RESEARCH ARTICLE

Relationship between serum irisin and leptin levels and gonadal axis in obese subfertile men

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Obesity is a growing global health concern with detrimental effects on male reproductive function. Excess body fat disrupts hormonal balance, increases inflammation, and reduces sperm quality. Irisin, a myokine produced by skeletal muscle and adipose tissue, is involved in metabolism, and has potential therapeutic implications for obesity. Leptin, another adipokine primarily produced by white adipose tissue, regulates body composition and energy homeostasis. This study investigated the roles of irisin and leptin along with testosterone, FSH, and LH, in obese sub-fertile men to assess the relationship between irisin, leptin, and BMI on semen parameters. Ninety-one men aged 20-45 years were recruited and grouped based on semen analysis and BMI categories. Serum levels of irisin, leptin, testosterone, FSH, and LH were measured using ELISA kits. The results showed significantly higher irisin levels in the control group compared to all other groups, while leptin levels were significantly lower in the control group. Correlation analysis revealed a negative correlation between irisin levels and BMI in the normal weight control group, but a positive correlation in overweight and obese subgroups with varying sperm parameters. Leptin levels showed a positive correlation with BMI in several groups. These findings suggested that irisin might play a role in regulating male fertility and could be a potential therapeutic target for metabolic and reproductive dysfunction in obese men. Further research is necessary to unravel the complex interplay between irisin, leptin, and other hormones in the context of obesity and male infertility.

Keywords: irisin; leptin; gonadal axis; obesity; sub-fertility.

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Introduction

The global rise in overweight and obesity has reached epidemic proportions, posing a significant public health concern due to its association with various chronic diseases including type 2 diabetes, cardiovascular disease, and certain cancers [1, 2]. Beyond its impact on overall health, obesity has also emerged as a critical factor influencing male reproductive function [3, 4]. Excess body fat disrupts the delicate hormonal balance necessary for spermatogenesis, increases inflammation and oxidative stress, and ultimately reduces sperm quality and fertility [5, 6]. Obesity disrupts the hypothalamic-pituitary-gonadal (HPG) axis, the intricate hormonal feedback loop that regulates testosterone production and spermatogenesis. Increased aromatase activity within adipose tissue converts testosterone to estrogen, resulting in lower testosterone levels [7]. Additionally, leptin resistance, a hallmark of

obesity, impairs the sensitivity of the hypothalamus to leptin, leading to decreased gonadotropin-releasing hormone (GnRH) secretion and consequently reduced luteinizing hormone (LH) and follicle-stimulating hormone (FSH) production [8]. These hormonal imbalances disrupt spermatogenesis and impair sperm quality and function.

Obesity is characterized by chronic inflammation, which contributes to male infertility through various mechanisms. Adipose tissue secretes pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which can directly impair sperm function and damage testicular tissue [9]. Oxidative stress, an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses, is another key factor in obesity-related male infertility. Excess ROS can damage sperm DNA, leading to reduced sperm motility and increased rates of apoptosis [10, 11]. In addition to hormonal imbalances and inflammation, obesity can also directly affect testicular function. Adipose tissue deposition around the testes, known as peritesticular adipose tissue (PAT), can lead to increased testicular temperature and reduced blood flow, impairing spermatogenesis [12]. Furthermore, obesity has been associated with increased apoptosis of germ cells and decreased production of inhibin B, a hormone that regulates FSH secretion and spermatogenesis [13].

Irisin, a recently discovered myokine primarily secreted by skeletal muscle and adipose tissue, has emerged as a potential link between metabolism and reproduction [14, 15]. Irisin is primarily released in response to physical activity and is believed to play a role in browning white adipose tissue, leading to increased energy expenditure and improved insulin sensitivity [16]. Studies have detected irisin in various tissues including the central nervous system, reproductive organs (seminiferous tubules, Leydig cells, epididymis), and cerebrospinal fluid [17-19]. This suggests a potential role for irisin in reproductive function, although its specific mechanisms and effects remain under investigation [20]. Leptin, another adipokine primarily produced by white adipose tissue, plays a crucial role in regulating body composition, energy homeostasis, and insulin sensitivity [21]. Leptin is also involved in the neuroendocrine control of reproduction and is essential for normal sexual development and function [22]. However, evidence suggests that the elevated leptin levels observed in obese individuals can have detrimental effects on sperm parameters including decreased sperm count, motility, and increased DNA fragmentation [23], which suggests a complex relationship between leptin, obesity, and male fertility [24].

