using cannabis and cigarettes, using anabolic steroids, drinking too much alcohol, experiencing emotional stress, being older, wearing tight clothing, being in high temperatures too long, living a sedentary lifestyle, being exposed to chemicals and pesticides, radiofrequency electromagnetic radiation, cytotoxic drugs, and cadmium [13,14,15]. It is essential to remember that certain elements, like aging, pollution in the environment, or radiation, are unavoidable [16]. On the other hand, other studies indicate that using antioxidants—like resveratrol—might be a therapeutic substitute [17]. Additionally, current research indicates that keeping a healthy lifestyle is essential for maintaining adequate reproductive functions and that food is strongly related to the quality of semen [18,19].

Male infertility and Genetic associations

Four primary etiological groups are distinguished in masculine fertility problems: spermatogenic numerical flaws , vascular blockage or malfunction , alterations affecting the hypothalamic-pituitary axis, along with spermatogenic qualitative defects[20]. Roughly fifteen percent of male infertility is thought to be caused by hereditary causes. The most typical type of male infertility is unexplained oligoasthenoteratozoospermia (OAT), which is accompanied by the condition known as OAT is mostly caused by primary testicular failure, which shows up as quantitative deficiencies in spermatogenesis. Other prevalent causes of male infertility include duct blockage or defects in their morphology. The other two phenotypic groups include qualitative problems in spermatogenesis and hypothalamic-pituitary axis perturbation, which leads to subsequent testicular failure[21] .Only around 20% of infertile males can receive a genetic diagnosis after a standard diagnostic workup. Little chromosomal deletions, typically less than 5 Mb in size, known as Y chromosome microdeletions are difficult to identify by standard karyotyping methods. After discovering de novo deletions on the Y chromosome long arm (Yq) in azoospermic males in 1976, Tiepolo and Zuffardi postulated the presence of essential genes on Yq that are necessary for healthy spermatogenesis.[22] Later, the term "azoospermia factor" (AZF) region was coined to refer to the complete gene cluster located in the distal region of the Y chromosome long arm. The AZF area was characterised by Vogt et al. and Skaletsky et al., who also found the genes necessary for male fertility in this region.[19, 22] The long arm of the Y chromosome's AZF region is further divided into the AZFa (792 kb), AZFb (6.2 Mb), and AZFc (4.5 Mb) sections[23]. For X-linked genes, men are inherited as a and inherit a single X chromosome. Previous genomic research has demonstrated that spermatogenesis genes are concentrated on the X chromosome[24]. In recent decades, several X chromosomal genes associated with male fertility have been discovered. According to Wang et al., the X chromosome contains a number of genes that are mostly involved in the premeiotic phases of mammalian spermatogenesis[25]. The first X-linked meiosis gene, Tex11, is expressed in both male and female gametogenesis and creates unique foci on meiotic chromosomes. Male Tex11-deficient animals exhibit impaired double-strand break repair and dysregulated crossing over, which ultimately lead to spermatocyte death during the pachytene stage and sterility[26].

Retinoic Acid	•Gene - BCM01:rs11645428 •Impact - Meiosis I/II and post meiotic spermatid development [27]
Vitamin B12	•*Gene - FUT2*: rs602662 •Impact - Sperm count, quality and motility [28]
Vitamin C	•*Gene - GSTT1: insertion or deletion* •Impact - Semen volume, concentration, sperm count, morphology and motility [29]
Vitamin D	•*Genes - CYP2R1: rs10741657 ,GC: rs2282679* •Impact - Sperm motility and morphology,sex hormone binding globulin (SHBG) [30]
Vitamin E	•*Genes - CYP4F2: rs2108622 ,SCARB1: rs11057830 ,APOA5: rs12272004* •Impact - Acrosome reaction,sperm morphology [31,32,33]
Folate	•*Gene - MTHFR*: rs1801133 •Impact - Sperm density and morphology [34,35]
Choline	•*Gene - CHDH: rs12676 ,PEMT: rs4646343 ,PEMT: rs7946* •Impact - Sperm motility [36,37,38]
Betaine	•*Gene - CHDH +432: rs12676 ,PEMT -744: rs12325817* •Impact - Spermatogenesis [39,40]
Iron	•*Gene - TMPRSS6: rs4820268 ,TFR2: rs7385804 ,HFE: rs1800562 ,SLC17A91: rs17342717 ,HFE: rs179945 ,TF: rs3811647* •Impact - Spermatogenesis,sperm volume, density, motility and morphology.,excess leads to oxidative DNA damage [41,42,43,44,45,46,47].

