

The impact of nutrition and lifestyle on male fertility

Mahmoud Benatta^{1,2}, Redha Kettache^{1,3}, Noor Buchholz¹, Alberto Trinchieri¹

¹ U-merge Ltd. (Urology for Emerging Countries), London, UK.

² Department of Urology, Djilali Lyabes University Hospital, Sidi Bel Abbas, Algeria;

³ Department of Urology, EPH Bachir Bennacer, Biskra, Algeria.

Summary *Background and aims: Male unexplained infertility has long been suspected to result from environmental, lifestyle and nutritional factors. However, the literature on the subject is still scarce, and clinical studies providing robust evidence are even scarcer. In addition, some similar studies come to different conclusions. Dietary pattern can influence spermatogenesis by its content of fatty acids and antioxidants. Yet, in an age of industrialized mass food production, human bodies become more exposed to the ingestion of xenobiotics, as well as chemicals used for production, preservation, transportation and taste enhancement of foods. We attempted in this paper to collect the available evidence to date on the effect of nutritional components on male fertility. Material and methods: A systematic search of the relevant literature published in PubMed, ScienceDirect and Cochrane Central Register of Controlled Trials Database was conducted. Literature was evaluated according to the Newcastle-Ottawa-Scale.*

Results: Epidemiological observations are concordant in demonstrating an association of low-quality sperm parameters with higher intake of red meat, processed and organ meat and full-fat dairy. On the contrary, better semen parameters were observed in subjects consuming a healthy diet, rich in fruit, vegetables, whole grains and fish. Evidences of the negative impact on male fertility of by-products of water disinfection, accumulation in food chain of persistent organochlorine pollutants, pesticides, phthalates from food and water containers and hormones used in breeding cattle have been reported. Clinical trials of the effects of micronutrients on semen parameters and outcomes of assisted fertilization are encouraging, although optimal modality of treatment should be established.

Conclusions: Although quality of evidence should be ameliorated, it emerges that environmental factors can influence male fertility. Some nutrients may enhance fertility whereas others will worsen it. With diagnostic analysis on a molecular or even sub-molecular level, new interactions with micronutrients or molecular components of our daily ingested foods and leisure drugs may lead to a better understanding of so far suspected but as yet unexplained effects on male spermatogenesis and fertility.

KEY WORDS: Male fertility; Nutrients; Micronutrients; Dietary supplements; Lifestyle; Xenobiotics.

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INTRODUCTION

Male infertility is attracting increasing interest due to its worldwide prevalence and the evidence of decline in semen quality of young health men (1). Prevalence of

reported male infertility ranges from 2.5% to 12% with highest rates in Africa and Central/Eastern Europe (2). Rates of male infertility in North America, Australia, and Central and Eastern Europe varied from 4.5-6%, 9%, and 8-12%, respectively. Male infertility is defined as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse as reported by couples or female partners of a couple.

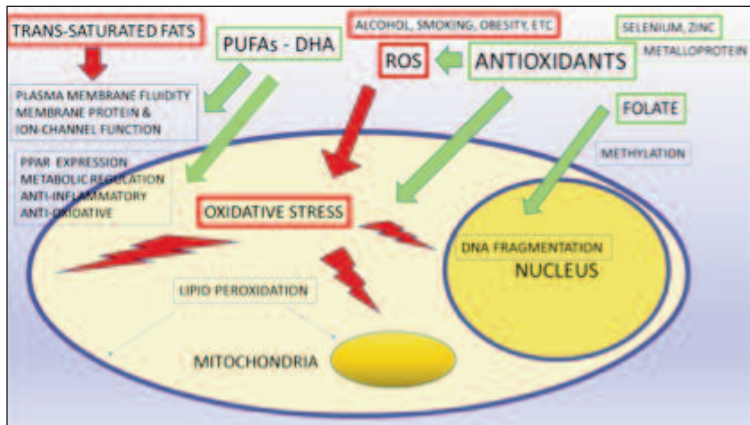
Seminal quality is a prognostic factor of fertility which can be considered a proxy of male infertility although fecundity also depends from other couple-based covariates (3). Along the last 50 years a progressive decrease of the quality of the seminal parameters has been observed. A recent systematic review of 185 studies involving more than 40.000 men who provided semen analysis in the period 1973-2011 demonstrated a significant decline between 1973 and 2011 (4). This trend may arise from genetic, developmental and lifestyle factors. Particularly, involvement of nutritional factors has been highlighted by many studies.

