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Impact of insulin resistance on sperm parameters and serum osteocalcin levels: A prospective cross-sectional comparative study

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Abstract

This prospective cross-sectional comparative study aimed to elucidate the effects of insulin resistance and the role of osteocalcin protein in male infertility. A cohort of 171 infertile men aged 25-55 was examined at an assisted reproduction clinic. Hormone profiles, glucose/insulin levels, osteocalcin concentrations, lipid profiles, and semen parameters were assessed. Using the HOMA index, patients were classified as insulin-resistant (n=87) or insulin-sensitive (n=84). Insulin-resistant patients had significantly lower total testosterone (p<0.001), free androgen index (p<0.001), and carboxylated osteocalcin levels (p=0.039) compared to insulin-sensitive patients. Linear regression analysis revealed a negative correlation between HOMA-IR and both total testosterone levels (p=0.022) and sperm motility (p=0.037). No association was found between HOMA-IR and osteocalcin levels (p=0.417). These findings suggest that insulin resistance negatively impacts male reproductive function, particularly testosterone levels and sperm motility. Larger studies are needed to confirm the role of osteocalcin in male infertility and its potential as a therapeutic target. *(Afr J Reprod Health 2025; 29 [12]: 18-24).*

Keywords: Male infertility, osteocalcin, insulin resistance, sperm parameters

Résumé

Cette étude comparative prospective transversale visait à élucider les effets de la résistance à l'insuline et le rôle de l'ostéocalcine dans l'infertilité masculine. Une cohorte de 171 hommes infertiles âgés de 25 à 55 ans a été examinée dans une clinique de procréation assistée. Les profils hormonaux, les taux de glucose/insuline, les concentrations d'ostéocalcine, les profils lipidiques et les paramètres spermatiques ont été évalués. À l'aide de l'indice HOMA, les patients ont été classés comme résistants à l'insuline (n=87) ou sensibles à l'insuline (n=84). Les patients résistants à l'insuline présentaient des taux significativement plus bas de testostérone totale (p<0,001), d'indice androgénique libre (p<0,001) et d'ostéocalcine carboxylée (p=0,039) par rapport aux patients sensibles à l'insuline. L'analyse de régression linéaire a révélé une corrélation négative entre l'HOMA-IR et à la fois les taux de testostérone totale (p=0,022) et la motilité spermatique (p=0,037). Aucune association n'a été trouvée entre l'HOMA-IR et les niveaux d'ostéocalcine (p=0,417). Ces résultats suggèrent que la résistance à l'insuline a un impact négatif sur la fonction reproductive masculine, en particulier sur les taux de testostérone et la motilité des spermatozoïdes. Des études plus larges sont nécessaires pour confirmer le rôle de l'ostéocalcine dans l'infertilité masculine et son potentiel en tant que cible thérapeutique. *(Afr J Reprod Health 2025; 29 [12]: 18-24).*

Mots-clés: İnfertilité masculine, ostéocalcine, résistance à l'insuline, paramètres spermatiques

Introduction

Infertility is defined as the inability to achieve pregnancy despite 1 year of regular unprotected intercourse. Approximately 45% of infertile couples are attributed to male infertility.[1] Genetic, environmental, and hormonal factors are the primary etiologies of infertility in men. Based on our understanding of the necessity for a healthy hypothalamic-pituitary-gonadal axis for fertility, pituitary hormones that influence the secretion of gonadotropins and androgens have been extensively investigated in male infertility. In light of recent findings regarding the impact of glucose and lipid metabolism on spermatogenesis, scientific inquiry has focused on examining the potential association between insulin resistance and male infertility.[2,3] Osteocalcin (OC), which is an osteoblast-specific

noncollagenous protein, is expressed in white adipose tissues, muscles, pancreatic cells, and Leydig cells of the testis.[4] In a study using a murine model, Oury et al. demonstrated that exposure to osteocalcin resulted in enhanced testosterone production and a concurrent reduction in the quantity of apoptotic germ cells.[5] They speculated that the osteoblast-derived hormone osteocalcin may be an endocrine regulator of male fertility. Osteocalcin is hypothesized to play a significant role in insulin secretion and sensitivity.[4-6] In studies investigating the effect of insulin resistance (IR) on male infertility, osteocalcin has been identified as a reliable marker.[7-10] However, the mechanism of infertility and the interplay between osteocalcin and insulin resistance remain unclear.