Given the potential roles of irisin and leptin in both metabolic and reproductive health, this study aimed to investigate their levels in obese sub-fertile men compared to fertile controls. Additionally, the relationships between these adipokines and other reproductive hormones (testosterone, FSH, LH) were explored. We hypothesized that irisin levels would be lower and leptin levels would be higher in obese sub-fertile men compared to fertile controls, and these adipokines would exhibit correlations with reproductive hormones and semen parameters. By elucidating these relationships, this study aimed to contribute valuable insights into the development of targeted interventions for improving male fertility in obese individuals.

Materials and methods

Patients Information

Ninety-one (91) men aged 20-45 years were recruited for this study from private laboratories in Al-Hilla city, Babylon Province and Al-Najaf city, Al-Najaf Province in the middle region of Iraq between December 2022 and October 2023. The study protocol was approved by the Institutional Review Board of Ethical Committee in University of Babylon (Babylon, Hillah, Iraq) (Approval No. DST-6654). Written informed consent was obtained from all participants following a detailed explanation of the study procedures and

potential risks and benefits. Participants were divided into five groups based on semen analysis results according to World Health Organization (WHO) 2021 criteria [25], including 20 patients in control group (fertile men), 16 patients in oligospermia group (low sperm count), 16 patientis in asthenospermia group (low sperm motility), 22 patients in oligoasthenospermia group (low sperm count and motility), 17 patients in normospermia group (normal semen parameters). Following semen analysis, all participants within each semen parameter group were further categorized based on their Body Mass Index (BMI) that was calculated as weight in kilograms divided by height in square meters. The three BMI categories were defined according to WHO classifications as normal weight group (BMI = 18.5 - 24.9 kg/m^2), overweight group (BMI ≥ 25 kg/m^2), obese group (BMI ≥ 30 kg/m^2) [26].

Blood sample collection and hormone measurement

Five (5) milliliter blood samples were collected *via* venous puncturing after an overnight fasting between 8:00 AM and 11:00 AM. Serum levels of irisin, leptin, testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Pars Biochem, Nanjing, Jiangsu, China) following manufacturer's instructions.

Statistical analysis

Statistical analysis was performed using SPSS version 23 (IBM, Armonk, New York, USA). Numerical data were presented as mean ± standard error of the mean (SEM). One-way analysis of variance (ANOVA) was employed to compare hormone levels and BMI between groups. Post-hoc tests with Least Significant Difference (LSD) correction were used for multiple comparisons with a significance level set at $P < 0.05$. Pearson's correlation coefficients were calculated to assess the relationships between hormonal parameters and BMI.

Results

Hormonal parameters

The serum irisin levels were significantly lower in the obese sub-fertile men with oligoasthenozoospermia (12.29 ± 1.11 pg/mL) compared to that in the control group (20.50 ± 2.28 pg/mL) and the normozoospermia obese sub-fertile men (13.42 ± 1.51 pg/mL) ($P < 0.05$). There were also significant differences in serum irisin levels between the control group and the normozoospermia obese sub-fertile men ($P < 0.05$) (Figure 1A). Serum leptin levels were significantly higher in all obese sub-fertile men groups compared to that in the control group ($P < 0.05$). Obese sub-fertile men with oligoasthenozoospermia and asthenozoospermia had significantly higher serum leptin levels of 3.94 ± 0.32 µg/L and 4.54 ± 0.47 µg/L compared to 2.02 ± 0.32 µg/L in control group ($P < 0.05$). Obese normozoospermia sub-fertile men also had significantly higher serum leptin level of 4.59 ± 0.64 µg/L compared to that of the control group ($P < 0.05$) (Figure 1B). There were no significant differences in serum leptin levels among all obese sub-fertile men groups.