Cross-sectional population studies or case-control studies using food questionnaires evaluated the association of dietary patterns or quality of foods with seminal parameters (count, concentration, motility, morphology, DNA fragmentation) or with testis volume or sex hormone levels. In addition, some studies from fertility clinics considered more robust outcomes such as implantation rate, rate of clinical pregnancy and of live birth. Most of studies focused on the content of saturated fats that could have a negative impact on fertility or on the content of antioxidants and folates that could improve fertility. Molecular pathways of the effects of these nutrients in male fertility have been studied but they are not yet fully explained (Figure 1) (5-7).

Saturated fats are prevalent in animal-derived foods as red meat, processed meat and full-fat dairy product while fats from vegetable foods and fishes are polyunsaturated. Sperm cell are characterized by a high content of polyunsaturated fatty acids, as *docosahexaenoic acid* (DHA).

Concentrations of DHA with respect to saturated or trans fatty acids influence the melting point of plasmatic membrane, regulate the expression of *peroxisome proliferator-activated receptor gamma* (PPARG), anti-apoptosis and hormone activity. Particularly, omega-3 PUFAs in fish are precursors of eicosanoids, which contribute to sperm

Figure 1. Molecular pathways of the effects of fatty acids and antioxidants in sperm cell (negative effect in red, positive in green).



structure) and have a positive impact on testicular function. On the contrary, trans saturated fats interfere with the incorporation of long-chain polyunsaturated fatty acids into sperm membranes during epididymal maturation, and have a negative impact on testicular function, with reduction in total and free testosterone.

Antioxidants molecules, that are abundant in fruits and vegetables, have a positive effect on male fertility and in general on health conditions, by contrasting the activity of reactive oxygen species (ROS).

ROS (reactive oxygen species) show a biphasic effect on sperm cell function, because at physiological concentrations ROS from mitochondria have an important role in capacitation by activation of different intracellular mechanisms (high levels of cAMP, activating the PKA pathway, and leading to tyrosine phosphorylation). On the contrary, oxidative stress from excess ROS production causes peroxidation of lipids in the plasmatic membrane together with a damage of spermatic DNA. ROS have a negative effect on sperm motility by damaging plasmatic membrane and mitochondrial function.

Folates are involved in DNA synthesis and in methylation processes connected with protein synthesis. Folate deficiency causes instability and fragility of DNA by reducing availability of methyl groups that are a protection factor of DNA.

Other micronutrients are involved in the development of male infertility, as divalent cations such selenium, zinc or manganese that have a role in oxidative stress being incorporated in enzymes such as glutathione peroxidase or superoxide dismutase (8). Optimal levels are requested for spermiogenesis, whereas both deficiency and excess intake are associated with alterations of seminal parameters and serum testosterone levels.

In addition to the effects of nutrients, food intake can be associated to exposure to food-contaminating toxic substances or hormones that can have a relevant impact on male fertility. In an age of progressive industrialization, and moreover industrial mass food production using herbicides, pesticides, antibiotics, hormones, and chemicals to preserve and enhance the taste of heavily processed foods, these components can be absorbed into the human body. Evaluation of the effects of toxic contamination of

foods is difficult by using dietary questionnaires whereas more reliable results can be obtained by using biological markers to evaluate exposure to toxic substances.

The effects of the intake of some foods on seminal parameters can be biased by the concomitant effect of contamination. By example, it is difficult to differentiate the impact of consumption of vegetables from that of pesticides that are used in agriculture or the effect of red meat from that of residual hormones that could have been used in breeding or that of fish consumption by the risk of contamination from sea water pollution.

Finally, other information can be derived from the evaluation of the effect of the administration of dietary supplements to ameliorate seminal parameters of subfertile men attending fertility centres.

In this paper, we tried to review and summarize the available evidence on the topic. Our results are subdivided in two chapters describing review of epidemiological observations and clinical studies respectively.

METHODS

A systematic search of the relevant literature published in PubMed, ScienceDirect and Cochrane Central Register of Controlled Trials Database was conducted. We reviewed separately epidemiological observations as reported in the literature and clinical trials with various nutritional components and their influence on male fertility.

For this reason, two separate searches (up to December 2018) were done using a combination of terms as both, Medical Subject Headings (MeSH) and keywords.

