Commentary

The role of food supplements in the treatment of the infertile man

Frank H Comhaire1, Ahmed Mahmoud
Centre for Medical and Urological Andrology, Ghent University Hospital, De Pintelaan, 185, B 9000 Gent, Belgium
1Correspondence: frank.comhaire@rug.ac.be

Abstract

Recently, concerns have been raised about the presumptive increased risk of serious undesirable side effects in children born after IVF and intracytoplasmic sperm injection (ICSI). These treatments must, therefore, be reserved as the ultimate option after evidence-based and cause-directed treatment of the male patient with deficient semen has been exhausted. The present authors found that sperm quality and function improved with the intake of complementary food supplementation using a combination of zinc and folic acid, or the antioxidant astaxanthin (Astacarox®), or an energy-providing combination containing (actyl)-carnitine (Proxeed®). Also, double blind trials showed that the latter two substances increase spontaneous or intrauterine insemination- (IUI-) assisted conception rates. Rates of Pitun maritima bark (Pycnogenol®), which inhibits the cyclo-oxygenase enzyme, reducing prostaglandin production and inflammatory reaction, and extracts of the Peruvian plant Lepidium meyenii were shown to improve sperm morphology and concentration, respectively, in uncontrolled trials. Linseed (flaxseed) oil contains alfa-linolenic acid and lignans. The former corrects the deficient intake of omega-3 essential fatty acids, which is correlated with impaired sperm motility among subfertile men. Lignans are precursors of enterolacton, which inhibits aromatase and reduces the ratio of 16-OH over 2-OH oestrogen metabolites. The resulting reduction in oestrogen load may favourably influence Sertoli cell function.

Keywords: antioxidants, food supplementation, male infertility, nutriceuticals

Historical perspective on the management of male infertility

It has been known for a long time that the ejaculate of some men contains too few, or qualitatively inadequate, spermatozoa. However, it is only since 1940–1950 that reliable scientific data have been available regarding the values of the basic sperm variables needed for optimal fertility (MacLeod, 1942; Hellinga, 1965) and biochemical analysis of seminal plasma (Eliasson, 1976). Also, the role of antibodies against spermatozoa (Rümke, 1965) and biochemical analysis of seminal plasma (Eliasson, 1968) have been highlighted. Many cases of ‘hidden’ male infertility were detected, but only few modalities of treatment were available. Sperm freezing, artificial insemination and the use of donor sperm were developed (Figure 1).

In the 1970s and 1980s, much attention was given to the alleged causes and associations of male infertility. A specific task force of the World Health Organization (WHO) launched large-scale multi-centre trials. These resulted in a diagnostic approach and standardized classification of male infertility (Comhaire et al., 1987) and the publication of manuals for the standardized techniques of semen analysis (WHO, 1980, 1987, 1999).

The best methods for the diagnosis of varicocele were determined (Comhaire et al., 1976), and the efficacy of treatment of this disease was established in a prospective randomized trial (Hargreave, 1995). Placebo-controlled trials did not reveal any benefit in terms of improving the spontaneous conception rate using antibiotic treatment of male accessory gland infection (Comhaire et al., 1986) and of idiopathic oligozoospermia with clomiphene citrate (WHO, 1992) or with mesterolone (Gerris et al., 1991). By contrast, treatment of the latter condition with Tamoxifen has been shown to be effective (Comhaire, 1976, 2000).

The introduction of assisted reproductive technology, namely IVF and intracytoplasmic sperm injection (ICSI) (Palermo et al., 1992), caused a true revolution in reproductive medicine, while also revealing the magnitude of the male factor contributing to couple infertility. Conventional treatment of the infertile male was considered outdated by some, but others have continued unravelling the mechanisms involved in male defective reproductive capacity.