Serum testosterone levels were significantly lower in all study groups compared to that in the obese normozoospermia sub-fertile men group ($P < 0.05$). Obese sub-fertile men with oligoasthenozoospermia, oligozoospermia, and asthenozoospermia had significantly lower serum testosterone levels of 2.61 ± 0.21 ng/mL, 3.10 ± 0.10 ng/mL, and 3.00 ± 0.23 ng/mL, respectively, compared to 3.30 ± 0.18 ng/mL in the obese normozoospermia subfertile men group ($P < 0.05$). Control group also had significantly lower serum testosterone level of 2.65 ± 0.23 ng/mL compared to that of the obese normozoospermia sub-fertile men ($P < 0.05$) (Figure 1C). There were no significant differences in serum testosterone levels among the obese sub-fertile men groups of oligoasthenozoospermia, oligozoospermia, asthinozoospermia, and control group ($P > 0.05$).

Serum FSH levels showed significantly lower in the control group as 6.77 ± 0.50 ng/mL than that in obese sub-fertile men groups as 10.27 ± 0.37

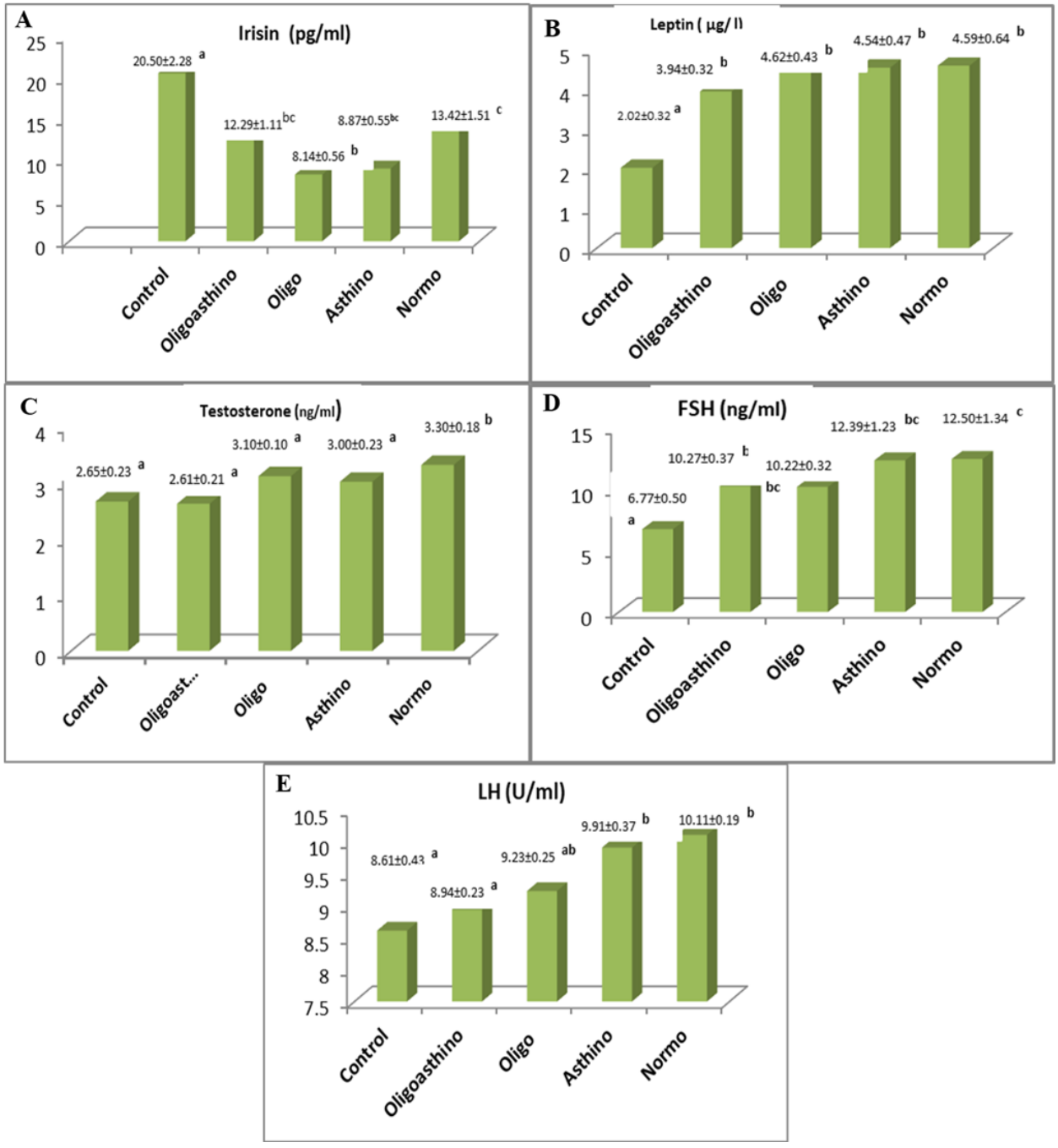

Figure 1. Different hormone levels in different study groups. **A.** Irisin. **B.** Leptin. **C.** Testosterone. **D.** FSH. **E.** LH. Different lowercase letters denoted significant differences ($P < 0.05$) between groups.

ng/mL in oligoasthinozoospermia, 10.22 ± 0.32 ng/mL in oligozoospermia, 12.39 ± 1.23 ng/mL in asthinozoospermia, and 12.50 ± 1.34 ng/mL in normozoospermia ($P < 0.05$). Also, there was a significant increase in serum FSH levels in normozoospermia compared with oligoasthinozoospermia and control groups (Figure 1D). Serum LH levels were significantly lower in control group as 8.61 ± 0.43 U/mL than that 9.91 ± 0.37 U/mL in the obese asthinozoospermia subfertile men and 10.11 ± 0.19 U/mL in obese normozoospermia subfertile

