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Effects of Metformin on Hormonal Profile and Seminal Fluid Analysis in Obese Infertile Male

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Abstract

Background Overweight and obese men have an up to 50% higher rate of sub-fertility when compared with normal weight men. Possible management options include weight reduction by dieting or surgery and medical treatment to correct specific endocrine abnormalities, but as yet none has been proven to be effective.

Objective To verify the impact of decreasing body mass index by giving metformin on hormonal profile and seminal fluid analysis in obese infertile male.

Methods Eighteen obese patients whose body mass index was 30-40 kg/m2 and with mean age of 29 years (range: 22-42 years) with idiopathic asthenozoospermia were enrolled in the study. Standard semen analysis according to WHO and hormones assay which include: follicular stimulating hormone, luteinizing hormone, prolactin, testosterone, and estradiole were performed at baseline and after 12 weeks of therapy. The enrolled patients were asked to take metformin 850 mg twice daily orally for 12 weeks.

Results A significant decrease ($p<0.001$) in sperm count and sperm activity after 12 weeks of treatment with metformin. While there is no significant differences with respect to other spermiological parameters. A statistically significant decrease in the level of serum prolactin after 12 weeks of treatment with metformin whereas no significant differences with respect to the level of other hormones.

Conclusions Although metformin has the capacity to decrease the level of prolactin, it decreases the number and activity of sperms. Further studies are recommended to investigate whether there is any association between infertility in human males and chronic metformin use

Keywords Metformin, infertility, male, prolactin, overweight, obese.

List of abbreviation: AMK = activated protein kinase, BMI = body mass index, FSH = follicular stimulating hormone, LH = luteinizing hormone, E_2 = estradiole.

Introduction

Metformin is one of antidiabetic drugs which belong to the biguanide class of oral antihyperglycemic agents. It was first synthesized in 1929 and was shown to be a potent hypoglycemic agent [(1)].

Metformin acts in the presence of insulin to increase glucose utilization and reduce glucose production, thereby countering insulin resistance. The effects of metformin include increased glucose uptake, oxidation and muscle glycogenesis, increased glucose metabolism to lactate by the intestine, reduced hepatic gluconeogenesis and possibly a reduced rate of intestinal glucose absorption [(2)].

The molecular mechanisms of metformin action are not fully known. Activation of the enzyme AMP-activated protein kinase (AMK) appears to be the mechanism by which metformin lowers serum lipid and blood glucose concentrations [(3)]. Metformin works through the Peutz-Jeghers protein, LKB1, to

regulate AMPK. LKB1 is a tumor suppressor and activation of AMPK through LKB1 may play a role in inhibiting cell growth [4].

The incidence of obesity is rapidly rising in almost every region of the world. Although obesity affects women more than men, male obesity is an issue of serious concern. In Europe, the International Obesity Task Force (2005) has indicated that obesity rates in adult men range from 10 to 27%, with this prevalence rising significantly in the last 10 years [5].

The adverse influence of obesity on various aspects of female reproduction and fertility has been realized for sometime [6] and management guidelines are now available [7]. More recently, data regarding male obesity and infertility have been accumulating [8,9]. There are now several population-based studies showing that overweight and obese men have an up to 50% higher rate of sub-fertility when compared with normal weight men [10,11]. One could argue that this could be related to confounding factors such as male age, smoking and alcohol use, and female partner obesity. However, once these factors have been excluded it was shown that for every three-point increase in a man's BMI, couples were 10% more likely to be infertile [12].

Kort *et al*. (2007) showed significant negative relationship between high body mass index (BMI) and sperm motility in 528 Danish men. In addition, men with BMI > 25 had fewer chromatin-intact normal-motile sperm cells per ejaculate [13]. Jensen *et al*. (2004) in accordance with other studies showed that overweight and obese men (BMI >25 kg/m2) had significantly lower sperm concentrations than those of normal-weight men (BMI 20–25 kg/m2) [14]. The prevalence of oligozoospermia was higher in overweight and obese men compared with normal-weight men. A substantial decrease in serum testosterone, sex hormone binding globulin and Inhibin B were also found with increasing BMI [14]. There are several etiological theories including endocrine abnormalities, genetic, sexual dysfunction and testicular hyperthermia. Of these, endocrine abnormalities are likely to be the most important, involving increased estrogen and increased insulin resistance, reduced androgens and reduced inhibin B levels. Possible management options include weight reduction by dieting or surgery and medical treatment to correct specific endocrine abnormalities, but as yet none has been proven to be effective [15]. The aim of current study was to assess the impact of decreasing BMI by giving metformin on hormonal profile and seminal fluid analysis in obese infertile male.

