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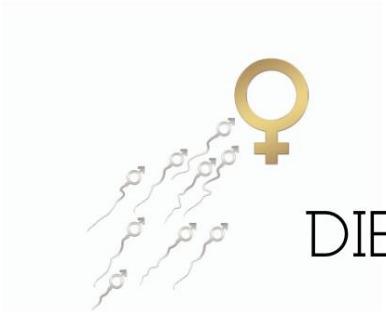
COMPENDIUM OF SCIENTIFIC ABSTRACTS



REGARDING

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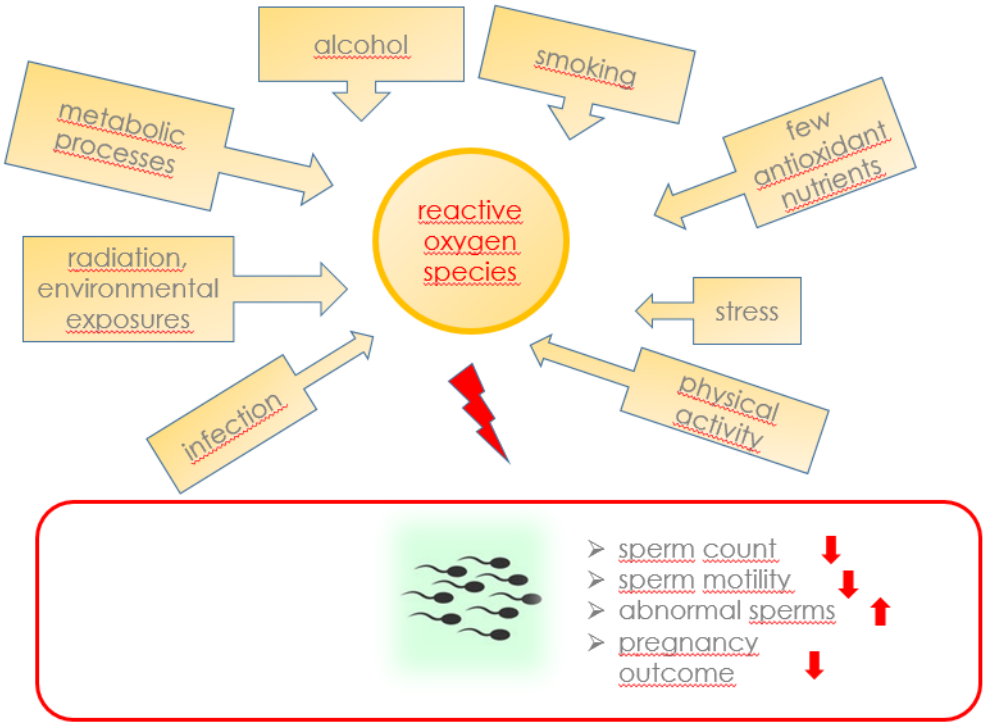
Introduction

The majority of couples of reproductive age desire children. However, healthy conception does not always come naturally. The population of individuals with potential infertility is estimated to be 10–15% of the overall population of reproductive age.
A World Health Organization (WHO) survey of 7,273 couples with infertility revealed that infertility was attributable to female factors alone in 41% cases, both male and female factors in 24%, male factors alone in 24%, and unknown causes in 11%.

Among factors not easily identifiable are those related to a couple's lifestyle. Particularly the diet has been well established to have an important impact on healthy reproduction and fertility (Nassan et al, 2018).
A lot of scientific literature has dealt with the question as to what the best diet for healthy fertility is and whether supplementation of certain micronutrients can make a difference. Supplementation in fact was the subject of heavy debate until 2011, when a big Cochrane review article by Showell et al finally confirmed the importance of antioxidant supplementation for male fertility in terms of amelioration of sperm quality and subsequently pregnancy rates (Showell et al, 2011).
Male fertility consists usually of two aspects: sexual performance and semen quality. Particularly in idiopathic cases of male fertility, an impairment is often linked to oxidative stress.

Oxidative stress

Whereas physiological levels of ROS (reactive oxygen species) are vitally needed for healthy reproduction (Ruder et al, 2008) in both male and female, excessive amounts of ROS can overwhelm antioxidant defense mechanisms and result in oxidative stress. Human spermatozoa are particularly susceptible to oxidative damage due to a high content of polyunsaturated fatty acids in their cell membrane and a lack of cytoplasm with its protective- and repair enzymes. Oxidative stress has been found to be involved in male subfertility by impairing sperm count and motility as well as fusion of sperm and oocyte (Sharma et al, 1996, Agarwal 2004, Ross et al, 2010).



Picture 1: impact of oxidative stress on sperm quality

Dietetic management of male subfertility

It has become indisputable that lifestyle and nutrition have a major impact on both the sperm quality itself and the health of future children. How exactly this works is the subject of many research projects. In 2019 it could be shown for the first time that sugar content of food can directly influence the motility of sperms. The underlying mechanism involved small RNAs that arise from tRNAs, so-called tsRNAs (Naett et al, 2019). The current consensus is that men can be counselled to follow a Mediterranean diet with ample seafood, poultry, nuts, whole grains, fruits, and vegetables (Ricci et al, 2019).
In addition to that, antioxidative treatment has been shown to improve semen quality and success rates of IVF treatment in idiopathic cases of male subfertility (Showell et al 2011 and

2014, Smits et al, 2019). Best results are seen after 3 – 6 months of treatment, covering at least one entire cycle of spermatogenesis.
State-of-the-art dietetic management includes a variety of water- and fat-soluble antioxidants, as well as a range of other micronutrients crucial for sperm health and sexual performance.

Diet and men's fertility: does diet affect sperm quality?

Nassan FL, Chavarro JE, Tanrikut C.

Male contribution to a couple's fecundity is important, and identifying the dietary factors that can influence male fertility potential is of high importance. Despite this importance, there are currently no clear clinical guidelines for male patients seeking fertility treatment. In this review, we present the most up-to-date evidence about diet and male fertility in humans. We focus on the dietary factors necessary for production of healthy functioning sperm with high fertility potential. Based on this review, men may be encouraged to use antioxidant supplements and to follow dietary patterns favoring the consumption of seafood, poultry, nuts, whole grains, fruits, and vegetables. Evidence is strongest for recommending the use of antioxidant supplements to men in couples undergoing infertility treatment-although the specific antioxidants and doses remain unclear-and increasing consumption of omega-3 fatty acids from fish and nuts.

Fertil Steril. 2018 Sep;110(4):570-577. doi: 10.1016/j.fertnstert.2018.05.025.

Mediterranean Diet and the Risk of Poor Semen Quality: Cross-Sectional Analysis of Men Referring to an Italian Fertility Clinic

E Ricci , F Bravi, S Noli, S Ferrari , V De Cosmi , I La Vecchia , M Cavadini , C La Vecchia , F Parazzini

BACKGROUND: Several diet patterns have been suggested as involved in processes of spermatogenesis and thus in male subfertility. To study the relation between Mediterranean diet and abnormal sperm parameters in men of subfertile couples, we performed a cross-sectional analysis of baseline data from a prospective cohort study.

METHODS: Patients were enrolled in an Italian Fertility Clinic. Couples undergoing assisted reproduction techniques (ART) were interviewed to obtain information on personal and health history, lifestyle habits, and diet, on the day of oocyte retrieval. On the same day, a semen sample was also collected and analyzed to proceed with ART. Adherence to Mediterranean diet was evaluated using a Mediterranean Diet Score (MDS). Odds ratios (OR) and 95% confidence intervals (CI) were calculated for semen volume <1.5 mL, sperm concentration <15 mil/mL, and total count <39 mil.

RESULTS: Three hundred nine men, age range 27-60, were enrolled: 19.3% had semen volume < 1.5 mL, 30.5% sperm concentration <15 mil/mL, and 32.1% total count <39 mil. MDS was low (0-3) in 86 men (27.8%), intermediate (4-5) in 131 (42.4%), and high (6-9) in 92 (29.8%). Semen volume was not associated with MDS. Compared to the highest MDS category (6-9), the ORs for low sperm concentration were 1.34 (95% CI 0.69-2.50) for MDS 4-5 and 2.42 (95% CI 1.21-4.83) for MDS 0-3, with significant trend (p = 0.011). The corresponding estimates for total

count were 1.26 (95% CI 0.66-2.42) and 2.08 (95% CI 1.05-4.12), with significant trend (p = 0.034). These findings were consistent in strata of history of reproductive organ diseases.

