Received: 16 June 2020 | Revised: 30 June 2020 | Accepted: 4 July 2020

DOI: 10.1111/and.13773

ORIGINAL ARTICLE

ANDROLOGIA WILEY

Insulin resistance and idiopathic infertility: A potential possible link

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Abstract

Among various health issues, infertility has been always considered as one of the major health problems. Idiopathic infertility is still a matter of debate since the underlying mechanisms stay obscure. Idiopathic infertility is related to expanded chance of metabolic syndrome components, obesity and increased risk of cardiovascular diseases. This study aimed to assess insulin resistance and serum levels of irisin as one of the adipokines in patients with idiopathic infertility. This study included 50 male patients aged 25–50 years old suffering from idiopathic infertility, together with 50 healthy individuals of matched age as controls. Patients showed significantly increased homeostasis model assessment for insulin resistance values than controls. For irisin results, idiopathic infertility patients had significantly decreased values than controls indicating the potential effect of irisin in development of insulin resistance in idiopathic infertility patients.

KEYWORDS

HOMA-IR, idiopathic infertility, Insulin resistance, irisin

1 | INTRODUCTION

Idiopathic male factor infertility implies that there is no cause could be discovered utilising the regular clinical, or research facility strategies (Cavallini, 2006). Approximately 60%–75% of male cases of in-fertility were classified to be idiopathic, since the mechanisms that underlie the defects are unclear (Filipponi & Feil, 2009). Biopsies from testicular tissue from those patients revealed variable results of spermatogenic impairment but do not establish particular pathogenesis (Nieschlag, Behre, & Nieschlag, 2010).

Idiopathic infertility is diagnosed in men when there is unjusti-fied decrease in the quality of semen presented by oligozoospermia, asthenozoospermia or teratozoospermia (Dohle et al., 2012).

Researchers are actively studying the possible relationship linking metabolic syndrome to male infertility for the purpose of giv-ing more therapeutic chances for affected males (Kasturi, Tannir, & Brannigan, 2008). Each part of the metabolic syndrome may participate in male infertility pathogenesis. Obesity and diabetes are recognised as detrimental factors in human fertility. Dyslipidaemia and its related high free fatty acids may be a leading cause to endothelial dysfunction through the higher production of free radicals and also through the inhibition of nitric oxide (NO) synthesis (Kumar, Agrawal, Sharma, & Swain, 2015). One of the key players of metabolic syndrome pathogenesis is insulin resistance (Eckel, Alberti, Grundy, & Zimmet, 2010).

After its discovery in 2012, the serum marker irisin which showed ability to decrease body weight and to improve insulin resistance has developed interest as a therapeutic target in metabolic disorders like obesity and diabetes (Boström et al., 2012). Besides its therapeutic values, there is a growing evidence that irisin may have a great role in controlling glucose homeostasis (Lee et al., 2015).

This study aimed to evaluate insulin resistance in patients with idiopathic infertility aiming to reveal the potential relation between the two conditions and also to measure serum levels of irisin as one of the adipokines to determine its role if present in those patients.

2 | PATIENTS AND METHODS

After granting local ethics committee of human research of Benha faculty of medicine approval, informed consent was obtained from each individual. This study was done in the period from March 2019 to October 2019. Our study included two groups; group A (Patients group) which included 50 idiopathic infertility patients (25–50 years old) who were unable to initiate pregnancy within 1 year of regular unprotected sexual intercourse with a healthy wife and the diagnosis was confirmed according to the WHO Laboratory Manual on Human Semen Examination (WHO, 2010) either having decreased sperm count (<15 × 10^6 per ml), reduced motility of spermatozoa (<40%) or abnormal morphology (<4% normal forms) with no apparent causes of infertility of their wives evaluated by experienced gynaecologists. Any patient with known cause of infertility (varicocele, hormonal causes, obstruction or genetic) was excluded from the study. The second group; group B (control group) included 50 participants of matched age and body mass index who had at least one offspring in the previous year with normal semen analysis.

Patients underwent history taking, general and local examination aiming to reveal any possible causes of infertility. Body mass index (BMI) was measured for all participants by dividing body weight by the square of the height (kg/m^2).