Table 1 The possible influence of genetic variance in the absorption of micronutrients on male fertility

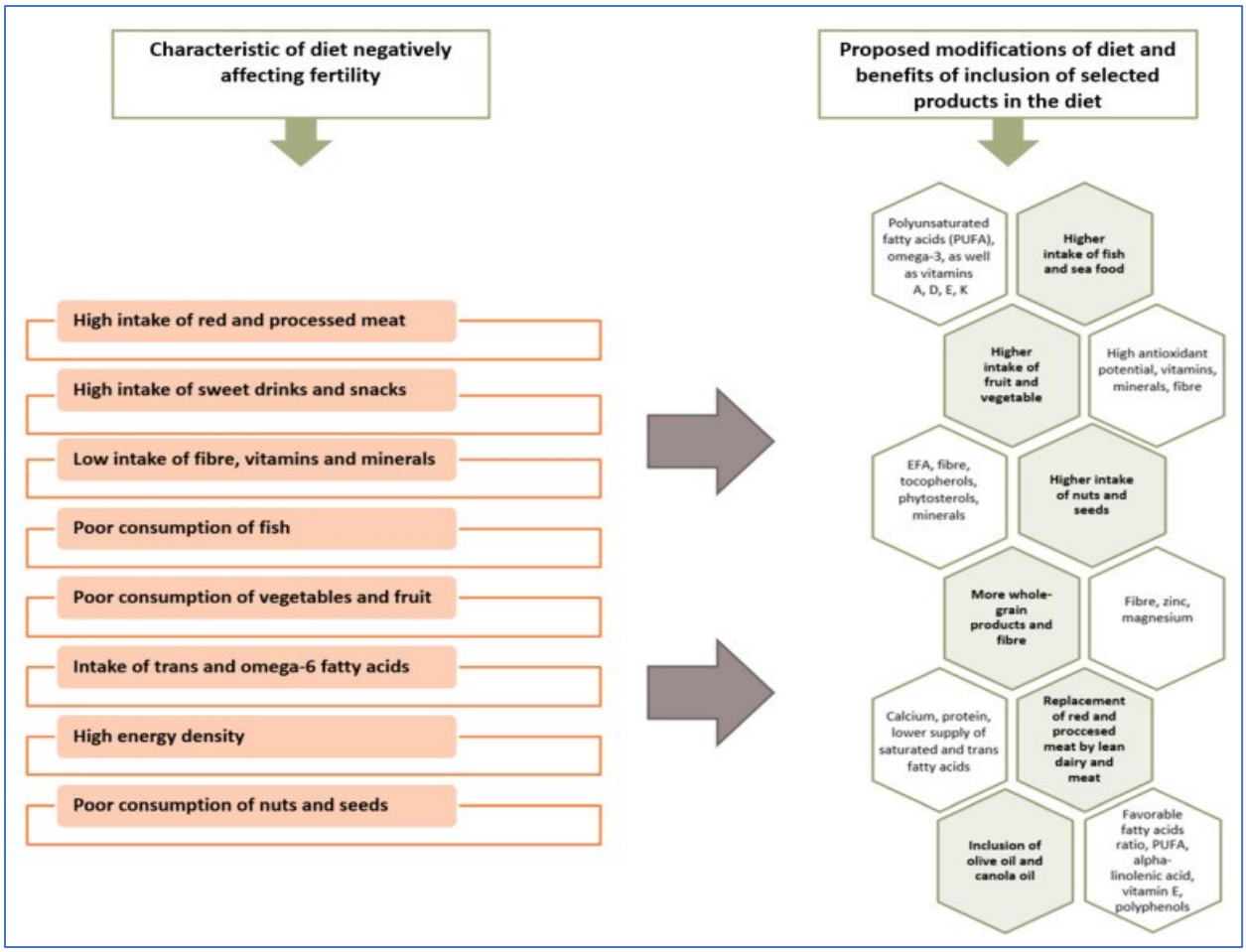

Figure 1 Features of an unfavorable diet that impact fertility and suggested changes [52].

A Dietary Model That Raises Male Infertility Risk

The so-called western diet has emerged as the primary dietary paradigm for both industrialized and developing nations in recent decades [48]. Saturated and trans fats, simple carbs, animal-based proteins, and a deficiency in dietary Fiber and essential unsaturated fatty acids (EFA) are the main components of the western diet. It also has an inadequate nutritional density and is inflammatory in nature, with a hypercaloric diet [49].It is evident that the metrics assessing the fertility of semen have declined as the western diet paradigm has spread [50,51].Lower semen parameters and decreased fertility are linked to a diet high in processed and, according to some sources, red meat, fatty dairy, coffee, alcohol, sweet drinks and sweets, potatoes, and simultaneously low in whole-grain products, vegetables and fruits, poultry, fish and seafood, nuts, and lean dairy [52, 53]. The picture presents characteristics of a diet that negatively affects fertility along with suggested adjustments. Obesity and a high-fat diet, which are encouraged by a bad lifestyle, have an impact on the development of progeny and their long-term health. Spermatozoa structure is also impacted. In fact, infertile males have been shown to follow incorrect dietary habits, which include skipping meals, consuming inadequate antioxidants, and consuming a high calorie density [54].