CONCLUSIONS: Mediterranean Diet Score was positively associated with normal sperm concentration and total count, but not with semen volume.

KEYWORDS: assisted reproduction techniques; diet; risk factors; sperm concentration; sperm motility; sperm total count.

Andrology. 2019 Mar;7(2):156-162.

Human sperm displays rapid responses to diet.

Nätt D, Kugelberg U, Casas E, Nedstrand E, Zalavary S, Henriksson P, Nijm C, Jäderquist J, Sandborg J, Flinke E, Ramesh R1, Örkenby L, Appelkvist F, Lingg T, Guzzi N, Bellodi C, Löf M, Vavouri T, Öst A.

The global rise in obesity and steady decline in sperm quality are two alarming trends that have emerged during recent decades. In parallel, evidence from model organisms shows that paternal diet can affect offspring metabolic health in a process involving sperm tRNA-derived small RNA (tsRNA). Here, we report that human sperm are acutely sensitive to nutrient flux, both in terms of sperm motility and changes in sperm tsRNA. Over the course of a 2-week diet intervention, in which we first introduced a healthy diet followed by a diet rich in sugar, sperm motility increased and stabilized at high levels. Small RNA-seq on repeatedly sampled sperm from the same individuals revealed that tsRNAs were up-regulated by eating a high-sugar diet for just 1 week. Unsupervised clustering identified two independent pathways for the biogenesis of these tsRNAs: one involving a novel class of fragments with specific cleavage in the T-loop of mature nuclear tRNAs and the other exclusively involving mitochondrial tsRNAs. Mitochondrial involvement was further supported by a similar up-regulation of mitochondrial rRNA-derived small RNA (rsRNA). Notably, the changes in sugar-sensitive tsRNA were positively associated with simultaneous changes in sperm motility and negatively associated with obesity in an independent clinical cohort. This rapid response to a dietary intervention on tsRNA in human sperm is attuned with the paternal intergenerational metabolic responses found in model organisms. More importantly, our findings suggest shared diet-sensitive mechanisms between sperm motility and the biogenesis of tsRNA, which provide novel insights about the interplay between nutrition and male reproductive health.

PLoS Biol. 2019 Dec 26;17(12):e3000559. doi: 10.1371/journal.pbio.3000559. eCollection 2019 Dec.

Male reproduction, oxidative stress and antioxidants

Oxidative stress and male reproductive health

INVITED REVIEW

Robert J Aitken, Tegan B Smith, Matthew S Jobling, Mark A Baker , Geoffry N De Iuliis

One of the major causes of defective sperm function is oxidative stress, which not only disrupts the integrity of sperm DNA but also limits the fertilizing potential of these cells as a result of collateral damage to proteins and lipids in the sperm plasma membrane. The origins of such oxidative stress appear to involve the sperm mitochondria, which have a tendency to

generate high levels of superoxide anion as a prelude to entering the intrinsic apoptotic cascade. Unfortunately, these cells have very little capacity to respond to such an attack because they only possess the first enzyme in the base excision repair (BER) pathway, 8-oxoguanine glycosylase 1 (OGG1). The latter successfully creates an a basic site, but the spermatozoa cannot process the oxidative lesion further because they lack the downstream proteins (APE1, XRCC1) needed to complete the repair process. It is the responsibility of the oocyte to continue the BER pathway prior to initiation of S-phase of the first mitotic division. If a mistake is made by the oocyte at this stage of development, a mutation will be created that will be represented in every cell in the body. Such mechanisms may explain the increase in childhood cancers and other diseases observed in the offspring of males who have suffered oxidative stress in their germ line as a consequence of age, environmental or lifestyle factors. The high prevalence of oxidative DNA damage in the spermatozoa of male infertility patients may have implications for the health of children conceived in vitro and serves as a driver for current research into the origins of free radical generation in the germ line.
*Asian Journal of Andrology (2014) **16**, (31–38); doi: 10.4103/1008-682X.122203; published online: 16 December 2013*

Free Radical Theory of Aging: Implications in Male Infertility

Review Article

Nisarg Desai, Edmund Sabanegh Jr., Taesoo Kim, and Ashok Agarwal

This review examines the effect of mitochondrial generation of reactive oxygen species (ROS) and aging on human spermatozoa and seminal antioxidants. We discuss the effect of continuous ROS production on biomarkers of aging, such as germ cell telomeres and telomerase, lipofuscin, and amyloid. These markers may be responsible for telomere shortening and subsequent decrease in sperm count, decline in testosterone concentration, and decline in motility with aging. Excessive ROS can also damage mitochondrial deoxyribonucleic acid and sperm nuclear DNA, contributing to paternally transmitted diseases. ROS generation has a central role in the pathophysiology of age-related decrease in male fertility.
UROLOGY 75: 14–19, 2010

Role of antioxidants in treatment of male infertility: an overview of the literature

Ashok Agarwal, Kiran P Nallella, Shyam SR Allamaneni, Tamer M Said

Seminal oxidative stress in the male reproductive tract is known to result in peroxidative damage of the sperm plasma membrane and loss of its DNA integrity. Normally, a balance exists between concentrations of reactive oxygen species and antioxidant scavenging systems. One of the rational strategies to counteract the oxidative stress is to increase the scavenging capacity of seminal plasma. Numerous studies have evaluated the efficacy of antioxidants in male infertility. In this review, the results of different studies conducted have been analysed, and the evidence available to date is provided. It was found that although many clinical trials have demonstrated the beneficial effects of antioxidants in selected cases of male infertility, some studies failed to demonstrate the same benefit. The majority of the studies suffer from a lack of placebo controlled, double-blind design, making it difficult to reach a definite conclusion. In addition, investigators have used different antioxidants in different combinations and dosages for varying durations. Pregnancy, the most relevant outcome parameter of fertility, was reported in only a few studies. Most studies failed to examine the effect of antioxidants on a specific group of infertile patients with high oxidative stress. Multicenter, double-blind studies with statistically accepted sample size are still needed to provide conclusive evidence on the benefit of antioxidants as a treatment modality for patients with male infertility.
Reproductive BioMedicine Online Vol 8. No 6.2004 616-627

A systematic review of the effect of oral antioxidants on male infertility.

Ross C, Morriss A, Khairy M, Khalaf Y, Braude P, Coomarasamy A, El-Toukhy T.

The use of antioxidants in treatment of infertile men has been suggested, although the evidence base for this practice is unclear. A systematic review of randomized studies was conducted to evaluate the effects of oral antioxidants (vitamins C and E, zinc, selenium, folate, carnitine and carotenoids) on sperm quality and pregnancy rate in infertile men. MEDLINE, EMBASE, Cochrane Library and CINAHL were searched for relevant trials published from respective database inception dates to May 2009. Study selection, quality appraisal and data extraction were performed independently and in duplicate. Seventeen randomized trials, including a total of 1665 men, were identified, which differed in the populations studied and type, dosage and duration of antioxidants used. Only two-thirds of the studies (11/17) reported using allocation concealment and three studies (18%) used intention-to-treat analysis. Despite the methodological and clinical heterogeneity, 14 of the 17 (82%) trials showed an improvement in either sperm quality or pregnancy rate after antioxidant therapy. Ten trials examined pregnancy rate and six showed a significant improvement after antioxidant therapy. The use of oral antioxidants in infertile men could improve sperm quality and pregnancy rates. Adequately powered robust trials of individual and combinations of antioxidants are needed to guide clinical practice.

Reprod Biomed Online. 2010 Jun;20(6):711-23. doi: 10.1016/j.rbmo.2010.03.008. Epub 2010 Mar 10.

Antioxidants for male subfertility.

Smits RM, Mackenzie-Proctor R, Yazdani A, Stankiewicz MT, Jordan V, Showell MG.

BACKGROUND:

The inability to have children affects 10% to 15% of couples worldwide. A male factor is estimated to account for up to half of the infertility cases with between 25% to 87% of male subfertility considered to be due to the effect of oxidative stress. Oral supplementation with antioxidants is thought to improve sperm quality by reducing oxidative damage. Antioxidants are widely available and inexpensive when compared to other fertility treatments, however most antioxidants are uncontrolled by regulation and the evidence for their effectiveness is uncertain. We compared the benefits and risks of different antioxidants used for male subfertility. This review did not examine the use of antioxidants in normospermic men.

OBJECTIVES:

To evaluate the effectiveness and safety of supplementary oral antioxidants in subfertile men.

