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Increased insulin resistance in men with unexplained infertility

Ragaa Mansour [a,*], Yahia El-Faissal [a,b], Ahmed Kamel [a,b], Omnia Kamal [a], Gamal Aboulserour [a], Mohamed Aboulghar [a,b], Ibrahim Fahmy [a,c]

[a] The Egyptian IVF-ET Centre, 11431 Cairo, Egypt
[b] Faculty of Medicine, Obstetrics and Gynecology Department, Cairo University, 11559 Cairo, Egypt
[c] Faculty of Medicine, Andrology Department, Cairo University, 11559 Cairo, Egypt

Ragaa Mansour graduated from medical college with honours in 1973, obtaining her MSc in Obstetrics and Gynaecology from Cairo University in 1978. She is the founder and director of the Egyptian IVF Center.

KEY MESSAGE
Insulin resistance in men with unexplained infertility may be a cause of reproductive and metabolic abnormalities. The benefit of insulin-sensitizing agents for these patients should be tested.

A B S T R A C T

This prospective case–control study aimed to test the presence of insulin resistance (IR) in men with unexplained infertility. We included two groups: the study group including 160 infertile men with unexplained oligozoospermia (sperm count $<10 \times 10^6$/ml) and normal hormonal profile, and the control group of 79 men with proven fertility within the preceding year. A fasting blood test measured IR, FSH, LH, total cholesterol, low-density lipoprotein, high-density lipoprotein and triglycerides. Insulin level was significantly higher in the study group (13.67 ± 10.44) compared with the control group (5.46 ± 3.15), $P < 0.0001$, and IR was significantly higher in the study group, $P < 0.0001$. FSH was significantly ($P < 0.0001$) higher in the study group (4.71 ± 2.57) than the control group (3.15 ± 1.92). LH was significantly higher in the study group (4.98 ± 2.41) compared with the control group (3.15 ± 1.12), $P < 0.0001$. Total cholesterol was significantly higher in the study group (198.29 ± 37.52) than the control group (182.45 ± 35.92), $P < 0.05$. In conclusion, IR in men with unexplained infertility may be a cause of reproductive and metabolic abnormalities. The benefit of insulin-sensitizing agents for these patients should be tested.

* Corresponding author.
E-mail address: ragaa.mansour@gmail.com (R Mansour).

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Introduction

Insulin resistance (IR) has been considered a major contributor to the pathogenesis of chronic oligoovulation or anovulation as well as other metabolic abnormalities in women with polycystic ovary syndrome (PCOS) (Diamanti-Kandarakis and Dunaif, 2012; Rosenfield, 1997). The genetic contribution of PCOS has been mapped reproducibly by several investigators (Day et al., 2015; Goodarzi et al., 2012; Hayes et al., 2015; Legro et al., 1998; Shi et al., 2012). Interestingly, similar reproductive and metabolic phenotype characteristics were found in first-degree male relatives to PCOS females (Legro et al., 2002; Liu et al., 2014; Recabarren et al., 2008a, 2008b). It seems that PCOS is a complex trait because of the interaction of genetic and environmental factors (Rosenfield and Ehrmann, 2016).

Unexplained or idiopathic male factor infertility means no aetiological factor could be found using the common clinical, instrumental or laboratory methods (Cavallini, 2006). It was considered that about 60–75% of male infertility cases are idiopathic, because the molecular mechanisms underlying the defects remain unknown (Filliponi and Feil, 2009). Testicular histopathology of those patients shows various degrees of spermatogenic impairment but fail to identify specific pathogenesis (Nieschlag and Kamischke, 2010).

Our hypothesis is that some cases of unexplained male infertility could be due to IR, leading to hypogonadism and other metabolic features (Mansour et al., 2013). The aim of this work was to test the presence of IR in men with unexplained infertility.