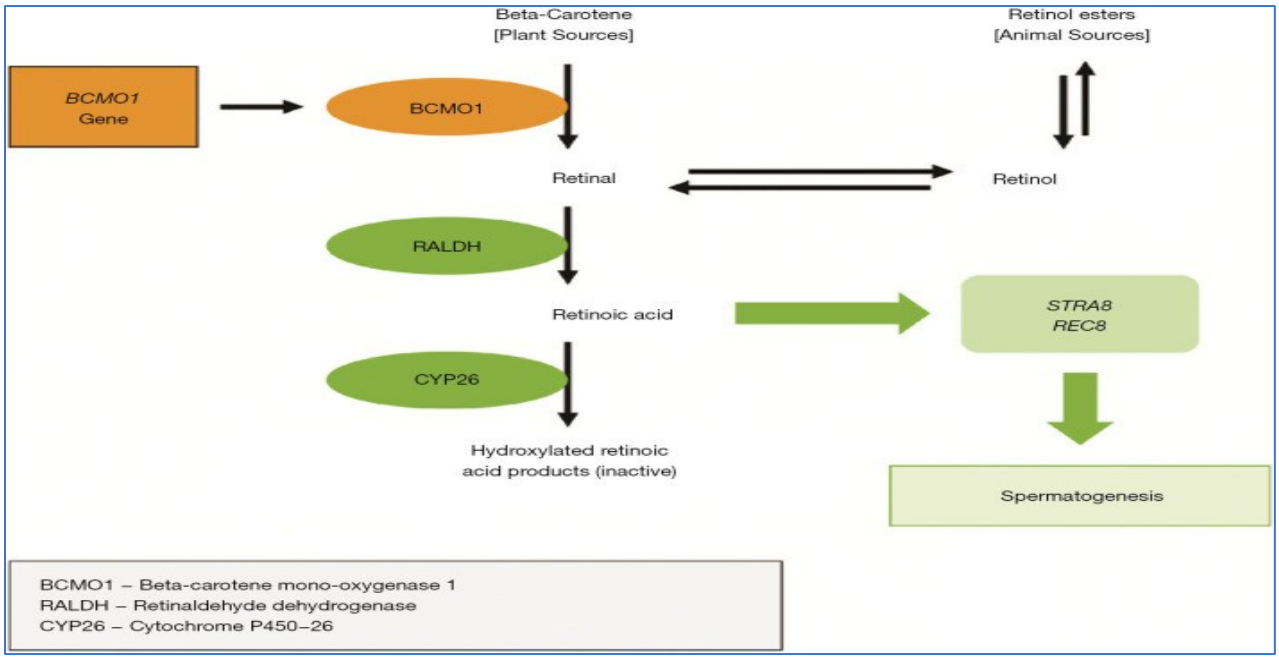

Figure 2 The metabolic route of vitamin A. Converting circulating beta-carotene to retinal (aldehyde) is the first step in the process of converting beta-carotene mono-oxygenase 1 (BCMO1) into retinoic acid. Spermatogenesis is aided by the induction of STRA8 and REC8 expression by retinoic acid[62].

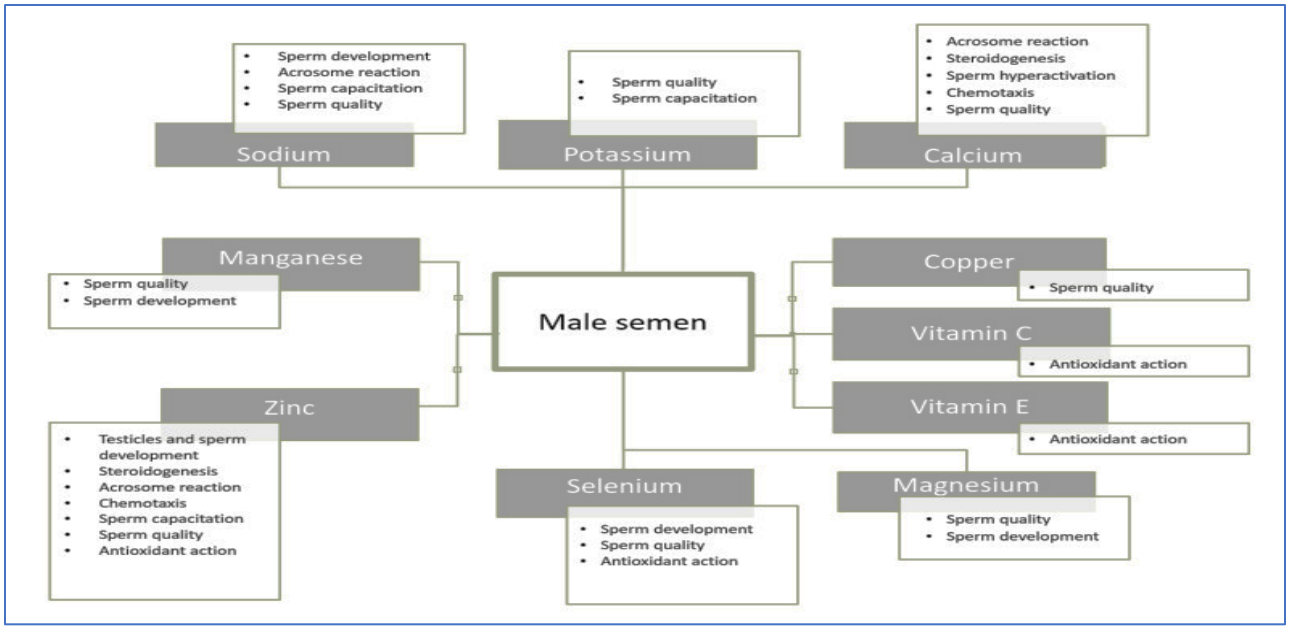

Figure 3 specific elements of male sperm and their functions [66].