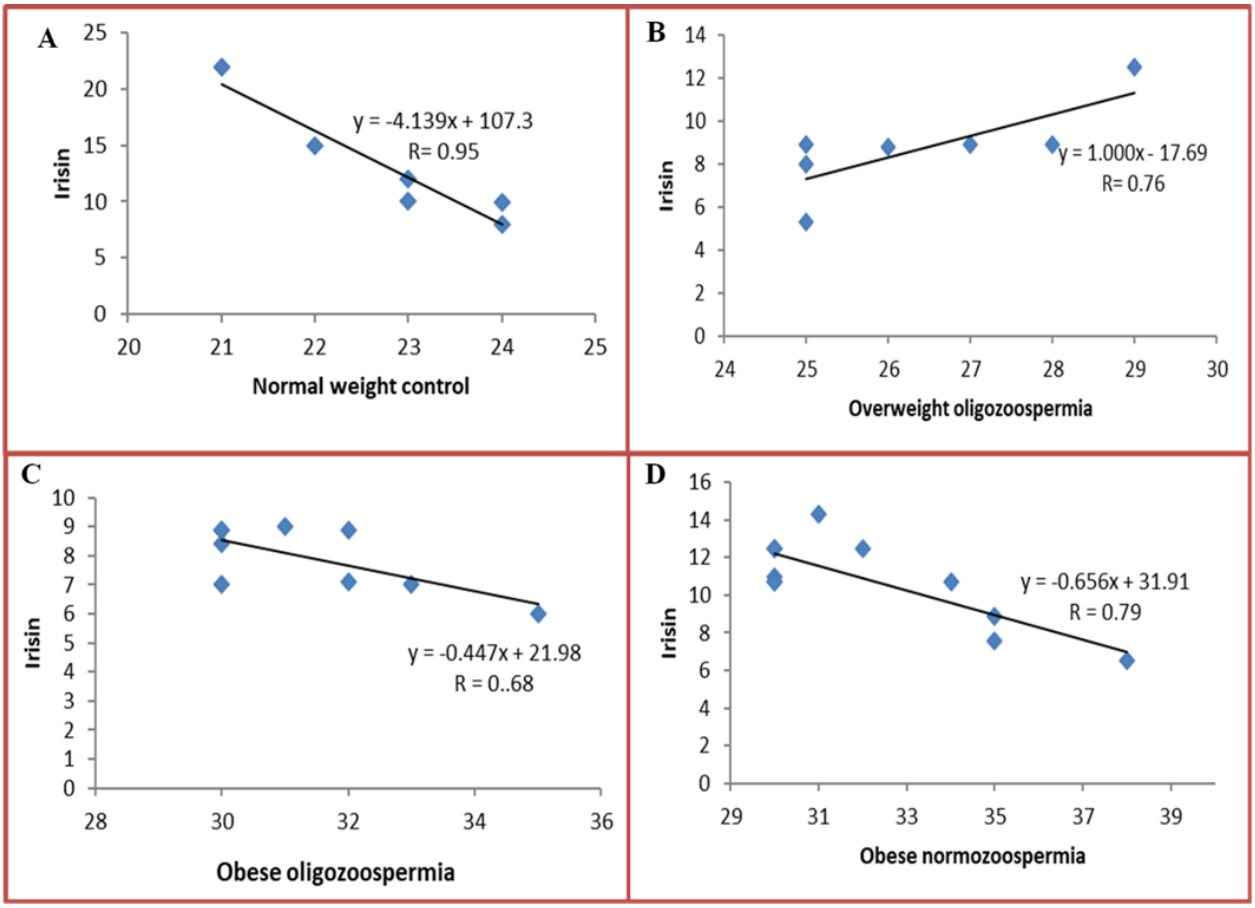

Figure 2. Relationship of serum irisin concentration (pg/mL) to BMI in different groups. **A.** Normal weight controls. **B.** Overweight oligozoospermia. **C.** Obese oligozoospermia. **D.** Obese normozoospermia.

men ($P < 0.05$). There were no significant differences in serum LH levels among the control group and obese sub-fertile men with oligozoospermia (9.23 ± 0.25 U/mL) and oligoasthenozoospermia (8.94 ± 0.23 U/mL) (Figure 1E). Interestingly, obese sub-fertile men with asthenozoospermia had significantly higher serum LH level compared to that in obese sub-fertile men with oligoasthenozoospermia ($P < 0.05$).

Relationship of hormonal parameters and fertility categories based on BMI categories

The relationships between serum irisin concentration and BMI across the study groups were shown in Figure 2. Interestingly, the pattern varied depending on the weight and sperm parameters of the participants. In the normal weight control group, a weak negative correlation emerged, indicating that serum irisin levels tended to decrease slightly as BMI increased (Figure 2A). Conversely, the overweight men with oligozoospermia displayed a weak positive correlation (Figure 2B), suggesting a slight increase in serum irisin levels with increasing BMI. For the obese sub-fertile men, the correlation differed based on sperm parameters. Both oligozoospermia (Figures 2C) and normozoospermia (Figure 2D) demonstrated a weak negative correlation between serum irisin and BMI, and similar to the normal weight controls, their serum irisin levels tended to decrease slightly with increasing BMI. It's noteworthy that despite statistically significant correlations in some groups, the correlation coefficients across all panels of Figure 2 remained