Materials and methods

Study population

One hundred and sixty men with idiopathic oligozoospermia participated in this study. The diagnosis of unexplained infertility was established after complete clinical and laboratory examination of the patients by our andrologists. At least two semen analyses 1–4 weeks apart were evaluated (WHO, 2010). The inclusion criteria were infertile men with sperm count less than 10×10^6/ml; men with normal hormonal profile (FSH = 1–10 mIU/ml and LH = 1.8–12 mIU/ml), normal secondary sexual characters, and normal sexual function were included. Cases with chronic debilitating illness (e.g. cardiac diseases, epilepsy, renal disorders), diabetes mellitus, clinically evident varicocele, persistent pyospermia, abnormal karyotype, and azoospermia factor microdeletion were excluded. The control group included 79 men with proven fertility within the preceding year.

Methods

Fasting blood samples from the study and control groups were taken to measure the following: serum insulin, glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), testosterone, FSH, LH and prolactin.

IR was calculated by inverting the value of insulin sensitivity. Insulin sensitivity was calculated using the quantitative insulin sensitivity check index (QUICKI). It was derived using the inverse of the sum of the logarithms of the fasting insulin and fasting glucose: 1/(log (fasting insulin mIU/l) + log (fasting glucose mg/dl)). This index correlates well with glucose clamp studies ($r = 0.78$), and is useful for measuring insulin sensitivity. It is the preferred method for certain types of clinical research (Katz et al., 2000).

Another method to calculate IR is the homeostatic model assessment (HOMA) test (Matthews et al., 1985). This is calculated by dividing by 405 the result of multiplying fasting serum insulin by fasting blood glucose, i.e. [fasting glucose (mg/dl) × fasting insulin (mIU/l)]/405.

Body weight, height and body mass index (BMI) were measured and calculated.

Clinical trial registration number: NCT 01509482 at clinical trials.gov.

Ethical approval

The Internal Review Board and Ethical Committee of The Egyptian IVF-ET Centre approved the study on 1 January 2012 (reference number 2012–1).

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 15 (SPSS Inc., USA) was used. The Mann–Whitney test was used to compare quantitative variables that were not normally distributed. Student's t-test was used to compare quantitative variables that were normally distributed. $P < 0.05$ was considered statistically significant. The sample sizes were calculated using the OpenEpi sample size calculator for unmatched case control studies. We assumed a confidence level of 95%, an 80% power, a 5% hypothetical proportion of controls with exposure and a 95% hypothetical proportion of cases with exposure (http://www.openepi.com/SampleSize/SSCC.htm).

Results

Fasting insulin level was significantly higher in the study group (13.67 ± 10.44 mIU/l) compared with the control group (5.46 ± 3.15 mIU/l), $P < 0.0001$. Fasting glucose was 95.86 ± 25.22 mg/dl in the study group, compared with 94.41 ± 30.40 mg/dl in the control group, with no significant difference. Using QUICKI, IR was higher in the study group (2.99 ± 0.33) compared with the comparator group (2.61 ± 0.33), $P < 0.0001$. Using HOMA, IR was higher in the study group (3.07 ± 2.81) compared with the control group (1.25 ± 0.75), $P < 0.0001$ (**Table 1**). Triglycerides were higher in the study group (142.82 ± 105.31 mg/dl) as compared with the comparator group (114.59 ± 61.42 mg/dl), but not significantly different. Total cholesterol was higher in the study group (198.29 ± 37.52 mg/dl) than in the control group (182.45 ± 35.92 mg/dl), $P < 0.05$. HDL and LDL levels were comparable in both groups with no statistical significance (**Table 1**). FSH levels were higher in the study group (4.71 ± 2.57 mIU/ml) as compared with the control group (3.15 ± 1.92 mIU/ml), $P < 0.0001$. LH values were higher in the study group (4.98 ± 2.41 mIU/ml) as compared with the controls (3.15 ± 1.12 mIU/ml), $P < 0.0001$. Testosterone levels were found to be lower in the study group (5.35 ± 3.02 ng/ml) as compared with the control group (6.62 ± 3.51 mIU/ml), with $P < 0.001$ (**Table 1**). The BMI was 29.79 ± 3.21 in the study group and 29.12 ± 3.75 in the control group. The mean age was not significantly different between the two groups (**Table 1**).

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