In recent years, concerns have been raised about the economical and ethical aspects (Comhaire, 2000; Katz et al., 2002), and side effects, of assisted reproduction techniques. IVF and ICSI were found to be associated with an increased prevalence of major congenital malformations (Kent-First et al., 1996; van der Ven et al., 1998; Sutcliffe et al., 1999; Koudstaal et al., 2000; Wennerholm et al., 2000; Hansen et al., 2002), impaired development (Stromberg et al., 2002), and increased risk of retinoblastoma (Moll et al., 2003) in the offspring. It seems, therefore, that the wheel has turned full circle, and that clinical andrology will recapture its well-deserved place in the armamentarium for the treatment of couple infertility.
Commentaries - The role of food supplements in treating male infertility - FH Comhaire & A Mahmoud

Male infertility: a multifactorial disease

Similar to other diseases, male infertility comes to expression as a result of the synergistic coincidence of four major factors: genetic defects or constitution; life style factors; professional and/or environmental exposure; and diseases of the urothoginal region or endocrine system (Figure 2). The latter include the diseases that constitute the traditional interest of the andrologist, such as varicocele, male accessory gland infection, congenital or acquired testicular damage, hypoandrogenism, immunological factors, etc.

The field of genetics is rapidly expanding and includes numerical and structural abnormalities of the chromosomal make-up, as well as microdeletions of the Y chromosome (Tiepolo and Zuffardi, 1976; Ma et al., 1992). Whether or not certain of these minor deletions will cause infertility may depend on the coincidental presence of unfavourable life-style factors or exposure to toxic substances or hormone disrupters. These, and the genital diseases, have been shown to increase the load of reactive oxygen species to the ejaculate and the spermatozoa, resulting in increased chromosome fractionation (Hughes et al., 1998; Irvine et al., 2000) and excessive production of oxidized DNA (8-hydroxy 2-deoxy guanosine) (Fraga et al., 1991).

Oxidative overload also changes the phospholipid composition of the sperm membrane (Alvarez and Storey, 1995; Zalata et al., 1998), reducing its fluidity and fusogenic capacity as well as the induced acrosome reactivity.

Among life style factors, nutrition, abuse of alcohol, tobacco or recreational drugs, tight clothing and hot baths have been incriminated. Also, men with infertile semen were found to consume less omega-3 fatty acids than fertile men, and a significant correlation was established between the consumption of alfa-linolenic acid (18:3 omega-3) on the one hand and sperm concentration and type a motility on the other hand (Christophe et al., 1998).

Exposure to professional toxicants was proven to impair sperm quality, including heavy metals such as lead (Bonde et al., 2002) and carbon disulphide (Vanhoorne et al., 1994). But it is the exposure to environmental agents with hormone disrupting effects, mainly pseudo- or xeno-oestrogens and anti-androgens, that has caused most concerns recently. The obvious, though regional, deterioration of both sperm variables and fertility, and the parallel increase in the prevalence of testicular cancer, have been linked to an increased internal exposure to artificial chemical substances that mimic or enhance the effects of oestrogens by binding on the human oestrogen receptor or by influencing oestrogen metabolism (for review see Sharpe, 2003).

Inhibin B

Inhibin B is a secretory product of the Sertoli cells that plays an important role in both endocrine feedback, inhibiting the pituitary secretion of FSH, and local regulation of spermatogenesis. Whereas serum inhibin B concentration is significantly related to sperm concentration (for review see Meachem et al., 2001), there is evidence of a direct suppressive effect of inhibin B on spermatogenesis (van Dissel-Emiliani et al., 1989). Both in-vitro tests (Depuydt et al., 1999) and in-vivo data (Mahmoud et al., 1998, 2000) suggest that oestrogens and certain heavy metals, such as lead, may inappropriately stimulate the secretion of inhibin B by the Sertoli cells. This results in decreased sperm production, in the presence of normal serum concentrations of inhibin B and FSH.

During treatment with the strong antioxidant astaxanthin (see below), the serum concentration of inhibin was reduced, in spite of unchanged sperm concentration, suggesting that reactive oxygen species stimulate inhibin secretion by the Sertoli cells, similar to the effect of oestrogens (Figure 3).