We collected 10 ml of venous blood samples at morning from fasting participants, and then the collected blood was left to coagulate at room temperature for 30 min and then were centrifugated for 20 min at 1,000 *g*. Then, supernatant was collected, if there was still precipitation, centrifugation was repeated, and finally serum was separated, aliquoted and stored at −20C.

FSH, LH and serum testosterone was measured using Tosoh hor-monal assay (immunochemiluminescence). Commercial Human Irisin ELISA (enzyme-linked immune sorbent assay) Kit for research use only (Cat #: 201-12-5328, SunRedBio, China) was used for measuring irisin serum level. The analytical sensitivity, assay range, and intra-assay and inter-assay variation rates were 0.157 ng/mL, 0.2-60 ng/mL, <10%, and <12%, respectively. A double-antibody sandwich ELISA was used to measure serum insulin by a commercial Human Insulin Quantitative ELISA Kit (Cat #: E29-072, IMMUNOSPEC, USA). The serum blood glucose level was estimated using glucose oxidase method by Biosystem A15 chemical autoanalyzer. .Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) formula was used for the estimation of insulin resistance through the equation:[Fasting glucose (mmol/L) × Fasting serum insulin (MicroU/L)]/22.5. Semen analysis was done of all patients under the guidance of WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn.) which was used for standardisation of semen analysis (WHO, 2010).

2.1 | Statistical analysis

Tabulating and analysing the collected data were done using the SPSS version 16 software (Spss Inc, Chicago, ILL Company). Categorical data were shown as number and percentages meanwhile quantitative data were presented as mean ± standard deviation, and range. Continuous data were examined using Student's *t* test Spearman's correlation coefficient (rho) were used for nonparametric variables. Cut-off values of irisin with optimum sensitivity and specificity were evaluated by Receiver operator characteristic curve (ROC) curve. *p*-values ≤ .05 were considered to be significant.

3 | RESULTS

Patients mean age in this study was 33.14 ± 5.01 years, while in controls was 33.70 ± 5.41 years, the mean BMI of patients was 30.01 ± 3.43 kg/m^2, while in controls was 28.59 ± 3.18 kg/m^2. Fourteen patients were smokers versus eight in control group. Nine patients were diabetics while only six controls were diabetics, eight patients in infertility group reported to have hypertension versus five in the control group. There were insignificant variations be-tween both groups in age, BMI, smoking, diabetes and hypertension (*p*-Value = .640, .070, .897, .195, and 1.000 respectively).

Nonsignificant difference was found between group A and B in testosterone, FSH, and LH serum values. While serum values of irisin were significantly lower in patients with idiopathic infertility than controls, both serum insulin and HOMA-IR values were significantly elevated in patients than controls (Table 1).

There were no statistically significant correlations between serum irisin levels and HOMA-IR with age, semen analysis values, FSH and LH level among studied patients. BMI values were posi-tively correlated with HOMA-IR values and negatively correlated with serum irisin levels. Statistically significant negative correlations were found between serum levels of irisin and both insulin levels and HOMA-IR values (Table 2).

Sensitivity and specificity of irisin values in diagnosing insulin resistance in idiopathic infertility patients were 100% and 96.67% with accuracy 98.75% when the cut-off point was ≤ 3.96 (Table 3; Figure 1).

4 | DISCUSSION

The present study results showed statistically higher values of HOMA-IR and insulin levels among idiopathic infertility patients than controls confirming the potential link between insulin resist-ance and idiopathic infertility. This was in line with Cazzaniga et al. (2017) who reported that insulin resistance is with increased susceptibility to nonobstructive azoospermia. Our findings agreed also with Mansour et al. (2017); who stated that insulin resistance was found to be higher in patients with unexplained infertility in comparison with controls.

