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Metformin Effects on Abnormal Semen Parameters in Patients with Metabolic Syndrome

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ABSTRACT

Background: Some of studies showed that metformin have positive effects on semen quality and quantity and have revealed different findings about influence of the metabolic syndrome upon syndrome parameters and effect of metformin on sexual hormones. The aim of this study was determining effect of Metformin on Abnormal Semen Parameters in Patients Suffering from Metabolic Syndrome.

Material and Methods: In this clinical trial study 70 consisted of male patients suffering from infertility and metabolic syndrome were selected and treated by 500 mg daily metformin for six months. Lipid and hormone profiles and semen indexes were evaluated in the before and after intervention.

Results: The mean of sperms before treatment was 8.08 ± 2.97 million and was significantly increased to 11.15 ± 2.83 million after the treatment (p-value<0.0001). The mean of morphologically abnormal sperms before treatment was 88.92 ± 8.53 million and sperms were significantly reduced after the treatment to 85.6 ± 8.66 million, (p-value<0.0001). The mean of sperms with directly forward motions before treatment was 40.57 ± 14.08 million and was significantly increased to 51.62 ± 13.48 million after the treatment (p-value<0.0001).

Conclusion: According to the results of this study, treatment of patients with Abnormal Semen Parameters and Suffering from Metabolic Syndrome led to improvement of semen characteristics and it may be help to treatment of infertility in men.

Key words: Metformin, Semen quality, Metabolic syndrome

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INTRODUCTION

The metabolic syndrome is one of the big health problems in all countries especially Iran and has been increasingly widespread in recent decades and its subsequent effects have been magnified. The metabolic syndrome is defined as presence of three or more following components: abdominal obesity (broad waist), hyperglycemia, hypertriglycemia, low level of cholesterol High-density lipoprotein (HDL), and hypertension [1]. Regarding the age metabolic syndrome is differently widespread and increases by age. For example, this syndrome is observed in 15% and 25% of Italian men with the age of 18-20 years and 70 years old respectively [2]. In patients suffering from visceral obesity, total and free testosterone and sex hormone–binding globulin (SHBG) levels are reduced. Conversely, estradiol (E2) is increased [3]. Accordingly, spermatogenesis significantly changes i.e. the patients are afflicted with reduction of sperms, teratospermia, and asthenozoospermia [4]. Metformin is an edible medicine for reducing blood sugar, which is recently proved to reduce the metabolic syndrome prevalence in people suffering from obesity and allergy to insulin, and therefore increases total and free testosterone [5].

A large number of studies have investigated the impact of metformin on semen quality and quantity and have revealed different (and sometimes conflicting) findings about influence of the metabolic syndrome upon syndrome parameters and effect of metformin on sexual hormones [6-10]. As a result, this study attempts to examine influence of metformin upon sperm parameters.

METHODS AND MATERIALS

This clinical trial was conducted on 70 male patients suffering from infertility who referred to clinics of Shahid Beheshti hospital in Isfahan, Iran, between January and September, 2014. Patients with confirmed metabolic syndrome and diagnosis of semen disorders (concentration, morphology, and motion) were eligible if they did not have systematic diseases including kidney and liver failures, glandular disorders, and adrenal or testicular neoplasm. Also, patients were excluded if they have non-consumption or irregular consumption of metformin in the study period, or used another treatment method during the study period, and avoidance of referral

for determining sperm parameters. The study protocol was approved by the Institutional Review Board and Ethics Committee of Isfahan University of Medical Sciences and all patients signed an informed consent form prior to the study.

Metabolic syndrome was evaluated according to the Adult Treatment Panel III criteria [11] and metabolic syndrome confirmed if patients met at least three of the following criteria: (1) Waist circumference>102 cm, (2) HDL cholesterol levels<40 mg/dL or being actively treated for low HDL levels, (3) Serum triglycerides levels ≥150 mg/dL or being actively treated for elevated triglycerides, (4) Fasting glucose levels ≥100 mg/dL or being actively treated for hyperglycaemia and (5) Diagnosis of elevated blood pressure or being actively treated for hypertension.