In the first search, male fertility-related keywords (“male fertility” OR “male infertility” OR “semen quality” OR “oligoasthenozoospermia” OR “sperm DNA fragmentation” OR “sperm DNA damage” OR “sperm aneuploidy” OR “Y chromosome”) were used in combination with key words relating to food or nutrient (“food” OR “diet” OR “nutrition” OR “meat” OR “fish” OR “sugar” OR “vegetables” OR “fruits” OR “dairy” OR “genetically modified food” OR “alcohol” OR “pesticides”

Figure 2. Systematic literature search 1.

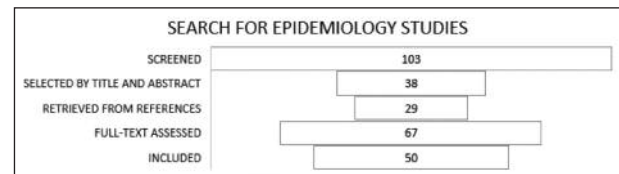


Figure 3. Systematic literature search 2.



OR “hormone food contaminated” OR “tobacco” OR “cannabis”) and combined with ‘questionnaire’ (Limit: Human, English). Reviews, clinical trials and case reports were excluded (Figure 2).

In the second search the same male fertility-related keywords were used in combination with key words relating to vitamin or micronutrient or herbal treatments (“selenium” OR “vitamin E” OR “coenzyme Q10” OR “zinc” OR “L-Carnitine” OR “folic acid” OR “L Arginine” OR “herbal”). (Limit: Human, English). Only clinical trials were included (Figure 3).

The first search screened 103 studies, that were reduced to 38 after evaluation by title and abstract; 29 studies were retrieved by references of the selected studies; a total of 67 studies was assessed and 50 were included in the review. In the second search, the number of study screened, selected by title/abstract, retrieved by references, assessed and included were 79, 43, 14, 57 and 19 respectively.

Information extracted from each study was charted

including: first author's last name; year of publication; number of subjects; food or nutrients or dietary pattern studied. Literature was evaluated using the Newcastle-Ottawa-Scale and evaluation forms. A narrative review of the data from the included studies was done.

RESULTS

Epidemiological observations

Nutrition and lifestyle are considered by several authors as main factors in reproduction and fertility (9-11). Recent studies indicate that male obesity (12), as well as lifestyle factors as smoking and alcohol intake affect negatively the sperm quality (13).

Diet plays a key role in the improvement of sperm parameters, particularly the Mediterranean diet which is rich in omega 3 fatty acids, antioxidants and vitamins (vitamin E, vitamin C, beta-carotene, lycopene, cryptoxanthin, lutein) that all are associated with better semen

Table 1.
Vitamin, mineral and antioxidant intake and sperm quality.

Author	Sample	Nutrient/food	Effect on semen quality	Parameters
Eskenza <i>et al.</i> (2005) (14)	97 healthy controls	Folate	No association	
		Zinc	No association	
		Vitamin C	Positive	Sperm count (P = 0.04), Sperm concentration (million/mL) (P = 0.05) Total progressively motile sperm count (million/mL) (P = 0.09)
		Vitamin E	Positive	Progressive sperm motility (%) (P = 0.04) Total progressively motile sperm count (million/mL) (P < 0.05)
		β-carotene	Positive	Sperm concentration (million/mL) (P = 0.06) Progressive motility (P = 0.06)
Mendiola 2010 (15)	31+30 men of couples attending a fertility clinic without/with poor semen quality	Folate	Positive	Semen quality
		Vitamin C	Positive	Semen quality
Minguez-Alarcón 2012 (16)	215 healthy controls (university students)	Lycopene	Positive	Semen quality
		Cryptoxanthin	Positive	Total motile sperm count P trend = 0.03
		Vitamin C	Positive	Total motile sperm count P trend = 0.04 Semen volume P trend = 0.04
		Lycopene	Positive	Total motile sperm count P trend = 0.03
		β-carotene	Positive	Total motile sperm count P trend = 0.04
Zareba 2013 (17)	189 healthy controls (university students)	β-carotene	Positive	Progressive motility
		Lutein	Positive	Progressive motility
		Lycopene	Positive	Sperm morphology
		Vitamin C	Nonlinear relationship	Sperm concentration (second quartile highest sperm concentrations top quartile of intake lowest concentrations)

Table 2.
Dietary patterns and sperm quality.