The objective of this study was to elucidate the impact of insulin resistance on various aspects of male reproductive health, including spermatozoal parameters, hormonal profiles, and serum osteocalcin levels. To the best of our knowledge, this is the first human study to simultaneously examine insulin resistance, sperm quality, and osteocalcin levels in infertile men. Investigating the intricate relationship between osteocalcin and insulin resistance may offer valuable insights into the development of novel therapeutic interventions targeting male infertility.

Methods

Male patients aged 25–55 years seeking fertility evaluation at Assisted Reproduction Unite of Zeynep Kamil Women and Children Diseases Training and Research Hospital were included in the study. Inclusion criteria were: male patients aged 25–55 years, presenting for infertility evaluation, who had regular unprotected intercourse with a female partner for at least 1 year without conception. Exclusion criteria included: azoospermia, previously diagnosed chronic systemic illnesses (e.g., diabetes mellitus, hypertension, hyperlipidemia), history of malignancy, current or past smoking, alcohol use, or illicit drug use, as well as presence of varicocele on physical examination or scrotal ultrasonography.

Participants were selected consecutively from patients presenting to the infertility clinic and were approached during their initial consultation. Prior to enrollment, all participants provided written informed consent. No formal sample size calculation was conducted due to the exploratory nature of the study; however, the final sample size was deemed sufficient to detect meaningful differences between groups based on previous studies assessing similar outcomes.

A thorough medical history was obtained, followed by anthropometric measurements including height, weight, Body Mass Index (BMI), and waist circumference. Height and weight were measured using a calibrated stadiometer and digital scale (SECA, Germany), and waist circumference was measured at the midpoint between the lower rib and iliac crest using a non-stretchable measuring tape. Each participant underwent a comprehensive systemic and genital examination.

Participants were categorized into two groups based on insulin resistance (IR) status: IR(+) and IR(−). Blood specimens were procured between 9:00 and 11:00 a.m. after an 8–10 hour fasting period and centrifuged immediately. Serum hormone levels were analyzed using commercially available ELISA kits: FSH, LH, TT, SHBG, PRL, and TSH were measured using the Access 2 Immunoassay System (Beckman Coulter, USA). Fasting glucose and insulin levels were assessed using the Cobas c502 module (Roche Diagnostics, Germany). Serum levels of carboxylated and undercarboxylated osteocalcin were measured using an ELISA kit (Takara Bio Inc., Japan), according to the manufacturer's instructions. Lipid profiles were also assessed using enzymatic colorimetric methods on the same analyzer. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index was calculated using the formula: HOMA-IR = (FG × FI × 0.055) / 22.5, where FI is fasting insulin (μIU/mL) and FG is fasting glucose (mmol/L).[11] Patients with a HOMA-IR ≥ 2.5 were classified as insulin resistant.[12] The Free Androgen Index (FAI) was calculated using the formula: FAI = (TT / SHBG) × 100%.

Semen samples were obtained through masturbation following 2–5 days of sexual abstinence. Samples were collected in sterile containers and analyzed within 1 hour of collection. Semen analysis followed the World Health Organization (WHO) 2010 guidelines which refer to at least a semen volume of 1.5 mL, sperm concentration of 15 million/mL, sperm total motility of 40%, and sperm with a normal morphology of 4% (Kruger criteria) for an adequate fertility capacity.[13] Parameters including volume, sperm concentration,

motility, and morphology were evaluated using a Makler counting chamber and phase-contrast microscopy (Olympus CX31, Japan).

Total motile sperm count (TMSC) which is calculated by multiplying the sperm concentration (sperm count per milliliter) (SC) x volume (ml) x motility (A + B) divided by 100%, is used to describe the quality of sperm, which presented as more predictive for fertility assessment in current studies.[14] While levels equal and/or greater 20 million were considered as normozoospermia, levels below 20 million were defined as 'oligo-astenozoospermia'.[15] Sperm morphology parameter is not used in this calculation.