The relation between insulin resistance and idiopathic infer-tility in this study could be explained as the increased level of in-sulin in blood may impair the process of spermatogenesis causing reduced male fertility (Bener, Al-Ansari, Zirie, & Al-Hamaq, 2009). Hyperinsulinemic and diabetes type 2 patients showed also more

TABLE 1 Laboratory results in patients and controls

		Range	Mean ± *SD*	*t* test	*p* value
FSH (mIU/mL)	Patients	2.09–15.50	7.90± 2.87	2.23	.09
	Controls	2.34–14.62	6.88± 2.55		
LH (mIU/mL)	Patients	2.50–9.20	4.80± 1.79	2.17	1.02
	Controls	1.1–8.5	4.55± 1.22		
Testosterone (ng/dL)	Patients	348–840	486.2± 120.44	1.89	.42
	Controls	420–811	522± 135.21		
Irisin levels (ng/ml)	Patients	1.88–4.22	3.02± 0.077	15.02	<.001*
	Controls	3.98–8.08	6.76± 2.26		
FBS (mmol/L)	Patients	3.88–8.67	5.32± 1.71	1.232	.222
	Controls	4.02–7.50	5.82± 0.34		
Insulin (MicroU/L)	Patients	14.10–40.90	34.56± 4.44	10.75	<.001*
	Controls	3.02–30.76	20.25± 4.92		
HOMA-IR	Patients	2.43–15.7	9.31± 2.90	10.22	<.001*
	Controls	0.53–10.25	4.88± 1.43		

Abbreviations: FBS, Fasting blood sugar; FSH, Follicular; HOMA-IR, Homeostasis model assessment for Insulin Resistance; LH, Luteinising hormone; *SD*, Standard deviation.
* Significant: *P*-Value ≤ .05.

TABLE 2 Correlation between irisin, HOMA-IR and different parameters in patients group

	Irisin (ng/ml)		HOMA-IR	
	r	*p*	*r*	*p*
Age (years)	0.194	.176	0.004	.978
BMI (kg/m^2)	−0.241	.042*	0.033	.023*
Sperm countt (million/ejaculate)	0.017	.907	−0.233	.104
Motility (%)	0.149	.303	0.092	.526
Abnormal forms (%)	−0.244	.088	0.067	.644
FSH (mIU/mL)	0.023	.873	0.120	.406
LH (mIU/mL)	−0.132	.359	−0.089	.539
FBS	−0.143	.323	0.596	<.001*
Insulin	−0.065	.050*	0.872	<.001*
HOMA-IR	−0.071	.023*	–	–

Abbreviations: BMI, Body mass index; FBS, Fasting blood sugar; FSH, Follicular stimulating hormone; HOMA-IR, Homeostasis model assessment for Insulin Resistance; LH, Luteinising hormone.
* Significant: *P*-Value ≤ .05.

damage to nuclear and mitochondrial DNA in spermatozoa (Agbaje et al., 2007).

Another explanation could be attributed to the fact that insulin resistance is the key factor of metabolic syndrome, and every part of metabolic syndrome may play a significant role in male infertil-ity pathogenesis (Kumar et al., 2015). For hypertension, clinical tri-als have shown that about 50 per cent of people with hypertension have hyperinsulinemia, and up to 80 per cent of people with type 2 diabetes have hypertension, linking hypertension with reproductive dysfunction are mainly based on endocrine abnormalities (Zhou, Schulman, & Zeng, 2012).

Another component of the metabolic syndrome is the dyslipi-daemia which has a harmful effect on testicular microenvironment through its associated oxidative stress causing fertility impairment (Kumar et al., 2015).

In the present study, the significant decrease in serum levels of irisin in patients with idiopathic infertility when compared to the controls, together with statistically significant negative cor-relations between levels of serum irisin and both insulin levels and HOMA-IR values may underscore the importance of this marker in prediction of insulin resistance in patients with idiopathic infertility.

Irisin is a hormone released from the skeletal muscles by the ef-fect of exercise. Mild increase in irisin in blood is responsible for the increase in energy expenditure without any changes in food intake. Irisin acts by two ways: it promotes the conversion of inert yellow fat (used to store energy) to the metabolically more active brown fat (in-volved in burning calories). Irisin also has the ability to facilitate the action of insulin, decrease the level of glucose in blood and protect the body from insulin resistance and weight gain (Aggarwal, 2012).

The mode of action of irisin in improving insulin resistance is through acting on insulin receptor in skeletal muscle and heart by increasing their sensitisation and also through improving he-patic glucose, pancreatic β cell functions and lipid metabolism (Liu et al., 2017), all these factors indicate the importance of irisin as a therapeutic target to improve insulin resistance which might be a precipitating factor in idiopathic infertility.