Author	Sample	Dietary pattern	Effect on semen quality	Parameters
Vujkovic 2009 (20)	161 men from subfertile couples	Health Conscious dietary pattern (high intakes of fruits, vegetables, fish and whole grains)	Positive	DNA fragmentation index (DFI)
		Traditional Dutch dietary pattern (high intakes of meat, potatoes and whole grains and low intakes of beverages and sweets).	Positive	Sperm concentration
Gaskins 2012 (21)	188 healthy controls (university students)	'Western' pattern (high intake of red and processed meat, refined grains, pizza, snacks, high-energy drinks and sweets)	No association	
		'Prudent' pattern (high intake of fish, chicken, fruit, vegetables, legumes and whole grains)	Positive	Percent progressively motile sperm in multivariate models (P trend = 0.04)
Cutillas-Tolin 2015 (22)	215 healthy controls (university students)	Mediterranean pattern (high intakes of vegetables, fruits and seafood)	Positive	Total sperm count (P trend = 0.04)
		Western pattern (high intakes of processed meats, French fries and snacks)	Positive	Morphologically normal sperm % (P trend = 0.008)
Liu 2015 (23)	7282 subjects attending medical screening program	Western diet	Negative	Sperm concentration P < 0.001 Sperm morphology P < 0.001
		High sweet snacks & sugar-sweetened drinks	Negative	Sperm concentration P = 0.001
		High-carbohydrate diet	Negative	Total sperm motility P = 0.012 Progressive sperm motility P = 0.025
		High-sodium diet	Negative	Sperm morphology P = 0.035
Jurewicz 2016 (24)	336 men attending infertility clinic	Prudent pattern (high intakes of fish, chicken, fruit, cruciferous vegetables, tomatoes, leafy green vegetables, legumes, and whole grains) versus Western pattern (high intakes of red and processed meat, butter, high-fat dairy, refined grains, pizza, snacks, highenergy drinks, mayonnaise, and sweets)	Positive Negative	Sperm concentration (P = 0.05) Level of testosterone (P = 0.03) Decreased DNA fragmentation index (P = .05) Same parameters

quality parameters (Table 1) (14-18). A better compliance with Mediterranean diet was found to be associated with better semen quality parameters (sperm concentration, count, and motility) (19).

Similarly, in non-Mediterranean Countries, the so called "Prudent" or "Health Conscious" diets, involving high intakes of fruits, vegetables, legumes, fish and whole grains, were related to better sperm quality than "Western" diet that is rich in red and processed meat, refined grains, high-energy drinks and sweets (Table 2) (20-24). Higher intakes of seafood, poultry, whole grains, fruits and vegetables have been consistently associated with better semen parameters in a wide range of studies in *North America*, *Europe*, the *Middle East* and *East Asia*. (Table 3) (10, 19-27). A recent review concluded that diets rich in red and processed

meats, potatoes, sweets and sweetened beverages were associated with decreased quality of semen parameters whereas higher intakes of fruits and vegetables, whole grains, seafood and poultry had the opposite effect (34). Soy foods have been inversely associated with the quality of semen in some studies (35) although soy food intake in men was not related to outcomes of in vitro fertilization in couples undergoing infertility treatment (36).

The intake of trans and saturated fats has been related to poor semen quality. Trans-saturated fat intake has also been related to other markers of poor testicular function, such as lower testosterone and lower testicular volume (37-40) (Table 4). On the contrary, omega-3 polyunsaturated fats were associated with better seminal parameters and testicular volume (37, 40).

Table 3.
Foods and sperm quality.