Also, semen disorder was diagnosed if one or more standard semen parameters were below the cut-off levels accepted by WHO in 1999, as follows: sperm density less than 20*106 per mL, sperm motility less than 50%, and normal morphology less than 30% [12].

Eligible patients were treated by metformin (500 mg) for 6 months. Patients received daily dose of metformin during first week, twice a day for second week, and thrice a day in the next remaining weeks. Patients were visited monthly during study period. Collected data in this study included, patients' height, weight, waist at baseline and HDL cholesterol, triglyceride (TG), and fasting blood sugar (FBS), hormone profile (follicle-stimulating hormone (FSH), luteinizing hormone (LH), E2, SHBG and testosterone), and semen parameters (concentration, morphology, and motion) that were recorded at baseline and after treatment. Body mass index (BMI) was calculated by dividing of patients' weight (in kilograms) on their height (in meters squared). Before and at the end of treatment, blood and semen samples were obtained from all patients. Patients were asked to refer after 3 to 5 days of sexual abstinence, so, the semen samples obtained by masturbation and were analysed immediately after complete liquefaction. Using patients' blood samples in a local laboratory, lipid profile were assessed using the enzymatic colorimetric method; FBS determined by the glucose oxidase method and hormone profile were measure by radioimmunoassay in duplicate at two dilutions. According to World Health Organization guidelines [13], semen parameters including concentration, motility and morphology were evaluated by the same analyst.

The sample size was calculated using the comparison of means formula with two-sided log-rank test, α=0.05, and 80% power. The collected data were analysed using SPSS software for Windows, version 22. Descriptive data are reported as mean (standard deviation). Measured variables after treatments were compared with measuring data at baseline using paired sample t-test. Statistical significance was accepted at P-value<0.05.

RESULTS

Based on the above-mentioned parameters 70 patients were selected of which 17 ones were excluded from the study due to different causes (four patients for failing to take the medicine and feeling severe nausea, five patients for irregular consumption of the drug, and eight patients for refusing to continue the treatment and measuring sperm and parameters). The mean of age in studied patients was 34.4 with standard deviation of 5.6, the youngest patient had 27 years old and the elderly was 41 years old. Table 1 shows means and standard deviations of hormone, lipid, and anthropometric parameters before and after the treatment. Accordingly, BMI level and waist after intervention were significantly different from before intervention. Also, levels of E2 and HSBG were significantly reduced. The mean of serum LH and testosterone after treatment were significantly higher than before treatment. Serum FSH level did not show any significant difference during the study period. Moreover, analysis of lipid and sugar profiles did not show any significant different in HDL and triglyceride levels after treatment in compare to before treatment. A significant reduction of serum levels of fasting blood sugar and insulin is observed after treatment in compare to before treatment.

Table 1: Means and standard deviations of hormone, lipid, and anthropometric parameters before and after the treatment

Parameters		Before treatment	After treatment	p-value
Anthropometric indexes	Body mass index	30.82 ± 4.29	30.7 ± 4.23	0.889
	wrist	104.04 ± 9.79	101.79 ± 15.95	0.24
Hormones	LH	4.395 ± 1.78	6.474 ± 2.98	<0.0001
	FSH	7.464 ± 2.37	7.57 ± 2.43	0.65
	E2	37.02 ± 6.01	25.7 ± 5.11	<0.0001
	SHBG	27.38 ± 7.18	18.4 ± 5.28	<0.0001
	Testosterone	211.1 ± 71.34	297.38 ± 78.79	<0.0001
Lipid profile and FBS	HDL	42.94 ± 8.32	44.74 ± 15.92	0.36
	TG	192.14 ± 87.42	201.91 ± 14.7	0.27
	FBS	92.09 ± 14.7	80.17 ± 9.81	<0.0001

	Insulin	16.77 ± 4.65	14.02 ± 3.33	<0.0001
Data are mean ± SD				
p-values calculated using Paired sample t-test				

Table 2 shows the comparison of means of sperm parameters before and after the treatment. Before treatment the means of sperms was 8.08 ± 2.97 which significantly increased to 11.15 ± 2.83 million after treatment (p-value <0.0001). Morphologically abnormal sperms were 88.92 ± 8.53 before treatment and decreased to 85.6 ± 8.66 after treatment, this difference between patients was statistically significant (p-value<0.0001). Means of sperms with directly forward motions after treatment were significantly higher than before treatment (40.57 versus 51.62 respectively, p-value<0.0001).

