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Lycopene therapy in idiopathic male infertility – a preliminary report

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Abstract. Excessive generation of reactive oxygen species (ROS) containing free oxygen radicals has been identified as one of the causes of male infertility. Lycopene is a component of human redox defence mechanism against free radicals. It is found in high concentrations in the testes and seminal plasma and decreased levels have been demonstrated in men suffering from infertility. We evaluated the effect of oral lycopene therapy in men with idiopathic infertility. Beginning March 2000, thirty men with idiopathic non-obstructive oligo/astheno/teratozoospermia were enrolled for the trial. All patients were administered 2000 mcg of Lycopene, twice a day for three months. Semen analysis was performed at three months and sperm concentration, motility and morphology were evaluated. All patients completed the trial without any complications. Twenty patients (66%) showed an improvement in sperm concentration, sixteen (53%) had improved motility and fourteen (46%) showed improvement in sperm morphology. In cases showing an improvement, the median change in concentration was 22 million/ml, motility 25% and morphology 10%. The improvement in concentration and motility were statistically significant. Baseline sperm concentration less than 5 million/ml was associated with no significant improvement. Higher baseline concentrations were associated with significant improvement and resulted in six pregnancies in 26 patients (23%). Oral Lycopene therapy seems to have a role in the management of idiopathic male infertility. Maximum improvement seems to occur in the sperm concentration (66% cases). Patients without severe oligospermia (sperm density >5 million/ml) may be given a trial of therapy with lycopene. However, larger randomised controlled trials are essential before definitive therapeutic guidelines can be made.

Key words: Andrology, Antioxidants, Carotenoids, Oxidative stress, Reactive oxygen species (ROS)

Introduction

Mammalian spermatozoal membranes are rich in highly unsaturated fatty acids. These are sensitive to oxygen induced damage by lipid peroxidation. A free radical is defined as a molecule containing one or more unpaired electrons. Reactive oxygen species (ROS) include super oxide anion (O_2^-) and hydroxyl radical ($^-$OH) which contain highly reactive oxygen radicals. High levels of ROS seen in some infertile patients may be the cause of idiopathic infertility and higher ROS levels have been detected in the seminal plasma of infertile men while no ROS was detected in the control group [1, 2]. Lycopene is a naturally synthesized carotenoid found in fruits and vegetables. It is also a component of the human redox mechanism that scavenges free radicals including ROS. This study aims at determining whether oral supplementation with Lycopene improves fertility in patients with idiopathic infertility.

Materials and methods

Beginning March 2000, thirty men who presented to our clinic with idiopathic infertility with oligo/astheno/teratozoospermia were included in the study. Clearance of the Hospital Ethical Commitee was obtained prior to beginning the study. The patients' age ranged from 23–45 years (mean 26.5 years). Mean duration of infertility was 2.3 years (range 1.2–20 years). All men underwent a detailed physical examination, two semen analyses, semen culture, antisperm antibody levels and baseline hormone profile including serum FSH, LH, Prolactin and testosterone to exclude correctable cause for infertility. We defined abnormal semen parameters based on the values suggested by Sigman et al. [3]. This included sperm concentration below 50 million per ml, less than 50% motile sperms and less than 50% sperms with normal morphology. Patients with no discernible cause for their abnormal semen parameters were included in the study. The

Table 1. Semen parameters in cases with improvement (Wilcoxon Rank Sum test of significance)

Parameter	n	Baseline		3 Months		Improvement		*P*-value
		Median	25–75 percentile	Median	25–75 percentile	Median	25–75 percentile	
Concentration (million/ml)	20	13.5	9.75–18.75	37.5	17.5–63	22	6.75–45.25	<0.05
Motility (% normal)	16	15	5–30	50	30–60	25	20–40	<0.05
Morphology (% normal)	14	30	20–37.5	40	30–48.75	10	10–10	NS

mean value of sperm density, motility and morphology from the two pre-operative semen values were used as the baseline for each patient. Twenty seven patients had oligospermia, 26 had impaired motility and 22 had abnormal morphology. 14 patients had all three parameters abnormal, 14 had two abnormal values while two had solitary factor abnormality.

All patients were administered 2000 mcg of Lycopene twice a day for three months. Semen analysis was performed at three months following initiation of therapy and the same parameters were evaluated. Any pregnancy during the follow up period was also documented. The values were compared with the baseline and the results are expressed as median values with intra quartile range. The Wilcoxon rank sum test, a non parametric test, was performed to verify statistical significance [4].

Results

All thirty men completed the trial with no adverse effects. Twenty patients (66.6%) showed improvement in the sperm concentration with median improvement of 22 million/ml. 53% cases showed improved sperm motility by a median value of 25% while 46% cases showed improved normal morphology by 10%. (Table 1). Twelve cases (40%) had improvement in all three parameters. Maximum sperm concentration improvement was noted in patients with baseline concentration greater than 5 million/ml (Figure 1).

The improvement in sperm concentration and motility was statistically significant. There were 6 pregnancies (20%). All pregnancies occurred in the group with baseline sperm concentration greater than 5 million/ml.

Discussion

Ten to fifteen percent of couples suffer from infertility [5] and in upto 50% cases, the male factor is involved [6]. After varicoceles, the most common diagnosis in the majority of these cases, 25% [3], is idiopathic. One of the problems involved in the diagnosis of male infertility is the near complete overlap in the semen values of fertile and infertile men, barring those with absolute azoospermia. Men with sperm concentrations below 12.5 million/ml have upto a 25% pregnancy rate [7] whereas those with counts between 12.5 and 25 million have upto a 44% spontaneous pregnancy rate. These would otherwise be considered as abnormal semen parameters.