Author	Sample	Foods	Effect on semen quality	Parameters
Mendiola 2009 (25)	31+30 men of couples attending a fertility clinic without/with poor semen quality	Lettuce and tomatoes, fruits (apricots and peaches)	Positive	Comparison of men with poor semen quality and normospermic controls
		Dairy and meat processed products	Negative	Comparison of men with poor semen quality and normospermic controls
Maldonado-Carceles 2019 (26)	206 healthy controls (university students)	Total meat	No association	
		Shellfish	Positive	Progressive motility P trend ≤ 0.001
		Organ meats	Negative	Progressive sperm motility $P = 0.001$ (higher luteinizing hormone levels $P = 0.03$)
Eslamian et al. (2012) (27)	169+72 men of couples attending a fertility clinic without/with poor semen quality	Processed meat	Negative	Volume, sperm concentration, motility and morphology Higher risk of asthenozoospermia OR 2.03
		Sweets intake	Negative	Higher risk of asthenozoospermia OR 2.05
		Total fruits & vegetables	Positive	Lower risk of asthenozoospermia P trend = 0.04
		Dark green vegetables	Positive	Lower risk of asthenozoospermia P trend = 0.01
		Skim milk	Positive	Lower risk of asthenozoospermia P trend = 0.02
		Poultry	Positive	Lower risk of asthenozoospermia P trend = 0.03
		Sea food	Positive	Lower risk of asthenozoospermia P trend = 0.04
Bravo 2012 (10)	250 men undergoing ICSI	Fruit & cereals	Positive	Sperm motility
		Red meat	Negative	Implantation rate Pregnancy chance
		Weight loss diet	Negative	Implantation rate Pregnancy chance
Afeiche 2013 (28)	189 healthy controls (university students)	Total dairy foods	Negative	Normal sperm morphology % P trend 0.004
		Full-fat dairy foods	Negative	Normal sperm morphology % P trend 0.002 Progressive motility P trend 0.04
Afeiche 2014 (29)	189 healthy controls (university students)	Low-fat dairy food	Positive	Progressive motility (%) P trend = 0.03
		Low-fat milk	Positive	Progressive motility (%) P trend = 0.003 Sperm concentration (million/mL) P trend = 0.05
Afeiche 2014 (30)	189 healthy controls (university students)	Processed red meat	Negative	Total sperm count P trend = 0.01 Ejaculate volume (mL) P trend = 0.003
Afeiche 2014 (31)	155 men of couples attending fertility center	Fish intake	Positive	Normal morphology P trend = 0.01 Sperm count P trend = 0.005
Ohw (2014) (32)	189 healthy controls (university students)	Sugar-sweetened beverage	Negative	Sperm motility (%)
Ohw (2015) (33)	155 men of couples attending fertility center	Total fruit & vegetables	No association	Semen quality parameters
		High pesticide residue fruit and vegetable intake	Negative	Total sperm count P trend = 0.003 Morphologically normal sperm % P trend = 0.02
		Low-to-moderate pesticide residue fruit and vegetable intake	Positive	Morphologically normal sperm P trend = 0.04
Chavama 2008 (35)	99 men of subfertile couples	Soy food	Negative	Sperm concentration
Minguez-Alarcon 2015 (36)	184 men of couples attending fertility center	Soy foods	No association	Fertilization rates, poor quality embryos, accelerated or slow embryo cleavage rate, and implantation, clinical pregnancy and live birth

Critical appraisal of this evidence highlights some possible limitations. In most cross-sectional studies populations were numerically limited and not always representative of the general population. Many studies were performed on volunteers recruited among university students aged 18 to 23 years, whereas other studies considered men from couples who attended fertility clinics. Translation of these results to the general population might be questionable. Only a few studies have been carried out in numerically consistent populations representing the general population (23, 38). Similarly, case-con-

trol studies were performed by comparing the dietary intakes of men from couples attending fertility clinics with and without alterations of seminal parameters.

Alcohol and caffeine

Alcohol induces testicular atrophy and alterations of Leydig and Sertoli cells and decrease *luteinizing hormone* (LH) and *follicle-stimulating hormone* (FSH) levels (41).

Daily consumption of alcohol affects sperm quality and decreases ejaculate volume, sperm counts, and sperm motility. Comparing the sperms of 66 "alcoholic" men to

Table 4.
Dietary fats and semen quality.

Author	Sample	Nutrient/Food	Effect on semen quality	Parameters
Attaman et al. (2012) (37)	99 male partners from infertile couples	Total fat	Negative	Total sperm count and sperm (P trend = 0.01)
		Saturated fat	Negative (NS)	Sperm levels (r = 0.09)
		Omega-3 polyunsaturated fats	Positive	Saturated fat intake was unrelated to sperm levels (r = 0.09) Normal morphology rate (P trend) = 0.02)
Jensen 2013 (34)	701 men from general population	High saturated fat Quartiles of fatty acid intake: total fat, saturated, monounsaturated, polyunsaturated, omega-3, omega-6	Negative	Sperm concentration Total sperm count No association between semen quality and intake of other types of fat was found
Chavama 2014 (38)	209 healthy controls (university students)	Trans fatty acid intake	Negative	Total sperm count (P trend = 0.03)
		Cholesterol	Negative	Ejaculate volume (P trend = 0.04)
Minguez-Marcón 2017 (39)	209 healthy controls (university students)	Monounsaturated fatty acids	Negative	Free testosterone, total testosterone, and inhibin B
		Trans fatty acids	Negative	Total testosterone and free testosterone (P trend = 0.01 and 0.02, respectively) Testicular volume
		Omega-3 polyunsaturated fatty acids	Positive	Testicular volume
		Omega-6 polyunsaturated fatty acids	Negative	Testicular volume (higher LH)

those of 30 "non-alcoholic" men, there was a significant decrease in sperm count, progressive motility, and vitality (42). Chronic high consumption of alcohol (more than 60 g per day or 6 glasses of wine) can lead to azoospermia (43). There is a significant inverse relationship between alcohol consumption and sperm concentration, sperm count and percentage of typical spermatozooids. Stopping consumption would restore normal spermatogenesis and azoospermia secondary to alcohol (44).