Nuts in fertility management

Nuts contain a variety of amino acids and are a rich source of protein in addition to lipids. Amino acids and proteins are involved in many physiological processes in the body and are crucial in cellular signalling. Moreover, nuts provide healthy components that support antioxidant activity,

raising the body's total antioxidant capacity [55]. Nuts' high dietary fiber content adds to their total nutritional worth. Depending on the type of nut, the amount of fiber it contains might vary from 5 to 30% of the daily required amount. Dietary fiber helps to keep the digestive system healthy, increase fullness, and control blood sugar. Nuts can be a useful dietary addition for increasing fiber. Numerous vital micronutrients, such as vitamins as well as antioxidants including vitamin B, folate, and vitamin E, are found in nuts. These micronutrients are essential for preserving general health and bolstering the body's defensive systems [56]. Nuts do contain a good amount of calcium, potassium, sodium, and magnesium, among other minerals. But usually speaking, nuts have extremely little sodium [57]. It has been established that nuts have antioxidant effects on the male reproductive system, semen parameters, and sperm quality [58].

When vitamin E was isolated from several nut oils, researchers discovered that hazelnut oil had the greatest concentrations, followed by almond, peanut, pistachio, and walnut oils, in that order [59].

Effect of Vitamin A in male fertility

For the health of both male and female reproductive systems, vitamin A is crucial. The immune system, which controls the production of reactive oxygen species (ROS) and shields the prostate and female reproductive systems from oxidative stress, is supported by vitamin A [60]. The body uses beta-carotene, which is an inactivated form of vitamin A, and retinol, which is an activated version. Another vitamin A metabolite, retinoic acid, may regulate the shape of sperm and quantity, which may have an impact on male fertility[61].

Magnesium, Calcium, Copper, Manganese

Providing a sufficient amount of both magnesium and calcium is also advised. The former is essential to sperm production, the movement of sperm, and the health of the female reproductive system. Additionally, calcium influences the sperm's increased activity, motility, and capitulation, which in turn influences the acrosome response and sperm penetration into the egg [63]. Furthermore, manganese influences sperm motility and the procedure for fertilization, and copper is also required for sperm to function properly[64,65].

Fat and male fertility

Dietary fat performs a number of vital roles in the body. It functions as an energy source, protects organs, and is essential for the synthesis of hormones, cell membranes, and tissue membranes, among other physiological functions [67]. However, high-fat diets have been associated with an increased risk of obesity and have been shown to raise blood and semen triglyceride levels, which may enhance oxidative stress in reproductive organs [68] .Dietary fat choice is influenced by genetics. The perception of dietary fat in general and the movement of fat in the blood throughout the body are both influenced by the cluster of differentiation 36 (CD36) gene. Because of this, "supertasters," or those who have the GA or GG variations, have an increased ability to detect dietary fat [69].

Sugar and its effect in male fertility

A maximum of 10% of calories should come from added sugars, according to the 2015–2020 Dietary Guidelines for Americans [71]. The generation of the glucose transporter type-2 (GLUT2) protein is determined by variation in the GLUT2 (rs5400) gene, and it impacts the body's glucose levels. It has been demonstrated that T allele carriers prefer glucose more than CC genotype carriers due to

their lesser sensitivity[72]. Consuming too much sugar can have a detrimental effect on fertility and be a significant contributor to daily calorie intake. Excessive sugar consumption can also accelerate the development of chronic illnesses including type 2 diabetes and obesity [73,74,75]. The literature that is now available concentrates on sugar-sweetened beverages (SBs) as one concentrated source of added sugar[76].