Statistical analysis

Statistical analysis was performed using SPSS version 21 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± standard deviation or number (n) and percentage (%). The Kolmogorov-Smirnov test was used to assess data normality. Comparisons between the IR(+) and IR(−) groups for continuous variables were made using the independent-sample t-test, while the chi-square test was applied for categorical variables. Linear regression analysis was conducted to examine the association between HOMA-IR and sperm parameters or osteocalcin levels. Statistical significance was set at $p < 0.05$. No multivariable adjustment for confounding factors was applied due to the limited sample size, although variables were compared for baseline similarity.

Ethical consideration

This study was approved by the Research Ethics Committee of our hospital (Approval No: 39/2018). All procedures involving human participants were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study

Results

This study was conducted between January 4 and June 28, 2018. The initial cohort consisted of 192 male patients, of whom seven were excluded due to azoospermia, one due to hyperprolactinemia, five due to hypothyroidism, and eight due to diabetes. A total of 171 patients were ultimately included in the study. Comparisons of age, height, weight, body mass index (BMI), fasting glucose and insulin levels, HOMA index, and semen parameters between groups are presented in Table 1. Based on the HOMA index calculation, 87 patients exhibited insulin resistance (IR), whereas 84 patients demonstrated normal insulin sensitivity. Upon analysis of patients according to semen parameters, it was determined that 55 individuals presented with oligo-asthenozoospermia, while 116 patients whose total motile sperm count (TMSC) was 20 million or greater were classified as normozoospermic.

The analysis revealed no statistically significant disparities between the groups regarding age, weight, height, BMI, sperm concentration, total sperm motility, or total motile sperm count. However, the mean HOMA index was markedly higher in the IR (+) group than in the IR (−) group (7.00±5.37 vs. 1.63±0.52, $p<0.001$). Moreover, substantial differences in glucose and insulin levels were observed between the groups ($p=0.000$). Notably, subjects in the IR (+) category displayed a significantly larger waist circumference compared to their IR (−) counterparts ($p=0.01$).

The groups were compared by analyzing the hormonal and lipid profiles in combination with serum osteocalcin measurements(Table 2). Statistical analysis revealed significantly higher levels of FSH, low-density and very-low-density lipoproteins, and triglycerides in the IR (+) group than in the IR (-) group ($p=0.024$, $p= 0.021$, and $p<0.001$, respectively). Conversely, total testosterone levels were significantly lower in the IR (+) group than in the IR (−) group ($p<0.001$). Similarly, the IR (+) group showed a significant reduction in unbound androgen concentration compared to the IR (-) group ($p<0.001$). The IR (+) group exhibited significantly lower levels of serum carboxylated osteocalcin than the IR (-) group ($p=0.039$). In contrast, the concentrations of undercarboxylated osteocalcin were comparable between the two groups.

Linear regression analysis was conducted to assess the effect of HOMA-IR on sperm parameters and blood osteocalcin concentrations. The results indicated an inverse relationship between serum HOMA-IR and both total testosterone levels ($p=0.022$) and overall sperm motility ($p=0.037$).

Table 1: Characteristics of the study groups

	IR (+) group n=87 (50.8%)	**IR (-) group** n=84 (49.1%)	**P value**
Age (years)	35.47 ± 4.20	34.22 ± 6.54	0.139
Weight (cm)	86.14 ± 10.53	83.91 ± 9.09	0.140
Height (kg)	175.91 ± 6.19	175.74 ± 5.89	0.855
BMI (kg/m^2)	27.92 ± 3.46	27.13 ± 2.85	0.105
Waist (cm)	93.60±8.80	89.92±9.73	0.01*
Overweight (n; %)	71, 81.6%	68, 80.9%	0.912
Obesity (n; %)	66, 47.5%	73, 52.5%	0.074
Fasting blood glucose (mg/dl)	95.05±9.19	88.82±11.76	0.000*
Fasting serum insulin (mIU/ml)	29.98±21.88	7.66±2.56	0.000*
HOMA-IR (mean ± SD)	7.00±5.37	1.63±0.52	0.000*
Sperm concentration (million/mL)	41.96±35.98	47.36±35.68	0.326
Total sperm motility (%)	46.57±18.65	48.60±20.69	0.501
Total motile sperm count ($x10^6$)	59.04±68.38	70.51±71.68	0.286

Results are expressed as mean±SD or n (%). *p<0.05. HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; IR(+): Insulin Resistance positive, IR(-): Insulin Resistance negative.