Our study also found that BMI values were positively correlated with HOMA-IR values and negatively correlated with serum iri-sin levels, indicating that increased BMI might be a very important

TABLE 3 Specificity and sensitivity of serum irisin levels in diagnosing insulin resistance in idiopathic infertility patients

	AUC	*p*	95% CI	Cut off	Sensitivity	Specificity	PPV	NPV	Accuracy
Irisin	0.993	<.001*	0.978–1.008	≤3.96	100.0	96.67	98.0	100.0	98.75

Abbreviations: AUC, Area under curve; CI, Confidence interval; NPV, Negative predictive value; PPV, Positive predictive value.

* Significant: *P*-Value ≤ .05.

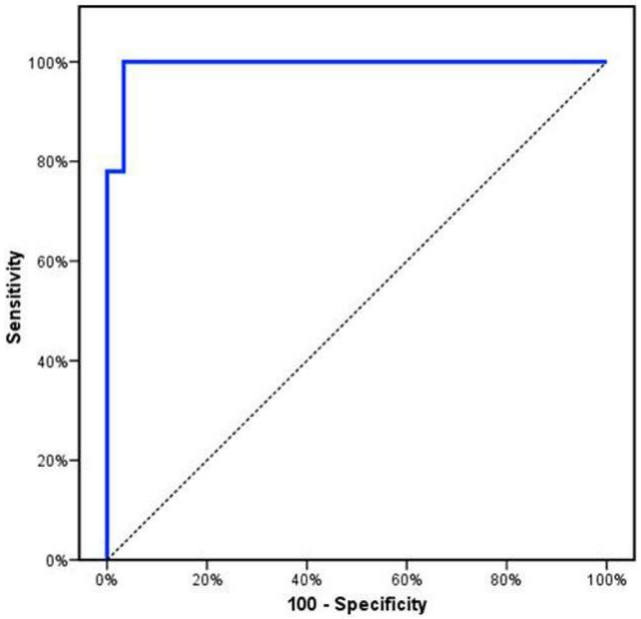

FIGURE 1 ROC curve for the performance of serum level of irisin in diagnosing insulin resistance in idiopathic infertility patients

contributing factor not only in insulin resistance but also in idiopathic infertility.

A systematic review of twenty-one studies originating from twelve countries was done aiming to assess the relationship between sperm count and BMI and revealed that morbidly obese men had a two-fold increase in risk of oligozoospermia (Sermondade et al., 2013).

Obesity can lead to high scrotal temperatures, sperm dysfunction, reduced sperm count and motility, increased damage to sperm DNA and hypogonadism (Kumar et al., 2015).

Many studies indicated the role of obesity in increasing ox-idative stress which plays a major role in insulin resistance and dyslipidaemia (Dandona, Aljada, Chaudhuri, Mohanty, & Garg, 2005; Davì & Falco, 2005). This increase in reactive oxygen spe-cies (ROS) is attributed to the higher than average metabolic lev-els needed for maintaining normal biological processes and also for the higher stress levels in the microenvironment of testicular tissue, both of which are naturally produced. ROS are regarded as important harmful products for male factor infertility, as they may damage plasma membrane integrity, damage DNA in sper-matozoa, and also destruct sperm mitochondrial genomes lead-ing into defects in normal sperm function and motility (Agarwal et al., 2006).

Another important mechanism by which obesity may affect male fertility and sperm functions is through the dysregula-tion of hormones like leptin which has the ability to impair the hypothalamus-pituitary-gonad (HPG) axis (Martins, Majzoub, & Agawal, 2019).

5 | CONCLUSION

There is a strong link between insulin resistance and idiopathic infertility. Irisin is a promising marker to detect insulin resistance in patients with idiopathic infertility and also could be a promising therapeutic target to improve those patients. BMI is a very impor-tant factor affecting the pathogenesis of both insulins resistance and idiopathic infertility.

CONFLICT OF INTEREST

No conflicts of interest.

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How to cite this article: Saleh AAEW, Amin EM, Elfallah AA, Hamed AM. Insulin resistance and idiopathic infertility: A potential possible link. *Andrologia*. 2020;00:e13773. https:// doi.org/10.1111/and.13773