Idiopathic infertility continues to be a vexing problem for andrologists and no significant success has been noted with any form of therapy. In view of the fact that men with subnormal semen analysis can also be fertile while, on the other hand, men with normal semen parameters continue to be infertile [8], there is a possible etiological role for factors other than the routinely investigated semen parameters. Defective sperm function has been postulated to be one such factor [9] with free radical induced oxidative damage being one of the underlying causes.

Oxidative stress with excessive generation of ROS may play a role in the etiology of male infertility [1, 2]. A prospective study demonstrated that men with higher ROS generation had seven times lower chances of effecting a pregnancy than men with low ROS [10]. The total antioxidant capacity of the seminal plasma in infertile men is lower than that in fertile men [11]. In oligospermic men, the spermatozoa produce higher levels of ROS compared to fertile men [12]. High levels of ROS are found in upto 40% oligospermic men who show poor oocyte penetra-

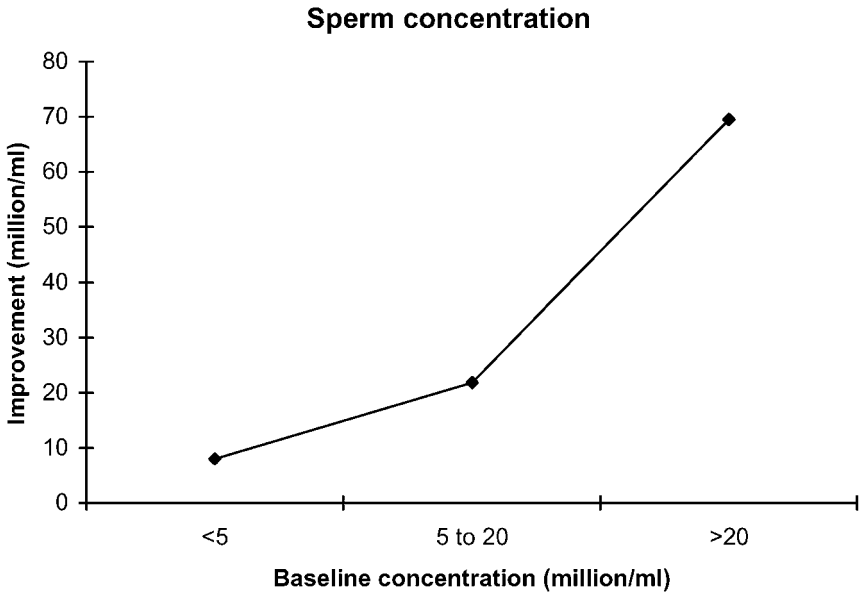

Figure 1. Improvement with relation to baseline concentration.

tion [13]. Armstrong et al showed spermatozoal ATP levels decrease after treatment with ROS in an experimental model and this was associated with poor forward motility [14]. ROS is hypothesised to cause its effects on sperm function through peroxidation of polyunsaturated fatty acids in the sperm plasma membrane [12, 15]. Based on the above evidence, it is logical to assume a potential role of antioxidant therapy in the management of ROS induced infertility. In-vitro experiments with vitamin E – one of the major membrane protectants against ROS – have shown significant protection of spermatozoa from peroxidative damage and loss of motility. Higher concentrations have also shown improvements in sperm function [12]. Oral vitamin E supplementation has proven to be efficacious in a double blind, placebo controlled randomised trial [16]. Another anti-oxidant, ascorbic acid, has also been found to have a positive correlation with normal sperm morphology [17].

Lycopene is one of 650 different carotenoids naturally found in fruits and vegetables. It has been found to have the highest physical quenching rate constant with singlet oxygen and its plasma level is higher than beta carotene [18]. Klebanov et al compared the antioxidant properties of Lycopene in three different model oxidative systems and confirmed its role as an important anti radical antioxidant in the protection of lipid peroxidation [19]. Lycopene deficiency may also be associated with immunoinfertility. Palan et al have demonstrated a significantly lower level of Lycopene in the seminal plasma of immunoinfertile men as compared to fertile men and they postulate a role for dietary antioxidants in the management of infertility [20].

This study was conducted with the hypothesis that oral supplementation of antioxidants would improve the oxidative stress status in patients with idiopathic infertility. Since lycopene has been shown to be an important anti-oxidant, and in the absence of any existing clinical trials using oral lycopene therapy, we performed this study to test the above hypothesis. The results suggest a significant improvement in both the sperm concentration and motility – the easily evaluable laboratory parameters. Improvement in sperm count could be the result of reduction of oxidative stress within the testis since Lycopene is known to exist within the testis and it associated with oligospermia [12]. Even among oligospermic men, it is associated with poor sperm function as demonstrated by poor oocyte penetration [13]. Since this parameter is not usually evaluated in semen analysis, it could be one of the causes for infertility in such men – the oligospermia may otherwise not be consequential. This is particularly true in cases without severe oligospermia since oxidative stress may not be the causative factor in cases where the sperm density decreases to below five million per ml. Poor motility has been demonstrated in earlier literature [14] and may be related

to ROS induced damage to the flagellar membranes through lipid peroxidation.

Conclusions

Oxidative stress due to deficiency of antioxidants in the seminal plasma may be an important cause for idiopathic infertility. Oral supplementation with antioxidant therapy has shown improvement in semen parameters of such men. Lycopene is one of the most abundant carotenoids in nature and it also forms an important part of the human free radical scavenging system. This study demonstrates a possible role of oral Lycopene therapy in the improvement of semen parameters of these men. A randomised, controlled clinical trial is essential to establish the indications for Lycopene therapy in idiopathic male infertility.

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