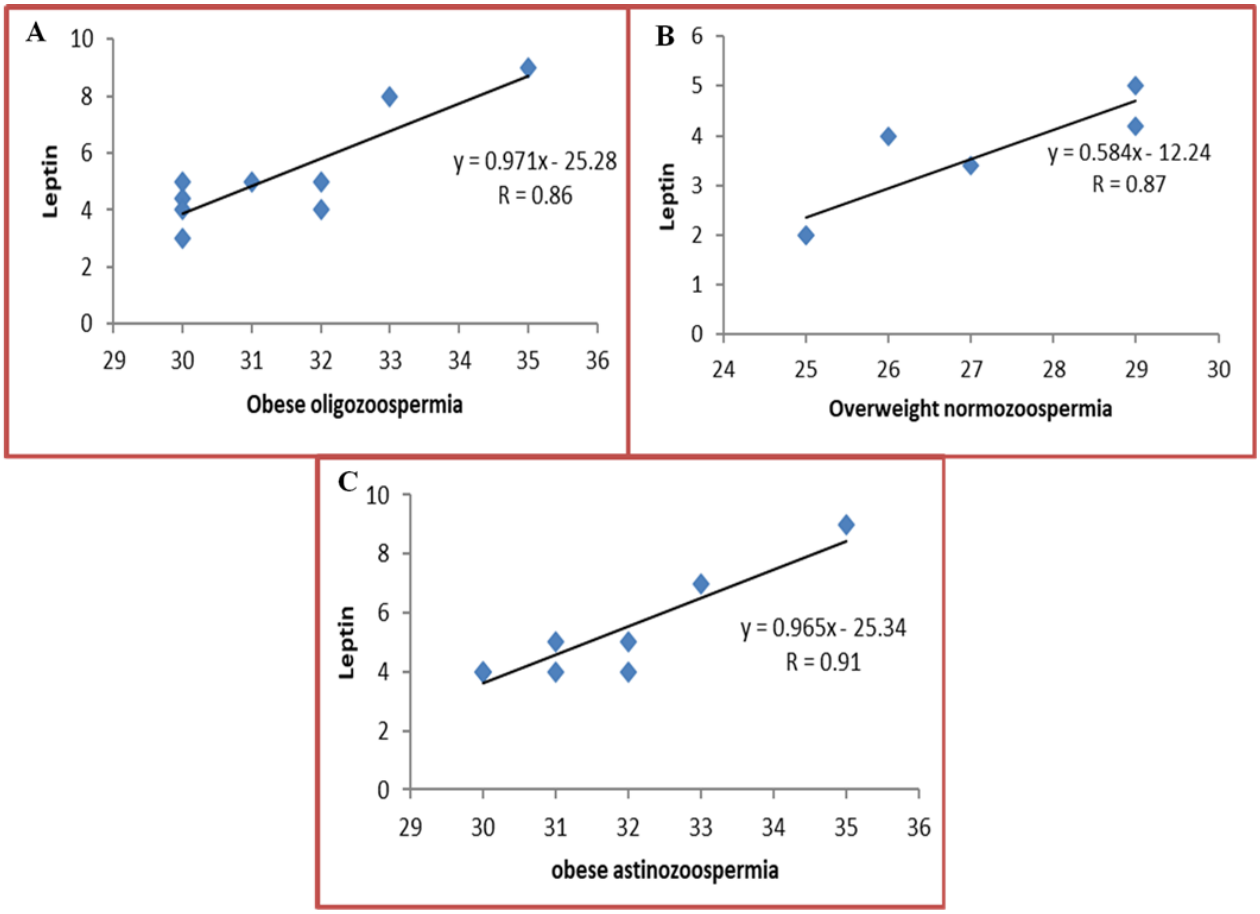

Figure 3. Relationship of serum leptin concentration (μg/L) to BMI in different groups. **A.** Obese oligozoospermia. **B.** Obese asthenozoospermia. **C.** Overweight normozoospermia.

relatively weak, which suggested a limited influence of BMI on serum irisin concentration in this study.

Relationship of serum Leptin concentration to BMI in obese oligozoospermia group showed that there was a positive correlation between serum leptin concentration and BMI (Figure 3A). The equation for the regression line was y = 0.971x - 25.28, and the correlation coefficient (R) was 0.86. The obese asthenozoospermia group also showed a positive correlation between serum leptin concentration and BMI (Figure 3B) with the equation for the regression line as y = 0.965x - 25.34, and the correlation coefficient (R) of 0.91. The overweight normozoospermia group showed the same positive correlation between serum leptin concentration and BMI (Figure 3C) with the equation for the regression line as y = 0.584x - 12.24, and the correlation coefficient (R) of 0.87. In all above three groups, there was a significant positive correlation between serum leptin concentration and BMI, which suggested that, as BMI increased, serum leptin levels also increased. The correlation coefficients were all relatively strong, indicating a clear relationship between these two measures.

The relationships of serum testosterone, FSH, and LH concentrations to BMI were as follows. There was a weak positive correlation between serum testosterone concentration and BMI in obese men with oligoasthenozoospermia, and the regression line showed a slight increase in testosterone levels with increasing BMI (Figure 4A). There was a positive correlation between