A meta-analysis confirmed that alcohol has a detrimental effect on semen parameters although spermatogenesis seemed to be not affected by a moderate consumption (45). Another meta-analysis of the effects of alcohol on *in vitro* fertilization (IVF) showed that live birth rates are significantly reduced when humans consume alcohol even in

lower doses in the month or even the week before attempted fertilization. Excessive consumption of alcohol must be avoided in humans during the attempted medical assisted fertilization, but a moderate consumption (one or two glasses of wine per day) might also have an opposite effect on the spermatogenic characteristics and the results of the medical assisted procreation attempt (46). A systematic review of the effects of coffee and caffeine intake on semen parameters found inconsistent evidences and conflicting results, although some studies showed a possible association with sperm DNA damage (47).

Food and water contamination

Most of the literature on the effect of water and food contaminants on male infertility is derived from experimental

Table 5.
Water and food contaminants and male infertility.

Contaminant	Source	Mechanism	Epidemiological data & markers of exposure
Trihalomethanes and haloacetic acids	By products of water disinfection	Interaction of disinfecting agents (chlorine and ozone) with naturally occurring substances in the water	Urinary trichloroacetic acid associated with lower sperm concentrations Serum trihalomethane levels conflicting results
Persistent organochlorine pollutants (POPs)	Pesticides industrial chemicals solvents	Accumulation in food chain with animal sources (particularly fish)	Serum polychlorinated biphenyl (PCB) metabolite levels associated with lower sperm concentrations Several POPs associated with lower sperm count CB-153 and p,p'-DDE levels associated with lower sperm count (conflicting results)
Pesticides	Agriculture	Dietary consumption (transcutaneous absorption and inhalation)	Organophosphate metabolites were found to be negatively associated with total sperm counts
Phthalates	Plasticizers in consumer and personal care products	Dietary contamination by food and water containers	Urinary dibutyl phthalate (DBP) associated with higher serum estradiol levels and estradiol: testosterone ratio, lower serum testosterone levels and sperm counts (most but not all studies) Urinary monobutyl phthalate (MBP) associated with decreased sperm counts
Glycol ethers	Industrial solvents, thinners, de-icers	Inhalational, transcutaneous, and dietary	Professional exposure associated increased risk of oligospermia and azoospermia in men

animal studies or studies of acute occupational exposure. Evidence of the effects in the general population of chronic low-dose exposures is limited because of the complexity of the design of the studies. Levels of biological markers of exposure have been correlated with seminal and hormone parameters in general population. Available data has been reviewed by *Gabrielsen and Tanrikut* (8). In Table 5 we summarized evidences about water and food contaminants that could affect male fertility.

Food contaminants often induce endocrine disorders, as in the case of commonly used glyphosate-based herbicides that act as a disruptor of mammalian cytochrome P450 aromatase activity from concentrations 100 times lower than the recommended use in agriculture and can also affect aromatase gene expression (48). Endocrine disorders can also be induced by the presence of residual hormones in red meat and processed meat. In some countries anabolic sex steroids are administered to cattle for growth promotion resulting hormone residues in beef. Although the possible biological significance of very low levels of estradiol is neglected, residual hormones are one possible explanation of lower semen quality parameters observed in consumers of processed or red meat (49). On the other hand, maternal beef consumption, and possibly xenobiotics in beef may alter testicular development in utero and adversely affect offspring reproductive capacity (50). Despite a lack of human studies, a link between infertility and *genetically modified foods* (GMF) has been postulated although GMF-related infertility seems to affect women more than men (51).

Tobacco

Smokers have an unusually high concentration of heavy metals in the seminal fluid, such lead and cadmium that are negatively correlated with sperm concentration, mobility and morphology (52). On the other hand, high levels of trans-3'-hydroxycotinine (3HC), a metabolite of nicotine, in seminal fluid are correlated with a decreased sperm mobility (53). The seminal plasma analysis of smokers shows a significantly higher proportion of inflammatory proteins. In fact, smoking seems associated with an inflammatory state of the accessory glands, which would eventually cause an alteration of the functional quality of spermatozooids, a decrease of acrosome integrity and mitochondrial activity, and an increased DNA fragmentation (54). Sperm concentration, total motility, and the number of typical spermatozooids is reduced in smokers (55).