SEARCH METHODS:

The Cochrane Gynaecology and Fertility (CGF) Group trials register, CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, and two trials registers were searched on 1 February 2018, together with reference checking and contact with study authors and experts in the field to identify additional trials.

SELECTION CRITERIA:

We included randomised controlled trials (RCTs) that compared any type, dose or combination of oral antioxidant supplement with placebo, no treatment or treatment with another antioxidant, among subfertile men of a couple attending a reproductive clinic. We excluded studies comparing antioxidants with fertility drugs alone and studies that included fertile men attending a fertility clinic because of female partner infertility.

DATA COLLECTION AND ANALYSIS:
We used standard methodological procedures recommended by Cochrane. The primary review outcome was live birth. Clinical pregnancy, adverse events and sperm parameters were secondary outcomes.

MAIN RESULTS:
We included 61 studies with a total population of 6264 subfertile men, aged between 18 and 65 years, part of a couple who had been referred to a fertility clinic and some of whom were undergoing assisted reproductive techniques (ART). Investigators compared and combined 18 different oral antioxidants. The evidence was of 'low' to 'very low' quality: the main limitation was that out of the 44 included studies in the meta-analysis only 12 studies reported on live birth or clinical pregnancy. The evidence is current up to February 2018.Live birth: antioxidants may lead to increased live birth rates (OR 1.79, 95% CI 1.20 to 2.67, P = 0.005, 7 RCTs, 750 men, I2 = 40%, low-quality evidence). Results suggest that if in the studies contributing to the analysis of live birth rate, the baseline chance of live birth following placebo or no treatment is assumed to be 12%, the chance following the use of antioxidants is estimated to be between 14% and 26%. However, this result was based on only 124 live births from 750 couples in seven relatively small studies. When studies at high risk of bias were removed from the analysis, there was no evidence of increased live birth (Peto OR 1.38, 95% CI 0.89 to 2.16; participants = 540 men, 5 RCTs, P = 0.15, I2 = 0%).Clinical pregnancy rate: antioxidants may lead to increased clinical pregnancy rates (OR 2.97, 95% CI 1.91 to 4.63, P < 0.0001, 11 RCTs, 786 men, I2 = 0%, low-quality evidence) compared to placebo or no treatment. This suggests that if in the studies contributing to the analysis of clinical pregnancy, the baseline chance of clinical pregnancy following placebo or no treatment is assumed to be 7%, the chance following the use of antioxidants is estimated to be between 12% and 26%. This result was based on 105 clinical pregnancies from 786 couples in 11 small studies. Adverse events: Miscarriage: only three studies reported on this outcome and the event rate was very low. There was no difference in miscarriage rate between the antioxidant and placebo or no treatment group (OR 1.74, 95% CI 0.40 to 7.60, P = 0.46, 3 RCTs, 247 men, I2 = 0%, very low-quality evidence). The findings suggest that in a population of subfertile men with an expected miscarriage rate of 2%, the chance following the use of an antioxidant would result in the risk of a miscarriage between 1% and 13%.Gastrointestinal: antioxidants may lead to an increase in mild gastrointestinal upsets when compared to placebo or no treatment (OR 2.51, 95% CI 1.25 to 5.03, P = 0.010, 11 RCTs, 948 men, I2 = 50%, very low-quality evidence). This suggests that if the chance of gastrointestinal upsets following placebo or no treatment is assumed to be 2%, the chance following the use of antioxidants is estimated to be between 2% and 9%. However, this result was based on a low event rate of 35 out of 948 men in 10 small or medium-sized studies, and the quality of the evidence was rated very low and was high in heterogeneity. We were unable to draw any conclusions from the antioxidant versus antioxidant comparison as insufficient studies compared the same interventions.

AUTHORS' CONCLUSIONS:
In this review, there is low-quality evidence from seven small randomised controlled trials suggesting that antioxidant supplementation in subfertile males may improve live birth rates for couples attending fertility clinics. Low-quality evidence suggests that clinical pregnancy rates may also increase. Overall, there is no evidence of increased risk of miscarriage, however antioxidants may give more mild gastrointestinal upsets but the evidence is of very low quality. Subfertilte couples should be advised that overall, the current evidence is inconclusive based on serious risk of bias due to poor reporting of methods of randomisation, failure to report on the clinical outcomes live birth rate and clinical pregnancy, often unclear or even high attrition, and also imprecision due to often low event rates and small overall sample sizes. Further large well-designed randomised placebo-controlled trials reporting on pregnancy and live births are still required to clarify the exact role of antioxidants.
Cochrane Database Syst Rev. 2019 Mar 14;3:CD007411

Systematic review of antioxidant types and doses in male infertility: Benefits on semen parameters, advanced sperm function, assisted reproduction and live-birth rate

ORIGINAL ARTICLE

Ahmad Majzoub, Ashok Agarwal

Abstract Objective: To explore the current evidence concerning the effect of oral antioxidant supplementation on various male fertility outcomes, as antioxidants are widely available compounds that are commonly used for the treatment of male infertility.
Materials and methods: PubMed, Medline and Cochrane electronic databases were searched according to a modified Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines looking for studies investigating the effect of antioxidant therapy on infertile men. The studies were explored looking for antioxidants: (i) types and doses; (ii) mechanism of action and rationale for use; and (iii) effect on the different outcome measures reported.
Results: In all, 26 studies reported a significant positive effect of antioxidant therapy on basic semen parameters, advanced sperm function, outcomes of assisted reproductive therapy, and live-birth rate. Vitamin E, vitamin C, carnitines, N acetyl cysteine, co-enzyme Q10, zinc, selenium, folic acid and lycopene were most commonly used. The vitamins' mechanism of action and reported doses is presented in Tables 1 and 2.
CONCLUSIONS:
Antioxidants generally have a favourable effect on male fertility. Further studies are needed to identify the optimal antioxidant regimen that can be used safely and efficiently in clinical practice.

Arab Journal of Urology (2018) 16, 113–124

Male Oxidative Stress Infertility (MOSI): Proposed Terminology and Clinical Practice Guidelines for Management of Idiopathic Male Infertility

Ashok Agarwal , Neel Parekh, Manesh Kumar Panner Selvam , Ralf Henkel , Rupin Shah , Sheryl T. Homa , Ranjith Ramasamy , Edmund Ko , Kelton Tremellen , Sandro Esteves, Ahmad Majzoub , Juan G. Alvarez , David K. Gardner , Channa N. Jayasena, Jonathan W. Ramsay, Chak-Lam Cho , Ramadan Saleh , Denny Sakkas , James M. Hotaling, Scott D. Lundy, Sarah Vij , Joel Marmar , Jaime Gosalvez , Edmund Sabanegh , Hyun Jun Park , Armand Zini, Parviz Kavoussi , Sava Micic, Ryan Smith , Gian Maria Busetto, Mustafa Emre Bakırcıoğlu, Gerhard Haidl30 , Giancarlo Balercia, Nicolás Garrido Puchalt, Moncef Ben-Khalifa, Nicholas Tadros , Jackson Kirkman-Browne , Sergey Moskovtsev, Xuefeng Huang, Edson Borges Jr , Daniel Franken, Natan Bar-Chama , Yoshiharu Morimoto , Kazuhisa Tomita , Vasan Satya Srini , Willem Ombelet , Elisabetta Baldi , Monica Muratori , Yasushi Yumura , Sandro La Vignera , Raghavender Kosgi , Marlon P. Martinez , Donald P. Evenson , Daniel Suslik Zylbersztejn, Matheus Roque , Marcello Cocuzza, Marcelo Vieira, Assaf Ben-Meir , Raoul Orvieto , Eliahu Levitas , Amir Wiser , Mohamed Arafa, Vineet Malhotra , Sijo Joseph Parekattil , Haitham Elbardisi, Luiz Carvalho , Rima Dada , Christophe Sifer, Pankaj Talwar, Ahmet Gudeloglu , Ahmed M.A. Mahmoud , Khaled Terras , Chadi Yazbeck , Bojanic Nebojsa , Damayanthi Durairajanayagam , Ajina Mounir, Linda G. Kahn , Saradha Baskaran , Rishma Dhillon Pai , Donatella Paoli , Kristian Leisegang,