Table 2: Means of sperm parameters before and after the treatment

Parameters	Before treatment	After treatment	p-value
Sperm count (per million)	8.08 ± 2.97	11.15 ± 2.83	<0.0001
Percent of abnormal morphology	88.92 ± 8.53	85.6 ± 8.66	<0.0001
Percent of normal motility	40.57 ± 14.08	51.62 ± 13.48	<0.0001
Data are mean (SD)			
p-values calculated using Paired sample t-test			

DISCUSSION

This study attempted to examine effect of metformin on abnormal semen parameters in patients suffering from the metabolic syndrome. Our findings show an improvement in numbers, morphologies, and motions of sperms after a 6-month metformin treatment. Additionally, metformin improves factors of metabolic syndrome including BMI, blood sugar, and insulin, as well as hormone profile.

Studies have concentrated on effects of metformin upon semen quality and quantity. Kort et al. showed that BMI greater than 25 kg/m^2 reduce sperms with healthy chromatin and normal motion [6]. MacDonald et al. did not find any significant correlation between BMI and sperm concentration and number [7]. Meeker et al. showed that FSH and LH levels are negatively interrelated with sperm concentration, motion, and morphology [8]. Mah et al. revealed a significant reduction of testosterone level of plasma due to obesity, metabolic syndrome, and diabetes mellitus [9]. Makhsida et al. did not find any significant relationship between hypogonadism and metabolic syndrome [10]. Morgante et al. pointed out that metformin improves semen parameters in patients suffering from oligo-terato asthenozoospermia [14]. In similar to other studies, our results show the positive effects of metformin on abnormal semen parameters in patients suffering the metabolic syndrome. Although, some differences between our finding and some other studies can be explained by the different methods of the studies.

In the other hand some previous studies assessed the effect of metformin on human spermatozoa *in vitro* or animal spermatozoa. Calle et al. showed that *in vitro*, metformin had an adverse effect on spermatozoa and the percentages of motile, progressive and rapid spermatozoa and sperm velocities reduced after the use of metformin [15]. Bertoldo et al. reported that metformin did not affect sperm quality at low concentrations but the quality of frozen semen in cryopreserving mouse spermatozoa is improved in the presence of metformin [16]. Ghasemnejad-Berenji et al. in an animal model study showed that sperm count and motility was improved after administration of metformin [17]. Also, Hurtado de Llera et al. concluded that the use of metformin inhibits boar sperm motility in fresh and refrigerated condition [18]. We find that in patients with metabolic syndrome, metformin cause to improve abnormal semen parameters. As mentioned above, these studies show conflict with findings in the effects of metformin on human or animal spermatozoa, so more studies are need to be done to more clarify metformin effects on human spermatozoa.

It is shown that the minimum effective dose for metformin is 500 mg/day with an optimum dose of 2000 mg/day [19]. Administration of metformin in this study is started with 500 mg/day to reduce side effects that may occur during the first few weeks of treatment. So, the dose increased to 1500 mg/day during 6 months of treatment to obtain optimum effect. This regimen caused to improve number, morphology, and motion of sperms after treatment period among our studied patients. This effect may be because of the role of metformin in improves peripheral insulin sensitivity, increased serum androgen levels, and reduction in sex-hormone-binding globulin levels, whereas, it is concluded that, in obese males, high insulin levels or insulin resistance may play an important role in infertility [20,21]. However, further studies with control group must be done to assess other regimens of metformin on infertile men.

In conclusion, however, in our study patients were assessed in one group as before and after intervention

but our results reveal that the use of metformin in patients with abnormal semen parameters who were suffering from metabolic syndrome led to improvement of semen characteristics that may be helpful for treatment of infertility in men.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests.

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