Tobacco also affects the intrinsic quality of spermatozooids. The analysis of the degree of fragmentation of sperm DNA showed a significantly higher fragmentation of DNA in smokers than in non-smokers (32% against 25.9%) (56). In an in-vitro fertilization trial, smoking among men was significantly and positively correlated with an increased risk of early spontaneous abortion (OR = 2.2) (57).

Paternal smoking can also influence the health of newborns by transmission of DNA damaged by oxidative stress. Alterations of the methylation of sperm DNA in male smokers are compatible with alterations observed in their offspring (58). In addition, de-novo mutations in paternal spermatozooids induced by smoking can be transmitted (59).

Cannabis

After consumption of cannabis, its metabolites are found in the seminal fluid, and spermatozoa are thus exposed during their passage through the epididymis (60). Cannabis interferes with spermatogenesis by central and peripheral mechanisms. The stimulation of receptors coupled to G protein inhibits adenylate cyclase levels decreasing cAMP levels in testicular tissue, spermatozoa, and hypothalamus. Cannabis blocks the hypothalamic release of GnRH and the anterior pituitary production of LH. Furthermore, it reduces the release of testosterone from Leydig cells via specific receptors (61).

In a large sample of the general male population of Denmark, there was a significant negative correlation between cannabis consumption and sperm concentration, count, and mobility. In case of regular exposure to cannabis (9 to 18 cannabis joints a week) a decrease in sperm concentration was observed with a significant negative correlation between the amount of cannabis consumed and the sperm count. Chronic and intensive use of cannabis (more than 10 cannabis joints per week) was also associated with an alteration of Leydig cell function resulting in a significant dose-dependent decrease in testosterone serum levels (62). In conclusion, cannabis use should be considered as a potential cause of alteration of spermatogenesis or a co-factor aggravating pre-existing spermatogenesis disorders.

Obesity

Obesity is related to excessive intake of food and reduced physical activity. Oligospermia is more frequent in obese men and in obesity an increase in DNA fragmentation was also described (63). Multiple interdependent mechanisms contribute to the negative effect of obesity on male fertility (64). Obesity is associated to alterations of the hypothalamic-pituitary axis because of various endocrine mechanisms such as production of estrogens by aromatization of testicular and adrenal androgens in excess adipose tissue, leptin resistance at kisspeptin neurons, and excessive production of endogenous opioids, leading to hypogonadotropic hyper-estrogenic hypogonadism. A significant decrease in free and total testosterone levels and a significant increase in estrogen levels are resulting, both contributing to alteration of spermatogenesis. The decrease in serum testosterone concentration is significantly associated with insulin resistance and a lower volume of ejaculate (65). Furthermore, obesity may directly alter spermatogenesis by its action on Sertoli cells, as suggested by the more severe decrease in inhibin B levels compared with the decrease in FSH. Finally, an increase in scrotal temperature caused by excessive testicular warming in the seated position may negatively affect spermatogenesis.

Clinical trials

Several interventional studies evaluated the effect of dietary supplementation on semen parameters of subfertile men or outcomes of assisted fertilization. Oral supplements include coenzyme Q10, L-Carnitine, vitamins, zinc and other antioxidants.

Coenzyme Q10

A significant improvement of spermatogenesis was evi-

dent with coenzyme Q10 therapy. Mean sperm concentration, sperm progressive motility, and rate of sperm with normal morphology improved significantly after 12 month of coenzyme Q10 therapy (66). A positive correlation was found between duration of Q10 treatment duration and sperm count, motility and morphology (67). Even the reduced form of coenzyme Q10 (ubiquinol) was significantly effective in men with unexplained oligoasthenoteratozoospermia (68).

L-Carnitine

L-Carnitine (LC) together with *acetyl-L-Carnitine* (LAC) are commonly used because of their ability to improve sperm quality and pregnancy rate in males suffering from asthenoteratozoospermia (69). LC and LAC improve the total oxyradical scavenging capacity of the seminal fluid (70) and prevent DNA oxidation of human spermatozoa (71). Treatment with LC increased the success rate of *intracytoplasmic sperm injection* (ICSI) (72). In a double-blind randomized controlled trial, a combination of LC and coenzyme Q10 increased sperm motility and rate of progressively motile sperm more than LC or coenzyme Q10 alone or than in the control group. The percentage of sperm DNA fragments was markedly low and the rate of clinical pregnancy was remarkably higher in the combination group than in controls (73).