Methods

Patient Selection

Eighteen obese patients (BMI = 30-40 kg/m2) (mean age, 29 years; range, 22–42 years) with idiopathic asthenozoospermia were enrolled in the study. The patients were selected at the Department of Pharmacology, Faculty of Medicine, Al-Nahrain University and Urology Clinic of Al-Imamain Al-Kadhimiyian Medical City, Baghdad, Iraq, at period extended from Apr. 2012 to Sep. 2012. All subjects underwent medical screening, including history and clinical examination, and presented with a clinical history of primary infertility of at least 3 years.

Eligibility Criteria

The exclusion criteria were: [1] Infertile men with azoospermia [2] diabetes mellitus. [3] infectious genital diseases, anatomical abnormalities of the genital tract including varicocele, and anti-spermatozoa antibodies [4] systemic diseases or treatment with other drugs in the 3 months before enrollment in the present study [5] smoking, alcohol, drug addiction, or occupational chemical exposure.

Safety Assessment

Safety assessment included medical history, physical examination, hematological screening, and serum chemistry at all visits and the monitoring of drug-related adverse events by recordation in patient diaries

Laboratory investigations

Hormones assay include: follicular stimulating hormone (FSH), luteinizing hormone (LH),

prolactin, testosterone, and estradiole (E_2) (by miniVIDAS 12 model)

Standard semen analysis**:** Freshly ejaculated semen samples were obtained by masturbation into sterile petri-dish containers under clean condition after (3-5) days of sexual abstinence. The specimens were placed in an incubator at 37^{o}C for (30) minutes to allow liquefaction, after liquefaction, semen samples were evaluated for semen volume, appearance, pH and viscosity, then specimens were analyzed for sperm concentration, progressive motility and normal morphology according to WHO criteria [16].

Study Design and Treatments

The enrolled patients were asked to take metformin (Merck, France), 850 mg twice daily orally for 12 weeks. Clinical examination, semen analysis, and hormonal assay were performed at baseline and after 12 weeks of therapy. All patients provided their written informed consent and completed the entire trial.

Statistical analysis

The data were analyzed using SPSS program. Results were reported as mean ± S.D. The total variations were analyzed by performing the statistical design T-test. Probability levels of less than 0.05 were considered significant [17].

Results

Metformin treatment was well-tolerated by all subjects. None of the subjects suspended the therapy due to side effects, although some experienced transient diarrhea and flatulence during the first month of treatment.

Effect on BMI

For the mean duration of the study (12 weeks), Metformin was given to 18 patients. The mean BMI decreased significantly during the treatment time, from 35.93 ± 5.7 to 34.85 ± 5.2 ($p < 0.001$).

Effect on seminal fluid analysis

The results of current study shows no significant differences with respect to semen volume, liquefaction time, pH, and normal morphology at baseline and after 3 months of treatment with metformin 850 mg two times / day. The (mean±SD) was (3.04 ± 1.12 vs. 3.08 ± 0.93) (39.17 ± 23.82 vs. 28.75 ± 2.26) (8.21 ± 0.50 vs. 8.21 ± 0.33) (62.08 ± 10.97 vs. 64.58 ± 4.98) before and after 3 months of treatment with metformin for semen volume, liquefaction time, pH, and normal morphology respectively.

In this study, the (mean±SD) before versus after 3 months of treatment with metformin 850 mg two times / day for sperm count and sperm activity was (19.00 ± 14.53 vs. 16.13 ± 13.76) (8.33 ± 5.77 vs. 3.83 ± 1.95) respectively. The results shows significant difference ($p < 0.05$) with respect to sperm count and sperm activity at the base line (before treatment) and after 3 months of treatment with metformin (Table 1 and Fig. 1).

Effect on hormonal analysis

The (mean±SD) before versus after 3 months of treatment with metformin of serum LH, FSH, E2, and testosterone was as follows respectively: (4.04 ± 4.21 vs. 3.63 ± 2.76) (7.19 ± 8.84 vs. 6.55 ± 7.77) (5.30 ± 5.54 vs. 4.21 ± 2.69) (4.33 ± 1.51 vs. 3.94 ± 1.18) and it shows no statistically significant differences between baseline and after 3 months of treatment with metformin.

The results of current study reveal statistically significant decrease in the level of serum prolactin before and after 3 months of treatment with metformin with mean±SD of 8.01 ± 5.73 vs. 6.93 ± 5.09.