Mohamed-Reza Moein , Sonia Malik, Onder Yaman, Luna Samanta , Fouad Bayane , Sunil K. Jindal , Muammer Kendirci , Baris Altay , Dragoljub Perovic , Avi Harlev
Despite advances in the field of male reproductive health, idiopathic male infertility, in which a man has altered semen characteristics without an identifiable cause and there is no female factor infertility, remains a challenging condition to diagnose and manage. Increasing evidence suggests that oxidative stress (OS) plays an independent role in the etiology of male infertility, with 30% to 80% of infertile men having elevated seminal reactive oxygen species levels. OS can negatively affect fertility via a number of pathways, including interference with capacitation and possible damage to sperm membrane and DNA, which may impair the sperm's potential to fertilize an egg and develop into a healthy embryo. Adequate evaluation of male reproductive potential should therefore include an assessment of sperm OS. We propose the term Male Oxidative Stress Infertility, or MOSI, as a novel descriptor for infertile men with abnormal semen characteristics and OS, including many patients who were previously classified as having idiopathic male infertility. Oxidation-reduction potential (ORP) can be a useful clinical biomarker for the classification of MOSI, as it takes into account the levels of both oxidants and reductants (antioxidants). Current treatment protocols for OS, including the use of antioxidants, are not evidence-based and have the potential for complications and increased healthcare-related expenditures. Utilizing an easy, reproducible, and cost-effective test to measure ORP may provide a more targeted, reliable approach for administering antioxidant therapy while minimizing the risk of antioxidant overdose. With the increasing awareness and understanding of MOSI as a distinct male infertility diagnosis, future research endeavors can facilitate the development of evidence-based treatments that target its underlying cause.
World J Mens Health Published online May 8, 2019

Evaluation of the antioxidative enzymes in the seminal plasma of infertile men: Contribution to classic semen quality analysis.

Otasevic V, Kalezic A, Macanovic B, Jankovic A, Stancic A, Garalejic E, Korac A, Korac B.

Protein expression/activity of antioxidative defense enzymes (AD) in seminal plasma of fertile men might be used as biomarkers of male fertility status. To test this concept, the present study examined the semen parameters of males among 14 normal idiopathic (normozoospermia) and 84 subnormal (teratozoospermia, oligoteratozoospermia, oligoasthenoteratozoospermia) infertile individuals\. We investigated levels of protein expression/activity of Cu, Zn superoxide dismutase (CuZnSOD), manganese superoxide dismutase (MnSOD), catalase and glutathione peroxidase (GSH-Px), their association with functional sperm parameters, as well as their potential to serve as biomarkers of specific sperm pathologies. Although the activity of CuZnSOD and protein expression of catalase were significantly correlated with several sperm parameters, underlying their potential role in etiology of various sperm abnormalities, investigation of their potential usefulness as a biomarker of semen quality showed that these AD enzymes could not distinguish subtle differences between various sperm pathologies. In contrast, GSH-Px activity was decreased in all groups with sperm pathologies and was a very good indicator of aberrations in functional sperm parameters, explaining up to 94.6% of infertility cases where functional sperm parameters were affected. Therefore, assessment of GSH-Px activity showed the potential to discriminate between infertile males with normal and subnormal semen characteristics and may prove useful in the evaluation of male (in)fertility. Abbreviations: AD: antioxidative defense; Cu, Zn SOD: copper, zinc superoxide dismutase; GSH-Px: glutathione peroxidase; MnSOD: manganese superoxide dismutase; NS: normospermia; OATS: oligoasthenoteratozoospermia; OTS: oligoteratozoospermia; ROC: receiver operating

characteristic; ROS: reactive oxygen species; TS: teratozoospermia; WHO: world health organization.

Syst Biol Reprod Med. 2019 Oct;65(5):343-349. doi: 10.1080/19396368.2019.1600171. Epub 2019 Apr 9.

Resistin in Human Seminal Plasma: Relationship with Lipid Peroxidation, CAT Activity, GSH/GSSG Ratio, and Semen Parameters.

Moretti E, Micheli L, Noto D, Fiaschi A, Menchiari A, Cerretani D.

esistin is an adipokine involved in inflammation and able to induce the expression of other proinflammatory cytokines. It is known that, in human semen, resistin is correlated with inflammatory cytokines and sperm quality. The aim of this prospective study was to explore the potential relationship between resistin, lipid peroxidation (LPO), catalase (CAT) activity, and reduced and oxidized glutathione (GSH/GSSG) ratio in semen samples of infertile patients with leukocytospermia (no. 19), infertile patients with varicocele (no. 17), and fertile men (no. 17). Semen analysis was performed following the WHO guidelines, and sperm apoptosis and necrosis were evaluated with annexin V/propidium iodide assay. Seminal plasma samples were used to determine resistin levels by an immunological method, MDA concentration by a HPLC analysis with UV detection, GSH/GSSG ratio by an enzymatic method, CAT activity by a spectrophotometric method. The results showed that, in both groups of infertile patients, semen parameters were significantly reduced ($P < 0.001$) and sperm apoptosis and necrosis percentages were increased. Resistin levels were significantly higher in leukocytospermia and varicocele groups ($P < 0.001$ and $P < 0.01$, respectively) as well as MDA concentration ($P < 0.001$) compared to controls. The MDA level was also significantly increased in the leukocytospermia group versus the varicocele group ($P < 0.05$). The GSH/GSSG ratio was higher in fertile controls than the leukocytospermia group ($P < 0.05$) and the varicocele group ($P < 0.001$) and in the leukocytospermia group versus the varicocele group ($P < 0.05$). Both the leukocytospermia and varicocele groups showed increased values of CAT activities ($P < 0.001$) than controls. Briefly, the correlation between variables, calculated in the whole patient population, showed that resistin levels positively correlated with MDA levels, CAT activity, sperm apoptosis, and necrosis and negatively with sperm parameters and GSH/GSSG ratio. These results support an active role of resistin in an inflammatory process causing LPO, increase of CAT activity, and decrease of GSH/GSSG ratio in seminal plasma of infertile men vs. fertile controls

Oxid Med Cell Longev. 2019 Oct 22;2019:2192093. doi: 10.1155/2019/2192093. eCollection 2019.

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Antioxidant N-acetylcysteine

Effects of N-acetyl-cysteine supplementation on sperm quality, chromatin integrity and level of oxidative stress in infertile men.

Jannatifar R, Parivar K, Roodbari NH, Nasr-Esfahani MH.

BACKGROUND:

Infertile men have higher levels of semen reactive oxygen species (ROS) than fertile men. High levels of semen ROS can cause sperm dysfunction, sperm DNA damage and reduced male reproductive potential. This study investigated the effects of supplementation with N-acetyl-cysteine (NAC) on the sperm quality, chromatin integrity and levels of oxidative stress in infertile men.

METHODS:

The study was carried out in the unit of ACECR Infertility Research Center, Qom, Iran. The patients consisted of 50 infertile men with asthenoteratozoospermia who received NAC (600 mg/d) orally for 3 months, after which they were compared with pre-treatment status. Semen was analyzed according to WHO (2010), followed by the assessment of protamine content [chromomycin A3 (CMA3)] and DNA integrity [terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL)]. Oxidative stress markers, i.e. total antioxidant capacity (TAC) and malondialdehyde (MDA), as well as hormonal profile (LH, FSH, Testosterone and Prolactin) were determined by ELISA kit.

RESULTS:

After NAC treatment, patients' sperm count and motility increased significantly whereas abnormal morphology, DNA fragmentation and protamine deficiency showed significant decreases compared to pre-treatment levels ($P < 0.05$). Hormonal profile improvement was associated with lowered FSH and LH levels and increased amount of testosterone ($P < 0.05$). TAC significantly increased and MDA decreased with an inverse significant correlation between TAC and MDA ($P < 0.05$).

CONCLUSION:

NAC oral supplementation may improve sperm parameters and oxidative/antioxidant status in infertile males.

Reprod Biol Endocrinol. 2019 Feb 16;17(1):24. doi: 10.1186/s12958-019-0468-9.