Effect of smoking, alcohol and caffein in fertility

It is also important to address the usage of stimulants. Scholars consistently express agreement about the detrimental effects of smoking—both cigarettes and cannabis—on male fertility [77,78]. Semen quality does not appear to be negatively impacted by occasional alcohol intake; nevertheless, frequent alcohol consumption causes sperm morphology and semen volume to deteriorate [79].Remarkably, a study of 28 observational studies involving 19,967 males revealed that the presence of caffeine in tea, coffee, and cocoa drinks did not appear to have any detrimental effects on the quality of semen. On the other hand, some studies have linked caffeine-containing sweet drinks to reduced sperm concentration and semen volume and count [80].

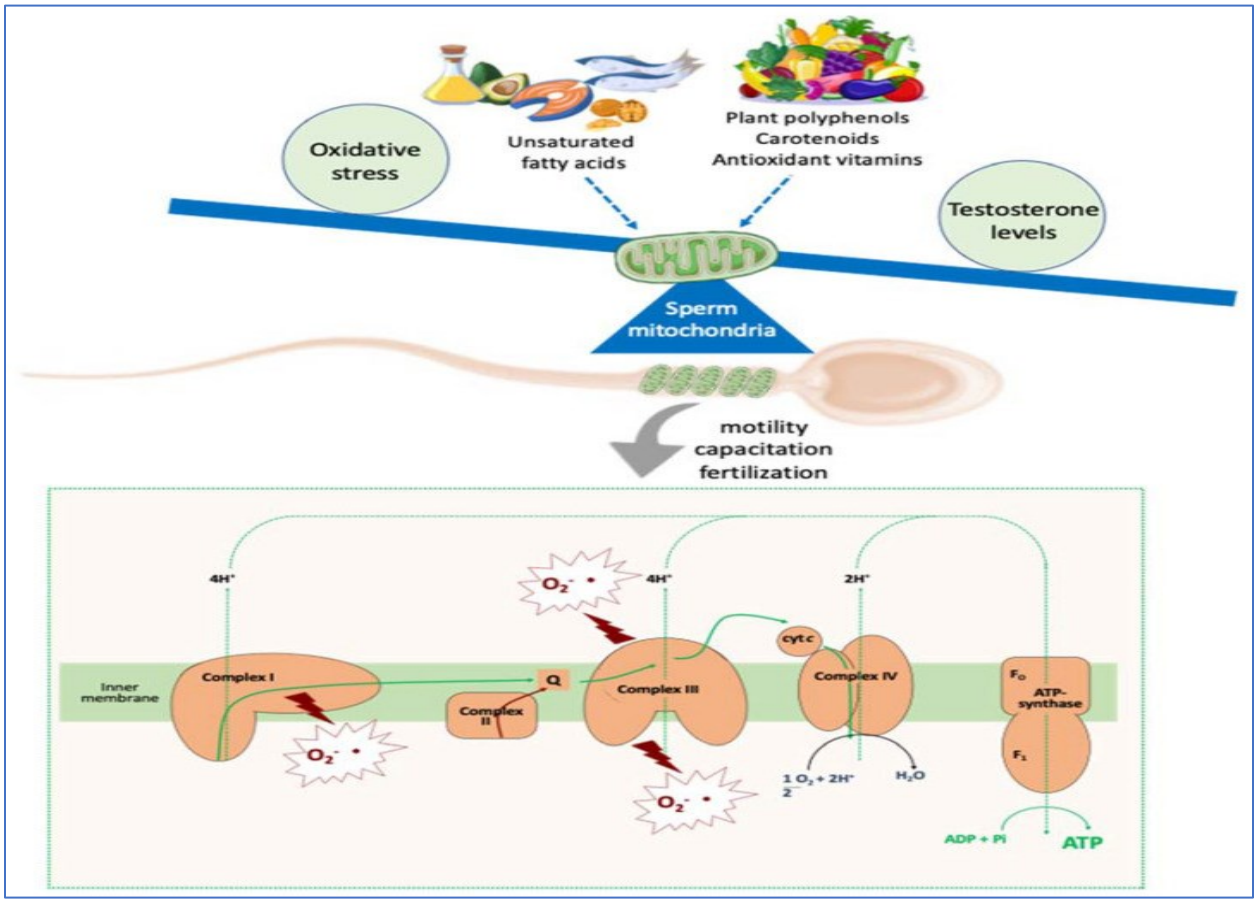

Figure 4 Nutritional factors that alter the mitochondrial activity of sperm [70].