Discussion:

Obesity has been shown to adversely affect male fertility, by reducing spermatogenesis. There are several etiological theories including endocrine abnormalities, genetic, sexual dysfunction and testicular hyperthermia. Of these, endocrine abnormalities are likely to be the most important, involving increased estrogen and increased insulin resistance, reduced androgens and reduced inhibin B levels [15].

Table 1. Semen analysis parameters before and after 3 months of metformin treatment

Semen parameters	Metformin Treatment		p value
	Before (mean± SD)	After (mean± SD)	
Semen volume (ml)	3.04 ± 1.12	3.08 ± 0.93	0.754
liquefaction time (min)	39.17 ± 23.82	28.75 ± 2.26	0.148
pH	8.21 ± 0.50	8.21 ± 0.33	1.000
Sperm count (10^6/ml)	19.00 ± 14.53	16.13 ± 13.76	0.018
Sperm activity %	8.33 ± 5.77	3.83 ± 1.95	0.009
Normal morphology (%)	62.08 ± 10.97	64.58 ± 4.98	0.352

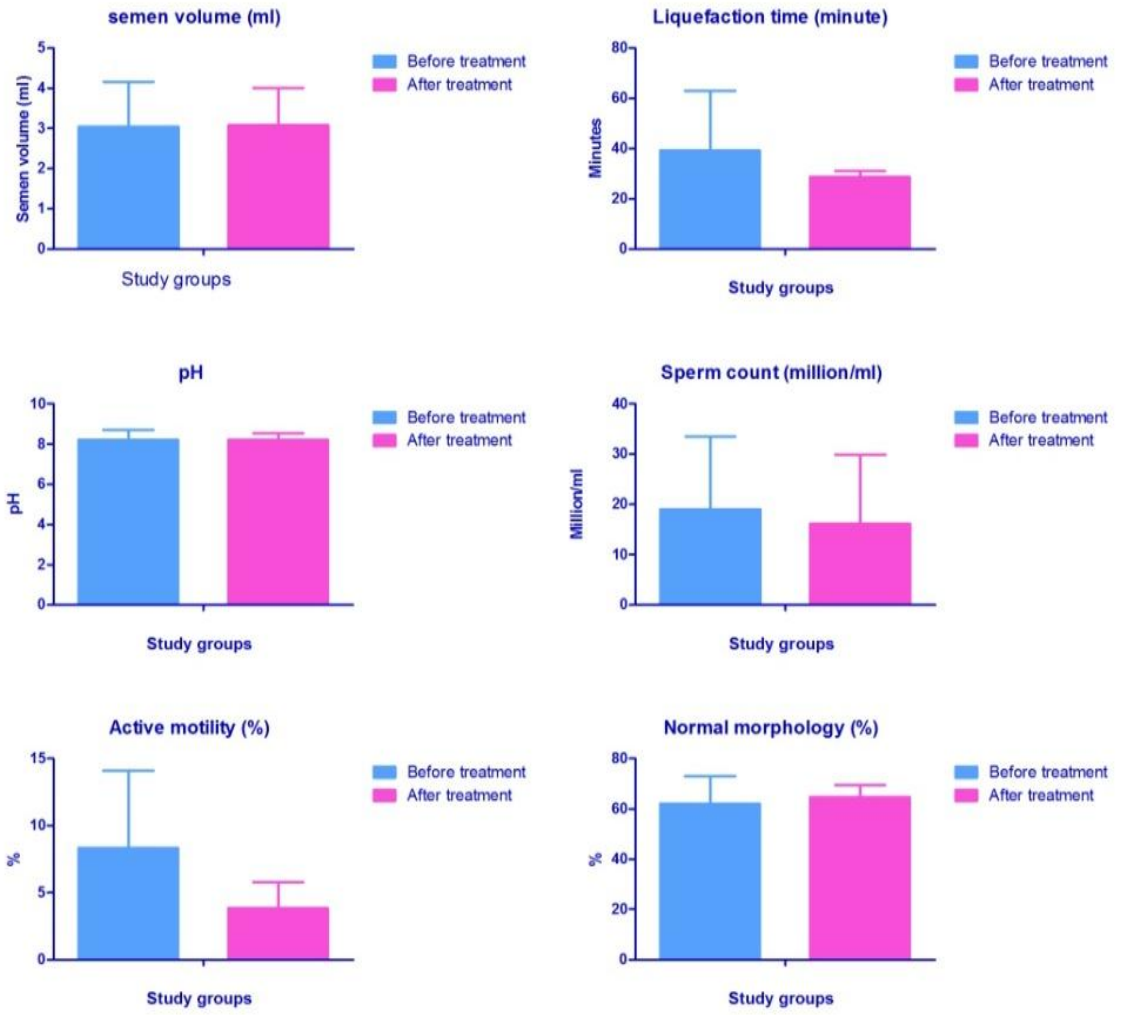

Fig. 1. Semen analysis parameters before and after 3 months of treatment with metformin

Insulin resistance could be the underlying pathogenesis of chronic hypospermatogenesis leading to oligospermia and azoospermia associated with other metabolic abnormalities in men. Metformin has proven as an effective medication for not only IR but several other aspects of the polycystic ovarian disease including reproductive abnormalities [15]. Therefore, insulin sensitizers, particularly metformin could probably have beneficial effects on overweight and obese patients with asthenozoospermia.