Exposure to Polystyrene Microplastics Causes Reproductive Toxicity Through Oxidative Stress and Activation of the p38 MAPK Signaling Pathway

Xiaoman Xie, Ting Deng, Jiufei Duan, Jing Xie, Junlin Yuan, Mingqing Chen

Microplastics (MP) are receiving increased attention as a harmful environmental pollutant, however information on the reproduction toxicity of MP in terrestrial animals, especially

mammals, is limited. In this experiment, we investigated the impact of polystyrene microplastics (micro-PS) on the reproductive system of male mice. Healthy Balb/c mice were exposed to saline or to different doses of micro-PS for 6 weeks. The results showed that micro-PS exposure resulted in a significant decrease in the number and motility of sperm, and a significant increase in sperm deformity rate. We also detected a decrease in the activity of the sperm metabolism-related enzymes, succinate dehydrogenase (SDH) and lactate dehydrogenase (LDH), and a decrease in the serum testosterone content in the micro-PS exposure group. We found that micro-PS exposure caused oxidative stress and activated JNK and p38 MAPK. In addition, we found that when N-acetylcysteine (NAC) scavenges ROS, and when the p38 MAPK-specific inhibitor SB203580 inhibits p38MAPK, the micro-PS-induced sperm damage is alleviated and testosterone secretion improves. In conclusion, our findings suggest that micro-PS induces reproductive toxicity in mice through oxidative stress and activation of the p38 MAPK signaling pathways.

Ecotoxicol Environ Saf. 2020 Mar 1;190:110133.

Protective Action of N-acetylcysteine on Sperm Quality in Cyclophosphamide-Induced Testicular Toxicity in Male Wistar Rats

Seyyid A Shittu, Shehu-Tijani Shittu, Opeyemi O Akindele, Olufadekemi T Kunle-Alabi, Yinusa Raji

Background: Reductions in sperm quality due to free radical formation during cancer chemotherapy are well documented, hence the need for an adjunct antioxidant treatment during chemotherapy. This study was designed to investigate the effects of N-acetylcysteine on sperm quality following cyclophosphamide exposure in male Wistar rats.

Methods: wenty male Wistar rats weighing 150-170g were randomly assigned into 4 groups of five rats each, and were orally administered distilled water (Control), Cyclophosphamide (6mg/kg), N-acetylcysteine (100mg/kg) or Cyclophosphamide + N-acetylcysteine for 21 days. Sperm count, histone-protamine replacement, chromatin integrity, testicular histomorphometry and BAX Protein expression were assessed using standard procedures. The data was presented as mean ± SEM and analyzed using students' t- test. A $p<0.05$ was considered significant.

Results: Sperm counts were significantly reduced ($p<0.05$) among the cyclophosphamide (69.95±7.78 x106/ml) and cyclophosphamide + N-acetylcysteine (64.78±3.52 x106/ml) treated rats, while it increased significantly ($p<0.05$) in the N-acetylcysteine (132.20±28.71 x106/ml) treated rats compared to the control animals (115.30±8.70x106/ml). Increased interstitial space distance, degenerated Leydig cells and impaired histone-protamine replacement observed among the cyclophosphamide-treated rats were ameliorated in the cyclophosphamide + N-acetylcysteine-treated rats. Sperm chromatin integrity, which was poor in the cyclophosphamide-treated rats, was considerably improved when compared with the Control and the N-acetylcysteine-treated rats. Bax protein expression was reduced in the cyclophosphamide (20%) and cyclophosphamide+N-acetylcysteine (20%) groups when compared with the Control (50%) and N-acetylcysteine (50%) groups.

Conclusion: We concluded that N-acetylcysteine might improve sperm histone protamine replacement, which is one of the stage-specific effect of cyclophosphamide toxicity.
JBRA Assist Reprod. 2019 Apr 30;23(2):83-90.

Protective Antioxidant Effects of N-acetylcysteine Against Impairment of Spermatogenesis Caused by Paranonylphenol

Mahdi Malmir, Malek Soleimani Mehranjani, Samira Naderi Noreini, Tayebe Faraji

Paranonylphenol (p-NP) is an environmental pollutant that causes oxidative stress. The purpose of this study was to evaluate the protective effect of N-acetylcysteine (NAC) as an antioxidant on sperm parameters and testis in mice after treatment with p-NP. Adult mice were randomly divided into four groups (n = 6, each group) including 1-control, 2- p-NP (250 mg kg-1 day-1), 3- NAC (150 mg kg-1 day-1) and 4- p-NP + NAC. After 35 days of oral treatment, the mean of spermatogenic index ($p < 0.02$), sperm count ($p < 0.01$), daily sperm production ($p < 0.01$), sperm tail length ($p < 0.02$), progressive movement ($p < 0.04$), normal morphology ($p < 0.04$) and viability ($p < 0.01$) of spermatozoa and also serum testosterone level ($p < 0.04$) were significantly reduced in p-NP group when compared to other groups. While the count of the positive TUNEL cells in the seminiferous tubules ($p < 0.01$) and level of the malondialdehyde (MDA) in testis ($p < 0.02$) and serum ($p < 0.01$) significantly increased. In the histopathologic assay in the p-NP group, apoptosis, atrophy, oedema, reduction in sperm density in lumens and vacuoles were observed. The findings of this study indicate that NAC as a potent antioxidant be able to compensate the adverse effects of p-NP in spermatogenesis, testis and levels of testosterone and MDA in the p-NP + NAC group significantly compared to the p-NP group.

Andrologia. 2018 Dec;50(10):e13114.

Effects of N-acetylcysteine on semen parameters and oxidative/antioxidant status.

Ciftci H, Verit A, Savas M, Yeni E, Erel O.

OBJECTIVES:
To examine whether a beneficial effect of N-acetylcysteine (NAC) on semen parameters and oxidative/antioxidant status in idiopathic male infertility exists. The production of reactive oxygen species is a normal physiologic event in various organs. However, overproduction of reactive oxygen species can be detrimental to sperm and has been associated with male infertility.

METHODS:
Our study included 120 patients who had attended our clinic and were diagnosed with idiopathic infertility according to medical history and physical and seminal examination findings, as initial evaluations. The patients were divided randomly into 2 groups. Those in the study group (60 men) were given NAC (600 mg/d orally) for 3 months; the control group (60 men) received a placebo. The oxidative status was determined by measuring the total antioxidant

capacity, total peroxide and oxidative stress index in plasma samples. The sperm parameters were evaluated after NAC treatment and were compared with those in the control group.

RESULTS:
NAC had significant improving effects on the volume, motility, and viscosity of semen. After NAC treatment, the serum total antioxidant capacity was greater and the total peroxide and oxidative stress index were lower in the NAC-treated group compared with the control group. These beneficial effects resulted from reduced reactive oxygen species in the serum and reduced viscosity of the semen. No significant differences were found in the number or morphology of the sperm between the 2 groups.

CONCLUSIONS:
We believe that NAC could improve some semen parameters and the oxidative/antioxidant status in patients with male infertility.

Urology. 2009 Jul;74(1):73-6. doi: 10.1016/j.urology.2009.02.034. Epub 2009 May 9.

Paternal folate and male reproduction

Paternal Folate Status and Sperm Quality, Pregnancy Outcomes, and Epigenetics: A Systematic Review and Meta-Analysis.

Hoek J, Steegers-Theunissen RPM, Willemsen SP, Schoenmakers S.

SCOPE:

The effectiveness of maternal folate in reducing the risk of congenital malformations during pregnancy is well established. However, the role of the paternal folate status is scarcely investigated. The aim of this study is to investigate the evidence of associations between the paternal folate status and sperm quality, sperm epigenome, and pregnancy outcomes.

METHODS AND RESULTS:

Databases are searched up to December 2017 resulting in 3682 articles, of which 23 are retrieved for full-text assessment. Four out of thirteen human and two out of four animal studies show positive associations between folate concentrations and sperm parameters. An additional meta-analysis of four randomized controlled trials in subfertile men shows that the sperm concentration increases (3.54 95% confidence interval (CI) [-1.40 to 8.48]) after 3-6 months of 5 mg folic acid use per day compared to controls. Moreover, two out of two animal and one out of three human studies show significant alterations in the overall methylation of the sperm epigenome. One animal and one human study show associations between low folate intake and an increased risk of congenital malformations.

CONCLUSIONS:

This systematic review and meta-analysis shows evidence of associations between paternal folate status and sperm quality, fertility, congenital malformations, and placental weight.