Sub/infertility: a multifactorial disease

Figure 1. Evolution over time of the proportion of subfertile men treated by the clinical andrologist (dashed line), and those in whom techniques of assisted reproductive technology were applied (dotted and dashed line). The solid line represents the proportion of infertile couples in which the ‘male factor’ has remained undetected.

Figure 2. The four major contributing factors that act in synergism to cause subfertility or infertility in men – a multifactorial disease. CAVD, congenital absence of the deferential ducts; CAVE ICSI, be cautious about the transmission of genetic defects to the offspring generated by intracytoplasmic sperm injection; PUFA, poly-unsaturated fatty acids; CS2, carbon disulphide; MAGI, male accessory gland infection.
Decreasing the secretion of inhibin by reducing the oestrogen effect on the Sertoli cells and the exposure to reactive oxygen species may be a target of medical treatment. Indeed, reducing inhibin secretion may counteract the feedback suppression of FSH secretion by the pituitary and thus may directly improve spermatogenesis.

**Food supplementation**

**Fatty acids**

Since there is a positive correlation between the intake of alfa-linolenic acid and sperm concentration and motility, and since the food intake of essential fatty acids of the omega-3 group was found to be sub-optimal among subfertile men (Christophe et al., 1998), it seems logical to supplement these patients with a source of 18:3 omega-3, namely linseed oil (also called flaxseed oil). When given in association with the co-factors zinc and vitamin B6, which enhance the elongase and desaturase enzymes, the alfa-linolenic acid will be converted into the long-chain, highly unsaturated omega fatty acids, namely ecosapantenoic acid and docosahexaenoic acid. The latter increase the fluidity of the sperm membrane, improving the induced acrosome reaction and fusogenic capacity of the spermatozoa (Comhaire et al., 2000).

Alternatively, fish oil supplements can be a source of ecosapantenoic acid and docosahexaenoic acid. These fatty acids are, however, highly susceptible to oxidative damage, which initiates an undesirable chain reaction of lipo-oxidation. If fish oil is given for food supplementation, it is mandatory to ascertain a favourable antioxidative internal environment at the same time.

**Antioxidants**

The resistance of LDL-cholesterol in serum to an in-vitro oxidative challenge reflects the oxidant–antioxidant balance of a particular person. The time lag before the initiation of LDL-cholesterol oxidation and the occurrence of conjugated dienes is a measure of oxidative stress, being higher if the time lag is shorter and vice versa. Subfertile patients were found to present a significantly shorter time lag than fertile men, shorter and vice versa. Subfertile patients were found to present an insignificant increase in the astaxanthin group, but not spontaneous, acrosome reactivity.

This agrees with the finding that vitamin E supplementation improves the in-vitro function of spermatozoa in the zona-free hamster oocyte test (Kessopoulou et al., 1995). In the present trial, the spontaneous pregnancy rate during the treatment period was 7.2% per month in the partners of (ex)-smokers, but remained at baseline among the partners of non-smokers (1.6%) (OR: 4.57, not significant).

Supplementation with vitamin C among smokers with abnormal sperm quality was reported to improve semen quality (Dawson et al., 1992), whereas no such effect was seen in another trial using high-dose vitamin C (Rolf et al., 1999). The latter may be related to the known pro-oxidative effect of high-dose vitamin C (Fraga et al., 1991), particularly in men with the haptoglobin type 1–2 or 2–2 (Bernard et al., 2003).

The oxido-reductase ubiqitoline Q10 increased sperm motility in cases of asthenozoospermia, when added in vitro or given orally (Lewin and Lavon, 1997). Also other antioxidants such as selenium (Scott et al., 1998) and glutathione (Lenzi et al., 1993) were found to improve sperm motility in subgroups of patients.