Table 2: Participant data on hormone levels, lipid profiles, and serum osteocalcin concentrations.

	IR (+) group n=87 (50.8%)	**IR (-) group** n=84 (49.1%)	**P value**
FSH (mIU/ml)	4.49±2.86	3.66±1.73	0.024*
LH (mIU/ml)	3.39±1.83	4.36±7.91	0.269
Prolactin (ng/ml)	10.90±4.70	10.43±5.85	0.558
TSH (mU/L)	1.48±0.71	1.55±0.79	0.542
Total testosterone (ng/ml)	3.63±1.35	5.32±1.90	0.000*
SHBG (nmol/L)	22.65±7.22	22.52±7.59	0.912
Free Androgen Index	18.09±10.78	26.48±14.15	0.000*
Total cholesterol(mg/dl)	191.25±44.47	188.02±112.85	0.805
High-density lipoproteins (mg/dl)	38.48±18.14	42.08±13.61	0.145
Low-density lipoproteins (mg/dl)	119.50±39.44	106.54±32.86	0.021*
Very-low-density lipoproteins (mg/dl)	35.67±15.89	26.30±15.90	0.000*
Triglycerides (mg/dl)	178.35±79.46	131.50±79.52	0.000*
cOsteocalcin (ng/ml)	6.45±3.86	7.75±3.99	0.039*
ucOsteocalcin (ng/ml)	0.99±0.91	0.85±0.71	0.286

Values are presented as mean±SD. *p<0.05. IR(+): Insulin Resistance positive, IR(-): Insulin Resistance negative, FSH: Follicle-Stimulating Hormone, LH: Luteinizing Hormone, TT: Total Testosterone, SHBG: Sex-Hormone-Binding Globulin, PRL: Prolactin, TSH: Thyroid-Stimulating Hormone, FG: Fasting Glucose, FI: Fasting Insulin, cOsteocalcin: Carboxylated Osteocalcin, ucOsteocalcin: Undercarboxylated Osteocalcin.

Table 3: Correlation between HOMA-IR levels in serum and sperm parameters and serum osteocalcin levels

	B	beta	t	P value
Sperm concentration	-0.005	-0.036	-0.350	0.727
Total sperm motility	0.047	0.203	2.107	0.037
Total motile sperm count	-0.15	-0.232	-1.909	0.058
Total testosterone (ng/ml)	-0.977	-0.396	-2.321	0.022
SHBG (nmol/L)	0.036	0.056	0.389	0.698
Free androgen index	0.003	0.009	0.045	0.964
cOsteocalcin (ng/ml)	-0.071	-0.062	-0.813	0.417

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, SHBG: Sex-Hormone-Binding Globulin, cOsteocalcin: Carboxylated Osteocalcin

Nevertheless, this study failed to demonstrate a statistically significant association between serum HOMA-IR and osteocalcin levels (p=0.417) (Table 3).

Discussion

The objective of this study was to examine the effect of insulin resistance on serum osteocalcin (OC) concentration and male reproductive function by assessing sperm parameters and reproductive hormonal profiles. The results demonstrated that subjects with insulin resistance exhibited lower levels of serum total testosterone, OC, and free androgen index compared to those with normal insulin sensitivity. Insulin-resistant subjects presented with increased waist circumference and elevated levels of serum follicle-stimulating hormone (FSH), low-density lipoproteins, very-low-density lipoproteins, and triglycerides relative to their non-insulin-resistant counterparts. Moreover, this study identified an inverse correlation between serum homeostatic model assessment of insulin resistance (HOMA-IR) levels and both total testosterone levels and sperm motility.

Evidence suggests that osteocalcin plays a critical role in both insulin secretion and efficacy.[6] Current research indicates that OC may potentially influence male fertility parameters, including semen quality and hormonal balance.[7,8] Saleh *et al*.[9] evaluated serum osteocalcin levels in infertile male patients and revealed higher serum follicle-stimulating hormone, luteinizing hormone, prolactin, and lower serum testosterone and osteocalcin levels in infertile patients compared with controls. Furthermore, they reported comparable fasting blood glucose levels between the groups. They postulated that osteocalcin could serve as a potential biomarker for the diagnosis of male infertility.