Mol Nutr Food Res. 2020 Feb 7:e1900696. doi: 10.1002/mnfr.201900696. [Epub ahead of print]

Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes

R. Lambrot, C. Xu, S. Saint-Phar, G. Chountalos, T. Cohen, M. Paquet, M. Suderman, M. Hallett & S Kimmins

Epidemiological studies suggest that a father's diet can influence offspring health. A proposed mechanism for paternal transmission of environmental information is via the sperm epigenome. The epigenome includes heritable information such as DNA methylation. We hypothesize that the dietary supply of methyl donors will alter epigenetic reprogramming in sperm. Here we feed male mice either a folate-deficient or folate-sufficient diet throughout life. Paternal folate deficiency is associated with increased birth defects in the offspring, which include craniofacial and musculoskeletal malformations. Genome-wide DNA methylation analysis and the subsequent functional analysis identify differential methylation in sperm of genes implicated in development, chronic diseases such as cancer, diabetes, autism and schizophrenia. While 4300 genes are differentially expressed in offspring placenta, only two correspond to genes with differential methylation in sperm. This model suggests epigenetic transmission may involve sperm histone H3 methylation or DNA methylation and that adequate paternal dietary folate is essential for offspring health.

NATURE COMMUNICATIONS 2013 | 4:2889 |

The Effect of Folate and Folate Plus Zinc Supplementation on Endocrine Parameters and Sperm Characteristics in Sub-Fertile Men: A Systematic Review and Meta-Analysis

Morvarid Irani, Malihe Amirian, Ramin Sadeghi, Justine Le Lez , Robab Latifnejad Roudsari

PURPOSE:

To evaluate the effect of folate and folate plus zinc supplementation on endocrine parameters and sperm characteristics in sub fertile men.

MATERIALS AND METHODS:

We conducted a systematic review and meta-analysis. Electronic databases of Medline, Scopus , Google scholar and Persian databases (SID, Iran medex, Magiran, Medlib, Iran doc) were searched from 1966 to December 2016 using a set of relevant keywords including "folate or folic acid AND (infertility, infertile, sterility)".All available randomized controlled trials (RCTs), conducted on a sample of sub fertile men with semen analyses, who took oral folic acid or folate plus zinc, were included. Data collected included endocrine parameters and sperm characteristics. Statistical analyses were done by Comprehensive Meta-analysis Version 2.

RESULTS:

In total, seven studies were included. Six studies had sufficient data for meta-analysis. "Sperm concentration was statistically higher in men supplemented with folate than with placebo (*P* < .001)". However, folate supplementation alone did not seem to be more effective than the placebo on the morphology (*P* = .056) and motility of the sperms (*P* = .652). Folate plus zinc supplementation did not show any statistically different effect on serum testosterone (*P* = .86), inhibin B (*P* = .84), FSH (*P* = .054), and sperm motility (*P* = .169) as compared to the placebo. Yet, folate plus zinc showed statistically higher effect on the sperm concentration (*P* < .001), morphology (*P* < .001), and serum folate level (*P* < .001) as compared to placebo.
CONCLUSIONS:
Folate plus zinc supplementation has a positive effect on sperm characteristics in sub fertile men. However, these results should be interpreted with caution due to the important heterogeneity of the studies included in this meta-analysis. Further trials are still needed to confirm the current findings.

Urol J. 2017 Aug 29;14(5):4069-4078.

Lycopene

A Randomized Placebo-Controlled Trial to Investigate the Effect of Lactolycopene on Semen Quality in Healthy Males

Elizabeth A Williams, Madeleine Parker, Aisling Robinson, Sophie Pitt, Allan A Pacey

Purpose: Poor sperm quality is a major contributor to infertility in heterosexual couples, but at present there are few empirical therapies. Several studies have examined the role of dietary factors and data from randomized controlled trials suggest that oral antioxidant therapy can improve some sperm parameters. Health benefits of lycopene supplementation have been proposed for a variety of health conditions and here we examine whether it can help improve sperm quality. This study aimed to investigate the effect of 14 mg daily lactolycopene for 12 weeks on semen quality in healthy men.

Methods: Sixty healthy male participants were recruited and randomized to this double-blind, placebo-controlled parallel study and received either 14 mg/d lactolycopene or a placebo for 12 weeks. The primary endpoint was a change in motile sperm concentration. Secondary endpoints were all other aspects of sperm quality, including the level of sperm DNA damage.

Results: Fifty-six men completed the intervention and the level of plasma lycopene was significantly increased in the men randomized to receive lycopene supplementation. There was no significant change in the primary endpoint (motile sperm concentration) post-intervention ($p = 0.058$). However, the proportion of fast progressive sperm ($p = 0.006$) and sperm with normal morphology ($p < 0.001$) did improve significantly in response to lactolycopene intervention.

Conclusions: Supplementation with 14 mg/d lactolycopene improves sperm motility and morphology in young healthy men.

Eur J Nutr. 2020 Mar;59(2):825-833.

Protective Effect of Lycopene on Testicular Toxicity Induced by Benzo[a]pyrene Intake in Rats

Anran Xu , Jianye Wang , Haiyu Wang , Yanqing Sun, Tianyu Hao

Benzo[a]pyrene (BaP) stimulates male reproductive toxicity. In this study, we want to examine the ameliorative potential of Lycopene (LYC) on BaP-induced testicular toxicity. Adult male Wistar rats were segregated into 5 groups: Control, LYC, BaP, BaP + LYC and BaP + PQ7. Sperm parameters, testosterone level, oxidant and antioxidant parameters were determined. MRNA and protein abundances of key genes were analyzed. Cell death and apoptosis were assessed by trypan blue exclusion and Annexin V-FITC staining assay, respectively. LYC inhibited BaP-caused decrease in sperm motility and epididymal sperm concentration, and increase in head, tail and total abnormal sperm rate. LYC inhibited BaP-caused decrease in testosterone level in serum and intratesticular fluids. LYC protected germ cells from BaP-caused oxidative stress. LYC also prevented BaP-caused germ cell death and apoptosis by inhibiting apoptotic pathway. Besides, LYC ameliorated BaP-mediated gap-junction dysfunction of sertoli cells, as shown by the inhibited sertoli cell death and apoptosis, the upregulation of Bcl2 and Cx43, the downregulation of Cleaved Caspase 3, Bax and CaM, and the decrease in Ca2+ level. LYC ameliorated BaP-caused testicular damage via inhibiting oxidative stress and apoptosis, and relieving the gap-junction dysfunction of sertoli cells.

Toxicology. 2019 Nov 1;427:152301.

Dietary Micronutrient Supplementation for 12 Days in Obese Male Mice Restores Sperm Oxidative Stress

Nicole O McPherson, Helana Shehadeh, Tod Fullston, Deirdre L Zander-Fox, Michelle Lane

Male obesity, which often co-presents with micronutrient deficiencies, is associated with sub-fertility. Here we investigate whether short-term dietary supplementation of micronutrients (zinc, selenium, lycopene, vitamins E and C, folic acid, and green tea extract) to obese mice for 12 days (designed to span the epididymal transit) could improve sperm quality and fetal outcomes. Five-week-old C57BL6 males were fed a control diet (CD, n = 24) or high fat diet (HFD, n = 24) for 10 weeks before allocation to the 12-day intervention of maintaining their original diets (CD, n = 12, HFD n = 12) or with micronutrient supplementation (CD + S, n = 12, HFD + S, n = 12). Measures of sperm quality (motility, morphology, capacitation, binding), sperm oxidative stress (DCFDA, MSR, and 8OHdG), early embryo development (2-cell cleavage, 8OHdG), and fetal outcomes were assessed. HFD + S males had reduced sperm intracellular reactive oxygen species (ROS) concentrations and 8OHdG lesions, which resulted in reduced 8OHdG lesions in the male pronucleus, increased 2-cell cleavage rates, and partial restoration of fetal weight similar to controls. Sub-fertility associated with male obesity may be restored with very short-term micronutrient supplementation that targets the timing of the transit of sperm through the epididymis, which is the developmental window where sperm are the most susceptible to oxidative damage.

Nutrients. 2019 Sep 12;11(9):2196.

The Effects of Lycopene Supplement on the Spermatogram and Seminal Oxidative Stress in Infertile Men: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Mehran Nouri, Reza Amani, Mohammadhossein Nasr-Esfahani , Mohammad Javad Tarrahi

a major, worldwide problem that is affected, and mediated, by several factors, in particular, oxidative stress. Thus, the aim of this study was to evaluate the effect of lycopene supplementation on spermatogram and seminal oxidative stress. In this randomized, double-blind, placebo-controlled trial study, 44 infertile men with oligozoospermia were randomly divided into two groups: The experimental group was supplemented with 25 mg of lycopene, and the control group received placebo for 12 weeks. Anthropometric, physical activity and dietary assessment, semen analysis, total antioxidant capacity (TAC), malondialdehyde, and glutathione peroxidase were measured pre- and post-intervention. At the end of the study, there was a significant increase in total sperm count and concentration in the lycopene group, and the latter total count remained significant after adjustment ($p < .05$). Intragroup analysis showed a significant increase in ejaculate volume, total sperm count, concentration total motility, nonprogressive, and nonmotility in lycopene group ($p < .05$). The TAC changes, in both groups, remained significant after adjustment ($p < .05$). Also, within-group analysis showed a significant increase in TAC levels ($p < .05$). Lycopene supplement can improve sperm parameters and oxidative stress biomarkers in oligozoospermia infertile men; however, further studies with larger sample size and duration are required.