Astaxanthin is a lipophilic carotenoid produced by the alga *Haematococcus pluvialis*, and it has a strong antioxidant capacity (Iwamoto et al., 2000; Goto et al., 2001). In a pilot double-blind randomized trial, 16 mg per day of the natural astaxanthin (Astacarox, Astacarotene AB, Gustavssvgs, Sweden) was given to the male partners of 20 infertile couples, whose semen characteristics were below the WHO recommended reference values. This food supplementation resulted in a significant reduction of seminal reactive oxygen species and serum inhibin B concentration among treated cases, but not in the placebo controls. Rapid linear progressive motility significantly increased, and sperm morphology presented an insignificant increase in the astaxanthin group, but sperm concentration remained unchanged. In the treated group, the total and monthly pregnancy rates were 54.5% and 23.1%, respectively, compared with 11.1% and 3.6% in the placebo group (OR: 9.6, P = 0.08) (Comhaire et al., submitted).
Carnitine

L-carnitine plays a pivotal role in the transport mechanisms necessary for the translocation of longer-chain-length fatty acids from the cellular cytosol into the mitochondrial matrix, where these can be oxidized and generate energy (Wildman and Medeiros, 2000) and stimulate respiratory chain complexes (Ruiz-Pesini et al., 2001). Free carnitine and acetyl-L-carnitine play an important role in the post-gonadal maturation of mammalian spermatozoa (Jeulin and Lewin, 1996), and the ratio of acetylcarnitine/carnitine was different in extracts of sperm with good or poor motility (Golan et al., 1984; Bartellini et al., 1987). Acetyl-L-carnitine is the prominent carnitine in spermatozoa, and its concentration is reduced in the semen of infertile men (Kohengkul et al., 1977; Soufir et al., 1984). The free carnitine concentration in seminal plasma is significantly correlated with sperm concentration and motility (P < 0.01) (Menchini-Fabris et al., 1984), and sperm motility can be stimulated by the addition of acetylcarnitine in vitro (Tanphaichitr, 1977).

Treatment with a food supplement containing a combination of L-carnitine (2 g per day) and acetyl-L-carnitine (1 g per day) together with fructose and citric acid (Proseed, Sigma-tau Health Science, Rome, Italy), was found to significantly increase sperm concentration and forward progressive motility (by 40% or more, P < 0.001) in both open label trials (Moncada et al., 1996), and the ratio of acetylcarnitine/carnitine was different in extracts of sperm with good or poor motility (Golan et al., 1984; Bartellini et al., 1987). Acetyl-L-carnitine is the prominent carnitine in spermatozoa, and its concentration is reduced in the semen of infertile men (Kohengkul et al., 1977; Soufir et al., 1984). The free carnitine concentration in seminal plasma is significantly correlated with sperm concentration and motility (P < 0.01) (Menchini-Fabris et al., 1984), and sperm motility can be stimulated by the addition of acetylcarnitine in vitro (Tanphaichitr, 1977).

Folic acid and zinc

Folic acid (5 mg per day) and zinc sulphate (66 mg per day) have been given orally both to men with normal spermatogenesis and to patients with moderate oligozoospermia in a placebo-controlled trial (Wong et al., 2002). This combination was found to significantly increase sperm concentration (by an average of 60%, P < 0.05) and morphology in the subfertile men. These changes occurred in spite of the absence of deficient blood levels of folic acid or zinc before supplementation in the subfertile men. It was hypothesized that the supplementation with lower, physiological doses of micronutrients may even have a larger beneficial effect, since these have a stronger influence on absorption, transport and metabolic processes. It remains, however, to be established whether the administration of the combination of folic acid and zinc will result in improvement of fertility.