Vitamin E

Levels of vitamin E in seminal plasma are related to sperm motility (74). Accordingly, lower levels of vitamin E were observed in the semen of infertile men (75). A prospective, multi-centered, randomized controlled study reported that vitamin E can improve sperm concentration, percentage of progressively motile sperm, and rate of natural pregnancies (76).

Zinc and folic acid

The zinc concentration of seminal plasma is significantly higher in fertile men in comparison to subfertile men (77). In a study, supplementation with zinc sulphate and folic acid did not ameliorate sperm functional parameters in oligoasthenoteratozoospermic men (78), whilst in another double-blind, placebo-controlled interventional study the total normal sperm count increased after a combined zinc sulfate and folic acid treatment in both subfertile and fertile men (79).

Combination treatment

A double-blind placebo-controlled study (80) using supplementation of *L-carnitine*, *fumarate*, *acetyl-L-carnitine*, *Fructose*, *CoQ10*, *vitamin C*, *zinc*, *folic acid* and *vitamin B12* reported an increase of sperm concentration, total motility and pregnancy rate in couples whose males had varicocele or not. No difference of semen volume and not significant improvement of progressive motility were observed. Another double-blind, multi-center, randomized controlled trial showed that a combination of antioxidants and vitamins (*vitamin C*, *vitamin D3*, *vitamin E*, *folic acid*, *zinc*, *selenium*, *L-carnitine*) did not improve semen parameters or DNA fragmentation in infertile men (81). An evidence-based review of randomized trials concluded that antioxidant supplements are beneficial in

improving semen quality and clinical pregnancy rates for men from couples undergoing infertility treatment (82). More recent meta-analyses confirmed the positive results of the administration of antioxidants in subfertile men, although the poor quality of the studies considered in their analyses was highlighted.

A Cochrane meta-analysis considered 61 *randomized clinical trials* (RCTs) with a total population of 6000 subfertile men of couples attending a reproductive clinic to evaluate the effect of the oral administration of a wide range of 18 antioxidants on assisted reproductive techniques outcomes pregnancy or live birth rate (83).

Only few small studies reported on pregnancy or live birth rate. Use of antioxidants increased, the chance of clinical pregnancy from an estimated baseline of 7% following placebo or no treatment to a 12% to 26% rate after antioxidants (OR = 2.97). Live birth rate after antioxidants ranged between 14 and 26% whereas a 12% rate was observed after placebo or no treatment (OR = 1.79).

Most studies were rated as 'low' to 'very low' quality with high heterogeneity and serious risk of bias (poor reporting of methods of randomisation, unclear or high attrition, low event rates and small sample sizes).

In another meta-analysis of 7 studies (84) a significant improvement of semen parameters (count, motility, morphology) was shown after administration of *selenium* (200 µg/day and 100 µg/day), combination of *L-carnitine* (2 g/day) and *acetyl-L-carnitine* (LAC; 1 g/day) and *co-enzyme Q10* (200 and 300 mg/day). Information of the effect on pregnancy rate was not obtained because it was evaluated in a limited number of trials. The systematic review of other trials identified promising results for supplementation with zinc combined with folic acid, eicosapentaenoic acid and docosahexaenoic acid.

Phytotherapeutic

A poly-herbal formulation (a combination of the roots of *Chlorophytum borivilianum*, seeds of *Mimosa pudica*, sap of *Acacia Senegal*, root of *Astragalus membranaceus*, seed coat of *Plantago ovate*, sap of *Bombax ceiba*, root of *Eurycoma longifolia* and rocky candy) was tested for its effect on the spermatogenic potential in oligospermic patients. After 90 days, there was a 256% increase in sperm concentration, a 154% increase in semen volume and a 215% increase in sperm motility, respectively (85).

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Correspondence

Mahmoud Benatta
benatta.mahmoud@gmail.com
Dept. of Urology, Djilali Lyabes University Hospital, Sidi Bel Abbès/Algeria

Redha Kettache
kettacher@gmail.com
Dept. of Urology, EPH Bachir Bennacer, Biskra/Algeria

Noor Buchholz (Corresponding Author)
scientific-office@u-merge.com
noor.buchholz@gmail.com
U-merge Scientific Office 21 Athens/Greece

Alberto Trinchieri
alberto.trinchieri@gmail.com
U-merge Scientific Office