The Mediterranean Diet

Within the framework of a diet that promotes fertility, the Mediterranean Diet (MD) is regarded as a nutritional model. Consuming a lot of fruit and vegetables, wholemeal products, nuts, fish, olive oil, and olive oil are characteristics of MD. The Mediterranean diet has been shown to offer several health advantages, mostly because of its lipid-lowering, anti-inflammatory, and antioxidant properties. As a matter of fact, this diet is advised to ward off heart disease, type 2 diabetes, neurological disorders, atrial fibrillation, and breast cancer [81,82]. In observational studies, the use of MDs has also been linked to improved semen quality; however, further interventional research in this area is needed to ascertain if MD use may increase the likelihood of a successful pregnancy outcome [83,84,85]

Antioxidant for male fertility

Studies on the effectiveness of antioxidant treatment are still conflicting, despite the fact that oxidative stress is typically the main cause of male infertility. Oral antioxidant supplementation appears to reduce DNA damage and enhance the metrics used to assess semen quality. Nevertheless, there are currently no trustworthy studies assessing the effect of antioxidant supplements on successful pregnancies and the live birth rate [86]. It was shown that antioxidant supplementation can increase the live birth rate in infertile males based on seven randomized trials examining the live birth rate after supplementation. The review's authors do, however, stress that there is a significant chance of mistake and that the studies are vague [87].

Future Prospects and Barriers of Male Infertility study

Human spermatogenesis is a very complicated process that is fueled by the controlled expression of several genes, as was previously mentioned. As a result, following semen assessment, the phenotypes associated with male infertility are more accurately described as a clinical endpoint of a range of different pathogenic processes [101]. Male infertility phenotypes that have been seen can be caused by autosomal recessive pathogenic variations acquired from fertile parents or by de novo variants. Genetic testing is presently being utilised to discover chromosomal abnormalities, Y chromosome microdeletions, and pathogenic variations associated with congenital hypogonadotropic hypogonadism in the routine diagnosis of male infertility. In fact, it has been more than 20 years since any novel genetic factors that influence clinical diagnostic workup or therapy choices were discovered [102,103,104]. As of right now, oligozoospermia and obstructive azoospermia caused by vas aplasia do not have any population-specific genetic markers. Modern genomic technologies enable the identification of several inherited pathogenic mutations in infertile males as well as the mapping of an entire exome or selected genes of interest (targeted gene resequencing). Another method that has been employed recently to find susceptibility loci linked to male infertility is genome-wide correlation analysis. The necessity to look into the genes linked to male infertility in other groups is unfulfilled in India. It needs to be highlighted, nevertheless, that certain genes—like NR5A1—that have been linked to male infertility in other groups are not linked to male infertility in Indian males[105]. Thus, it is necessary to rule out any genetic associations with infertile Indian males that have been found in other groups.

Dietary Component	Active Substances	Remarks
Oily sea fish	PUFA, omega-3 Fat-soluble vitamins A, D, E, K	Fish and seafood represent the main sources of DHA and EPA in the diet, therefore their incorporation in the diet may be associated with the improvement of semen quality [88]. Fish are often contaminated with mercury and other neurotoxic substances [89].
Vegetables and fruit	Antioxidants, folic acid, fibre, minerals	Vegetables and fruits provide the basis for pro-healthy nutrition models, which are associated with the improvement of semen quality and fertility [90]. It is worth choosing raw vegetables and fruits. Research suggests that pesticide residues may modify the beneficial effect of fruit and vegetable consumption on the quality of semen [91].
Nuts, seeds	EFAs, fibre, tocopherols, phytosterols, polyphenols, minerals	It is important to choose nuts and unroasted and unsalted seeds. The use of nuts in the diet may have a beneficial effect on the quality of sperm [92,93].
Whole-grain products	Fibre, zinc, magnesium	It is recommended to limit the consumption of refined flour products and choose whole-grain products, which are rich in fibre [94,95].
Lean dairy	Calcium, a wholesome protein	It is beneficial to choose low-fat dairy products, due to a lower saturated fat content [96].
Olive oil, rapeseed oil	PUFA, alpha-linolenic acid, vitamin E, polyphenols	It is advisable to substitute saturated fats with vegetable oils containing unsaturated acid residues [97,98,99,100].