Seed oil and lignans

Aside from alpha-linolenic acid (see above), linseed or flaxseed oil contains several lignans, which are converted in the intestine into enterodiol and enterolactone. These are phytoestrogens with weak and short-lasting oestrogenic effects. However, enterolactone is a rather strong aromatase inhibitor. Thanks to this inhibitory effect, enterolactone reduces the conversion of androgens (androstenedione and testosterone) into the potent oestrogens oestrone and oestradiol (Adlercreutz et al., 1993; Wang et al., 1994). Hence, food supplementation with linseed oil will decrease the level of endogenous oestrogens, which were commonly found to be increased in men combining oligozoosperma with normal serum concentrations of FSH and inhibin B (Mahmoud et al., 1998).

Plant extracts

Using immune histochemical techniques, Mayerhofer et al. (2002) have recently demonstrated that the cyclo-oxygenase iso-enzyme 2, which converts arachidonic acid (20:4 omega-6) into the inflammatory prostaglandin E2, is present in the testicular interstitial tissue of patients with idiopathic oligozoospermia, but not in men with normal spermatogenesis. Extracts of Pinus maritima bark (Pycnogenol; SiberHegner, PO Box 888, CH-8034 Zurich, Switzerland) contains substances that inhibit the cyclo-oxygenase enzyme (Baumann et al., 1980; Rohdewald, 2002), reduce the mRNA of the inflammatory cytokine interleukin-1β (Cho et al., 2001), and protect the effects of vitamin E on endothelial cells (Virgili et al., 1998). In an open label study including four subfertile men, oral administration of 200 mg per day of this extract improved sperm morphology by an average of 99% (Roseff and Gulati, 1999).

Extracts of Lepidium meyenii (maca), a plant growing in the central Andean region of Peru between 4000 and 4500 m altitude, increases sexual function of male mice and rats (Zeng et al., 2000) and invigorates spermatogenesis at the mitotic stages (Gonzales et al., 2001b). When given to eight men with normal spermatogenesis, this extract significantly increased sperm production (+85%, P < 0.05) and motility (+15%) without interfering with endocrine regulation (Gonzales et al., 2001a).

Though these plant extracts may show promise for the future, complementary studies are needed before they can be recommended for the treatment of male infertility.

Miscellaneous substances

For several years, arginine (De Aloysio et al., 1982; Aydin et al., 1995) and kallikrein (Schill et al., 1979) have been promoted for the treatment of men with oligozoospermia, but the alleged favourable effects of these supplements have been questioned (Pyor et al., 1978; Comhaire and Vermeulen, 1983).

Discussion

Several controlled and well-validated trials provide evidence that food supplementation with particular substances can improve semen quality and function in subfertile men. These substances include carnitine, zinc, folic acid, tocopherol and astaxanthin. There is evidence to suggest that certain of these supplements, when given as a complement to the WHO recommended conventional treatment (Rowe et al., 2000; Tournaye, 2003), can improve male fertility.

On a deductive basis, but without convincing data from clinical trials, certain other food supplements such as linseed oil and plant extracts may favourably influence sperm quality.
Although the exact mechanisms of action of these supplements on spermatogenesis and sperm function remain to be unravelled, a direct effect on the Sertoli cells (Figure 3) and via epididymal function seems conceivable.

It makes sense to further explore the therapeutic potential of food supplementation in the management of couple infertility due to the male factor.

References


Fraga CG, Motchkin PA, Shigenaga MK et al. 1991 Ascorbic acid protects against endogenous oxidative DNA damage in human sperm. Proceedings of the National Academy of Sciences of the USA 88, 11003–11006.


Goto S, Kogure K, Abe K et al. 2001 Efficient radical trapping at the surface and inside the phospholipid membrane is responsible for highly potent antiperoxidative activity of the carotenoid astaxanthin. Biochemical and Biophysical Acta 1512, 251–258.


Kessopoulou E, Powers HJ, Sharma KK et al. 1995 A double blind randomized placebo crossover controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated male infertility. Fertility and Sterility 64, 825–831.


*Paper based on contribution presented at the ‘TWIN–Meeting Alpha–Andrology 2003’ in Antwerp, Belgium, September 2003.*

*Received 17 March 2003; refereed 8 April 2003; accepted 1 May 2003.*