Phytother Res. 2019 Dec;33(12):3203-3211.

Evaluation of Ameliorating Effect of Lycopene Against Testicular Toxicity Due to Diethylnitrosamine Using Biochemical, Spermatological and Histopathological Data

Emre Kaya, Seyma Ozer Kaya, Seval Yilmaz, Ali Osman Ceribasi , Gaffari Turk

The aim of this study was to evaluate the possible therapeutic or protective effects of lycopene on diethylnitrosamine (DEN)-induced testicular lipid peroxidation and on the associated changes in spermatological parameters and histopathological architecture of rat testis. DEN is a carcinogenic substance that can be derived from chemicals used in agriculture, such as insecticides and nitrate. The rats were assigned to control, lycopene, DEN(1), DEN(2), lycopene + DEN(1), lycopene + DEN(2), DEN(1) + lycopene and DEN(2) + lycopene groups. During the study, lycopene was administered by oral gavage at a dose of 10 mg kg-1 bw-1 every other day for 10 days and DEN was administered at a dose of 200 mg kg-1 bw-1 as a single dose intraperitoneally. DEN was applied for 30 days in group DEN(1) and for 90 days in group DEN(2). Malondialdehyde (MDA) and reduced glutathione (GSH) levels, antioxidant enzymes activities, spermatological parameters, the weight of the reproductive organs (v. seminalis, prostate, testis and epididymis) and the histopathological structure were determined. MDA levels significantly increased, while GSH and antioxidant enzymes' activities decreased in DEN groups ($p < 0.001$). There was an increase in the rate of abnormal spermatozoa and a decrease in sperm density and motility, and reproductive organ weight (the weight of the right and left testis) in both DEN groups. Lycopene has normalised biochemical and spermatological parameters and reproductive organ weight. The histopathological examination of testicu-

lar tissue showed that the most significant histopathological change in DEN groups was the seminiferous tubule dilatation. These results suggest that besides the protective effects, the therapeutic effect of lycopene is possibly due to its antioxidant effects on DEN-induced testicular toxicity.
Andrologia. 2019 Jul;51(6):e13274.

Lycopene and male infertility.

Durairajanayagam D, Agarwal A, Ong C, Prashast P.
Excessive amounts of reactive oxygen species (ROS) cause a state of oxidative stress, which result in sperm membrane lipid peroxidation, DNA damage and apoptosis, leading to decreased sperm viability and motility. Elevated levels of ROS are a major cause of idiopathic male factor infertility, which is an increasingly common problem today. Lycopene, the most potent singlet oxygen quencher of all carotenoids, is a possible treatment option for male infertility because of its antioxidant properties. By reacting with and neutralizing free radicals, lycopene could reduce the incidence of oxidative stress and thus, lessen the damage that would otherwise be inflicted on spermatozoa. It is postulated that lycopene may have other beneficial effects via nonoxidative mechanisms in the testis, such as gap junction communication, modulation of gene expression, regulation of the cell cycle and immunoenhancement. Various lycopene supplementation studies conducted on both humans and animals have shown promising results in alleviating male infertility—lipid peroxidation and DNA damage were decreased, while sperm count and viability, and general immunity were increased. Improvement of these parameters indicates a reduction in oxidative stress, and thus the spermatozoa is less vulnerable to oxidative damage, which increases the chances of a normal sperm fertilizing the egg. Human trials have reported improvement in sperm parameters and pregnancy rates with supplementation of 4–8 mg of lycopene daily for 3–12 months. However, further detailed and extensive research is still required to determine the dosage and the usefulness of lycopene as a treatment for male infertility.
Asian Journal of Andrology (2014) 16, 420–425;

Citrulline

Oral L-citrulline supplementation improves erection hardness in men with mild erectile dysfunction.

Cormio L, De Siati M, Lorusso F, Selvaggio O, Mirabella L, Sanguedolce F, Carrieri G.
OBJECTIVES:
To test the efficacy and safety of oral L-citrulline supplementation in improving erection hardness in patients with mild erectile dysfunction (ED). L-arginine supplementation improves nitric oxide-mediated vasodilation and endothelial function; however, oral administration has been hampered by extensive presystemic metabolism. In contrast, L-citrulline escapes presystemic metabolism and is converted to L-arginine, thus setting the rationale for oral L-citrulline supplementation as a donor for the L-arginine/nitric oxide pathway of penile erection.

METHODS:
In the present single-blind study, men with mild ED (erection hardness score of 3) received a placebo for 1 month and L-citrulline, 1.5 g/d, for another month. The erection hardness score, number of intercourses per month, treatment satisfaction, and adverse events were recorded.

RESULTS:
A total of 24 patients, mean age 56.5 ± 9.8 years, were entered and concluded the study without adverse events. The improvement in the erection hardness score from 3 (mild ED) to 4 (normal erectile function) occurred in 2 (8.3%) of the 24 men when taking placebo and 12 (50%) of the 24 men when taking L-citrulline (P < .01). The mean number of intercourses per month increased from 1.37 ± 0.93 at baseline to 1.53 ± 1.00 at the end of the placebo phase (P = .57) and 2.3 ± 1.37 at the end of the treatment phase (P < .01). All patients reporting an erection hardness score improvement from 3 to 4 reported being very satisfied.

CONCLUSIONS:
Although less effective than phosphodiesterase type-5 enzyme inhibitors, at least in the short term, L-citrullinesupplementation has been proved to be safe and psychologically well accepted by patients. Its role as an alternative treatment for mild to moderate ED, particularly in patients with a psychologically fear of phosphodiesterase type-5 enzyme inhibitors, deserves further research.

Urology. 2011 Jan;77(1):119-22.

Oral L-citrulline supplementation improves erectile function and penile structure in castrated rats.

Hotta Y, Shiota A, Kataoka T, Motonari M, Maeda Y, Morita M, Kimura K.

OBJECTIVES:
To investigate the efficacy of oral L-citrulline for erectile dysfunction and penile structure disruption in a rat model.

METHODS:
Male Wistar-ST rats aged 15 weeks were randomly divided into three groups as follows: sham-operated rats (control group), surgically castrated rats (castrated group) and surgically castrated rats subsequently treated with 2% L-citrullinewater (castrated + L-citrulline). At 4 weeks postoperative, erectile function was assessed based on intracavernous pressure changes, followed by electrostimulation of cavernous nerves and calculation of maximum intracavernous pressure/mean arterial pressure. Penile structure was evaluated by Masson's trichrome staining and the smooth muscle-to-collagen ratio was calculated. The serum bioavailable testosterone, L-arginine, L-citrulline, N(G),N(G) -dimethylarginine and nitrogen oxide levels were evaluated.

RESULTS:
The bioavailable testosterone concentrations were decreased in the castrated and castrated + L-citrulline groups compared with the control group at 4 weeks after surgery. The intracavernous pressure-to-mean arterial pressure and smooth muscle-to-collagen ratios were significantly decreased in the castrated group compared with the control group, but significantly increased in the castrated + L-citrulline group compared with the castrated group. The serum L-citrulline, L-arginine and N(G),N(G)-dimethylarginine levels, and the L-arginine-to-N(G),N(G)-dimethylarginine ratios were significantly increased in the castrated +L-citrulline group compared with the castrated group. The serum nitrogen oxide levels were increased in the castrated + L-citrulline group compared with the castrated group.

CONCLUSIONS:
Oral L-citrulline can improve the erectile response to electric stimulation of cavernous nerve and penile structure in castrated rats.

Int J Urol. 2014 Jun;21(6):608-12. doi: 10.1111/iju.12362. Epub 2013 Dec 23.