According to a study, OC potentially impacts the reproductive capabilities of males by stimulating testosterone synthesis in Leydig cells and reducing the rate of germ cell apoptosis.[16] Another study conducted by El-Kamshoushi *et al*.[8] found that infertile males had higher serum LH and FSH concentrations, along with reduced levels of the active undercarboxylated form of osteocalcin (ucOC), than fertile males. However, their research did not reveal any statistically significant association between ucOC and semen parameters or hormone levels. A prospective case-control study by Mansour *et al*.[7] examined insulin resistance in males with unexplained infertility. Their research showed that men with insulin resistance had higher levels of serum FSH, LH, and total cholesterol, increased insulin resistance, and reduced serum total testosterone compared to those with normal insulin sensitivity. Our findings align with these results, as we observed decreased serum total testosterone and osteocalcin levels, along with lower free androgen index values in individuals with insulin resistance than in those without. Supporting our observations, Ma *et al*.[17] reported a significant reduction in serum testosterone levels and the proportion of progressively motile sperm in infertile men with lower HOMA-IR compared to those with higher HOMA index. These outcomes indicate that insulin resistance may play a role in male reproductive dysfunction by negatively affecting reproductive hormone levels.

The potential correlation between osteocalcin and insulin resistance in infertile male patients warrants further investigation, as it may lead to the development of innovative therapeutic strategies. Furthermore, the utilization of osteocalcin as a pharmacological agent could potentially ameliorate infertility associated with insulin resistance. Shafaat *et al*.[18] demonstrated that histological analysis of testes from an azoospermic mouse model injected with osteocalcin exhibited enhanced spermatogenesis, characterized by increased germinal layer thickness in the seminiferous tubules and elevated numbers of spermatogonial cells, spermatocytes, and elongated spermatids. These findings suggest that osteocalcin may play a significant role in spermatogenesis. Guedes *et al*.[19] speculated that osteocalcin might regulate male fertility in mice by improving insulin resistance and reducing inflammation. Studies investigating the relationship between osteocalcin and insulin resistance in humans have yielded inconsistent results. [20] The present study demonstrated no association between osteocalcin and HOMA-IR, which is consistent with previous research.[20-21] However, some studies have identified an inverse correlation between osteocalcin concentration and HOMA-IR.[22-23] We observed a negative correlation between HOMA-IR, total testosterone levels, and total sperm motility. A

review examining the role of osteocalcin in infertility highlighted its ability to enhance testosterone production and influence male fertility without involving the hypothalamic-pituitary axis.[24] The strength of this study is that, to the best of our knowledge, it is the first to examine the association between serum osteocalcin concentration and HOMA-IR in infertile male patients. A limitation of our study was the absence of long-term follow-up results. The acquisition of information regarding live pregnancy and birth outcomes for these patients subsequent to in vitro fertilization could potentially facilitate the development of innovative therapeutic approaches.

Conclusion

These findings suggest that insulin resistance negatively impacts male reproductive health by reducing serum testosterone levels, impairing sperm motility, and decreasing carboxylated osteocalcin concentrations. While the direct association between osteocalcin and insulin resistance was not statistically significant in this cohort, the observed hormonal and metabolic alterations in insulin-resistant men underscore the complex interplay between metabolic health and male fertility. Given the rising global prevalence of insulin resistance and metabolic syndrome, addressing these factors may represent a promising avenue for improving reproductive outcomes in men. The role of osteocalcin as a potential mediator between metabolic and reproductive systems remains an intriguing hypothesis that warrants further investigation.

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Data availability statement

The datasets used and/or analyzed in the study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that they have no conflicts of interest.

Contribution of authors

M.B.Y. contributed to the concept, study design, data analysis and interpretation, drafting, and critical revision of the manuscript. A.A. and A.N.A. contributed to the concept, assumptions, study design, data analysis and interpretation, and critical revision. R.G.I. contributed to the assumptions, data analysis and interpretation, drafting, and critical revision. Z.C. and H.H.P. contributed to the study design, data acquisition, data analysis and interpretation, and drafting of the manuscript. All authors read and approved the final version of the manuscript.

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