In our study, metformin was effective in reducing BMI significantly. These results are in accordance with recent observations made by several authors, such as Hosokawa *et al* [18] Garber *et al* [19] and De Fronzo *et al* [20] among others. The MOCA trial is the largest double-blind, randomized, placebo-controlled trial of metformin in obese non diabetic children and young people. The MOCA trial provides evidence that a short treatment course of metformin is clinically useful, safe, and well tolerated to halt further gain in adiposity and improve fasting glucose [21].

Table 2. Hormonal analysis before and after 3 months of metformin treatment

Hormones	Metformin treatment		P value
	Before (mean± SD)	After(mean± SD)	
Luteinizing hormone	4.04 ± 4.21	3.63 ± 2.76	0.403
Follicular stimulating hormone	7.19 ± 8.84	6.55 ± 7.77	0.074
Prolactin	8.01 ± 5.73	6.93 ± 5.09	0.019
Estradiole	5.30 ± 5.54	4.21 ± 2.69	0.235
Testosterone	4.33 ± 1.51	3.94 ± 1.18	0.196

In the current study metformin was given to 18 overweight and obese patients with asthenozoospermia in a dose of 850 mg twice a day for 12 weeks The results of present study demonstrate that administration of metformin decreases significantly sperm count and sperm activity while there is no statistically significant changes regarding semen volume, liquefaction time, pH, and normal morphology respectively.

A study by Naglaa *et al* showed that oral administration of metformin to both diabetic and non-diabetic rabbits resulted in a significant decrease in testicular weight, sperm count, sperm motility and serum testosterone with a significant increase in sperm anomalies and dead sperm percentage [22]. Naglaa *et al* has suggested that vitamin B_{12} deficiency may cause decreased sperm count and motility as it is well established that chronic use of metformin is associated with 20-30 % lower blood levels of vitamin B_{12}. This hypothesis is further strengthened by the finding that vitamin B12 supplements improve fertility in animals with abnormal sperm production. In this way, Naglaa *et al* have questioned the justification for the use of metformin in a frame of a therapeutic strategy for diabetes due to its resulting impact on male fertility and also put forward probable reasons behind this [22]. Moreover, vitamin B_{12} deficiency during pregnancy may induce irreversible damage in the germ cells of embryos and affect the maturation of spermatozoa. Chronic exposure of metformin induces DNA damage in mammalian cells [23] and also impairs the mitochondrial complex-1 activity which plays the vital role to maintain the normalcy of sperm motility [24].

However, another study by Morgante *et al* has shown that the use of metformin is associated with a statistically significant reduction in insulin resistance and sex hormone-binding globulin levels, a statistically significant increase in serum androgen levels, and a consequent improvement in semen characteristics [25].

The results of present study demonstrate that the (mean±SE) before versus after 3 months of treatment with metformin of serum LH, FSH, E_2, and testosterone shows no statistically significant differences while the level of serum prolactin reveal statistically significant decrease.

Metformin may change the affinity and/or the number of dopamine receptors or of receptors for other compounds regulating production, secretion and metabolism of prolactin, may enhance gastrointestinal absorption and/or

metabolism of bromocriptine, as well as may directly affect prolactin pharmacokinetics. Interestingly, animal studies carried out evidenced that metformin penetrates the blood–brain barrier, and its content in the pituitary is higher than in any other brain structure [(26)]. In the light of these results, it seems that the pituitary is an important target for metformin action and that the prolactin-lowering effect of this agent results, at least in part, from its action at the level of pituitary lactotropes. Taking into account that this drug was found to reduce plasma levels of other pituitary hormones [(27-28)].

In conclusion, results of the current study demonstrate that although metformin has the capacity to decrease the BMI as well as level of prolactin, it decreases the number and activity of sperms. Further studies are recommended to investigate whether there is any association between infertility in human males and chronic metformin use and *in vitro* effects of metformin on human spermatozoa to observe cytomorphometrical changes, biochemical alterations

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Conflict of interest

The author declares no conflict of interest**.**

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