Fertilovit® Mplus

Studies have revealed that Fertilovit Mplus is an excellent choice when it comes to dietetic management of male subfertile patients. It features antioxidants and other micronutrients with superior bioavailability and is the only product on the market offering a long-term antioxidant supply.
To ensure this, Fertilovit® Mplus features a combination of state-of-the-art techniques to provide precious micronutrients with superior bioavailability and a long-term effect:

Coating

Outer coating: Controlled diffusion systems, also known as matrix systems, are very popular for sustained release dosage forms. In this technology, the tablet has a casing typically made up of polymers. The type of polymer controls the release of the ingredients in the body.
Various polymers are used to formulate controlled release dosage forms. Hydroxy propyl-methylcellulose (HPMC) is used as the first choice for forming hydrophilic matrix systems as it provides a powerful mechanism for controlled release of components. Fertilovit® products are typically encapsulated in vegetarian HPMC capsules.

Additional coating of specific components: Components which are lost quickly due to their high water-solubility can be delivered to the body in form of microencapsulated particles surrounded by a coating. This allows for sustained release and helps to improve the physiological activity. All Fertilovit® products contain coated vitamin C.

Use of precursors
Fertilovit® products use precursors to boost endogenous synthesis to increase bioavailability and secure a long-term effect. N-acetyl-L-cysteine is used as a precursor that boosts endogenous glutathione synthesis effectively. Glutathione is the body's main antioxidant.
Another precursor used is L-citrulline. This amino acid allows for increase of endogenous production of L-arginine, which has very limited bioavailability when given orally. It is needed for healthy sperm development and perfusion of the male reproductive system.

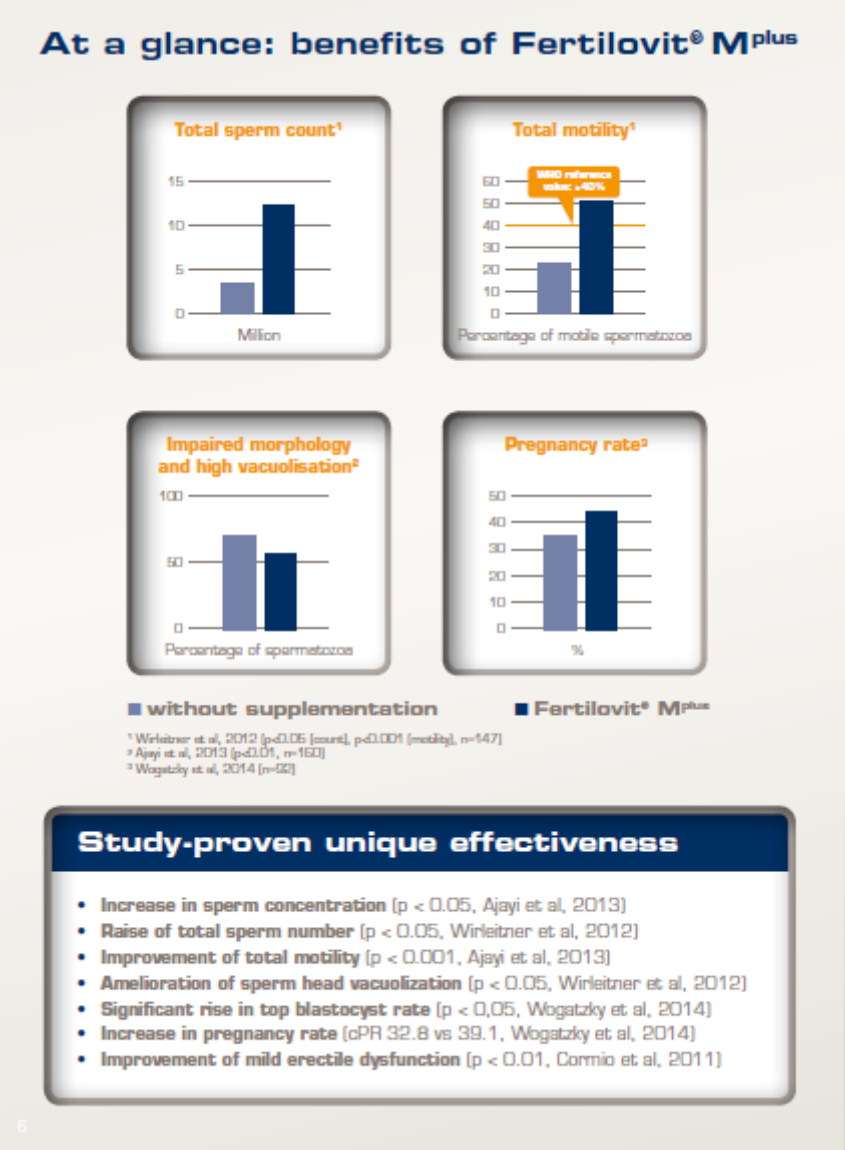
Daily dosage
The daily dosage of Fertilovit® Mplus has been divided into two capsules, one of which is to be taken in the morning and another one in the evening. This is another way to make sure that a steady level of antioxidant protection is present 24/7.

Efficacy of Fertilovit®M^{plus}

By providing this **holistic** and at the same time **long-term approach**, Fertilovit®M^{plus} has been shown to **improve sperm quality in OAT-patients** not only according to WHO (WHO 2010) criteria, but also with respect to MSOME criteria (Bartoov et al, 2002) .This is particularly important, as sperm head vacuolisation has been linked not only to success of fertility treatment, but also to DNA integrity (Vanderzwalmen et al, 2008). The proposed mechanism of action includes protection from oxidative stress, enhanced enzymatic function, ameliorated blood flow, improved mitochondrial function and anti-inflammatory aspects (Wirleitner et al, 2012; Ajayi et al, 2013).

In addition to that, a follow-up study with 92 couples was able to demonstrate that paternal supplementation with Fertilovit® Mplus can also increase success rates of ART treatment by improving top-blastocyst rates significantly and increasing pregnancy rates markedly (Wogatzky et al, 2014).

	First treatment cycle without supplementation	Second treatment cycle with supplementation	Significance
Female age (average)	36.8 +/- 4.2	38.1 +/- 3.9	n.s.
Oocytes retrieved (total)	1127	1092	n.s.
Oocytes (average)	12.4 +/- 5.9	12.1 +/- 5.7	n.s.
Fertilisation rate (%)	59.6	60.4	n.s.
Blastocysts (total)	267	288	n.s.
Blastocysts (average)	2.9 +/- 2.4	3.1 +/- 2.7	n.s.
Blastocyst rate (%)	39.7	43.7	n.s.
Top-blastocysts (total)	37	56	
Top-blastocysts (average)	0.4 +/- 1.1	0.6 +/- 1.0	
Top blastocyst rate (%)	**5.5**	**8.5**	**< 0.05**
Biochemical pregnancy rate (%)	**34.8**	**44.5**	n.s.
Clinical pregnancy rate (%)	**32.8**	**39.1**	n.s.


At a glance: benefits of Fertilovit® M plus
Total sperm count[1]
15
10
5
0
Milion
Total motility[1]
WHO reference value: ≥40%
60
50
40
30
20
10
0
Percentage of motile spermatozoa
Impaired morphology and high vacuolisation[2]
100
50
0
Percentage of spermatozoa
Pregnancy rate[3]
50
40
30
20
10
0
%
without supplementation
Fertilovit® M plus
[1] Wirleitner et al, 2012 (p<0.05 [count], p<0.001 [motility], n=147)
[2] Ajayi et al, 2013 (p<0.01, n=160)
[3] Wogatzky et al, 2014 (n=92)
Study-proven unique effectiveness
Increase in sperm concentration (p < 0.05, Ajayi et al, 2013)
Raise of total sperm number (p < 0.05, Wirleitner et al, 2012)
Improvement of total motility (p < 0.001, Ajayi et al, 2013)
Amelioration of sperm head vacuolization (p < 0.05, Wirleitner et al, 2012)
Significant rise in top blastocyst rate (p < 0,05, Wogatzky et al, 2014)
Increase in pregnancy rate (cPR 32.8 vs 39.1, Wogatzky et al, 2014)
Improvement of mild erectile dysfunction (p < 0.01, Cormio et al, 2011)

Gonadosan Distribution GmbH

Austrian-based Gonadosan Distribution GmbH is dedicated to the development and ongoing research of state-of-the-art nutraceuticals meeting the specific nutritional needs of men and women planning for pregnancy. The Fertilovit® range of supplements is based on the latest scientific data, tested in cooperation with big European ART centers and has been proven to support fertility treatment effectively. A variety of patent-protected preparations offer highly specific solutions for different male and female fertility patients, ranging from mature patients to patients with thyroid autoimmunity, endometriosis, PCOS, and idiopathic OAT.

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