Table 2 Attributes of a fertility-enhancing diet.

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Conclusion

The quality of testosterone may be impacted by nutrition in both favourable and negative ways. Greens and fruits, seafood, whole grains, nuts, seeds, poultry, low-fat dairy products, and meat and poultry products should all be included in the diet. Conversely, low levels of antioxidant-rich fruits and veggies, high calorie intake, diets high in trans and saturated fats, low levels of fish, and high levels of red and processed meat have been shown to adversely affect semen quality, which may potentially lead to decreased male fertility. Consequently, it appears that changing one's lifestyles specially in terms of nutrition is essential when it comes to male infertility linked to poor semen quality. Overall, available data points to the importance of nutritional status in male fertility as well as the effect of common genetic variants on nutrient metabolism and response to food on these processes. In order to improve fertility outcomes and advance our knowledge of reproductive function, the relationship between male fertility, nutrition, and genetic variation has not received much attention. However, there is evidence that these three variables are related, and their examination should be done in tandem in academic literature and clinical settings. Men who are having trouble becoming pregnant might consult certified dietitians to make sure their food consumption is meeting their needs for vital nutrients. By concentrating on individualized dietary recommendations based on genetic susceptibilities to deficiencies and toxicities, future study may shed light on this issue. One significant modifiable factor that may influence a man's ability to reproduce is his diet. Thus, it is important to emphasise the importance that daily nutritional exposure has in maintaining or preventing male infertility. A robust commitment to a plant-based, mostly fish-based diet is favourably connected with markers of fertility. While there is still much to learn about the intricate connection among sperm quality and nutrition, certain trends may be

identified. First, by influencing sperm energy utilisation, the quantity and calibers of nutrients added might impact the performance of sperm. The quality of sperm is thus adversely affected by diets high in unsaturated fatty acids (SFA) and low in polyunsaturated fats (PUFA) or by an imbalanced omega-6/omega-3 PUFA ratio. Conversely, sperm quality is improved by dietary SFA fortification.

By influencing oxidative stress and testosterone levels, which share the mitochondria as their common target, fats, carbs, and proteins have an impact on the quality of sperm. The mitochondria are an essential organelle that support a number of sperm processes. All chemicals that can modify their activities may have an impact on male fertility since they are involved in energy generation, ROS homeostasis, and steroid hormone biosynthesis. Natural polyphenols and dietary fatty acids are two of these chemicals that influence the mitochondrial activity of sperm. Indeed, the injection of polyunsaturated fatty acids (PUFA), particularly omega-3 PUFA, was found to decrease oxidative damage and boost the activities of mitochondrial enzymes involved in gamete energy metabolism. Furthermore, depending on their concentration, a variety of dietary natural polyphenols—mostly flavonoids—found in fruits and vegetables have varying effects on mitochondrial activity, either favourably or adversely. Therefore, enhancing sperm quality may be significantly aided by modifying sperm mitochondrial activity.

I acknowledge both the study of nutrition and male reproduction will only benefit somewhat from our investigation. Nonetheless, given the significance of nutrition in male infertility, which is becoming increasingly common, we think that more research into the molecular mechanisms underlying the effects of nutrients and natural compounds is required in order to create novel dietary strategies that will protect male reproductive potential.

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