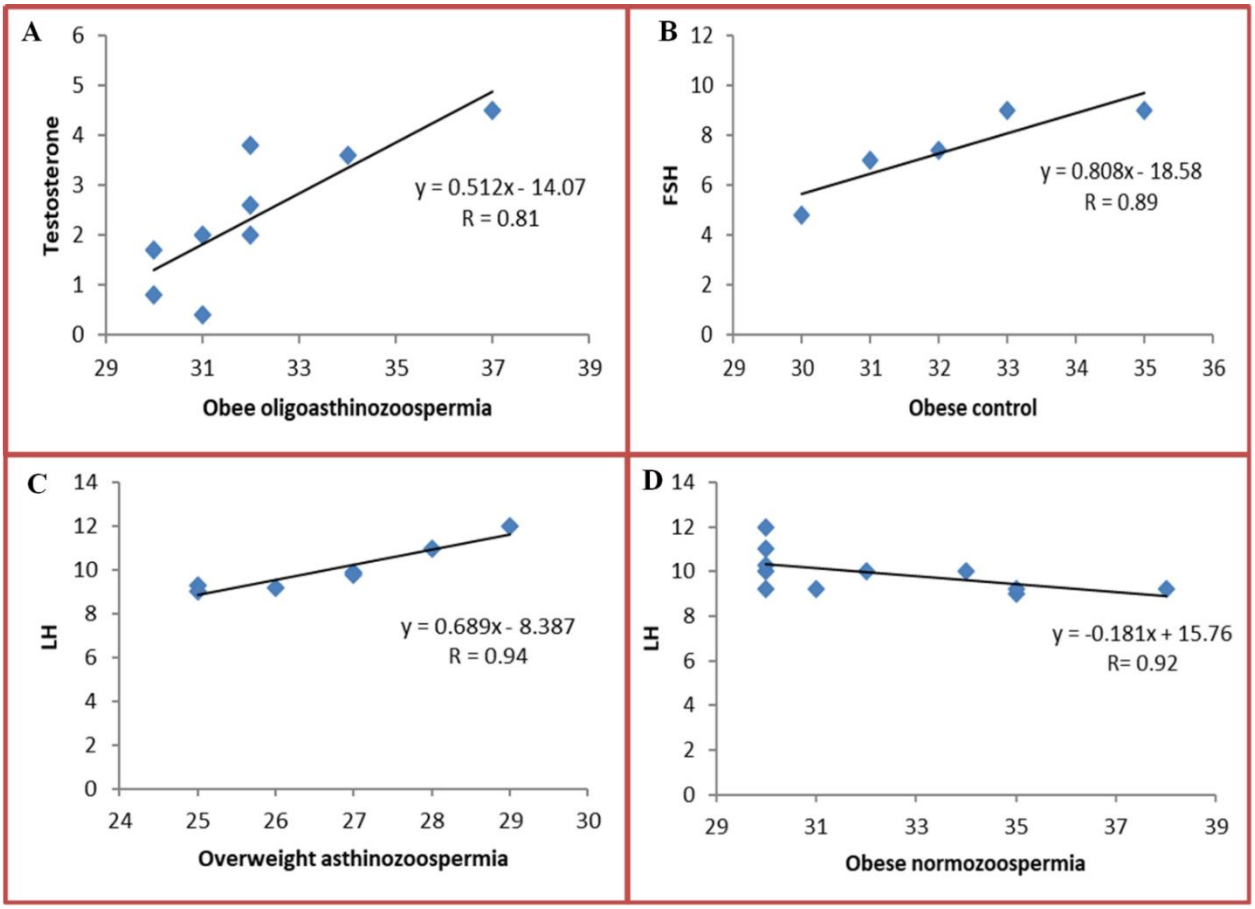

Figure 4. Relationship of serum concentrations of testosterone, FSH, LH to BMI in different groups. **A.** Testosterone (ng/mL) in obese oligoasthenozoospermia. **B.** FSH (ng/mL) in obese control. **C.** LH (U/mL) in overweight asthenozoospermia. **D.** LH (U/mL) in obese normozoospermia.

serum FSH concentration and BMI in the obese control group (Figure 4B), and a weak positive correlation between serum LH concentration and BMI in overweight men with asthenozoospermia (Figure 4C). The regression line indicated a slight increase in LH levels with increasing BMI. However, for obese men with normozoospermia, the correlation was weak and negative (Figure 4D). The regression line suggested a slight decrease in LH levels with increasing BMI. Overall, the findings for testosterone and LH showed weak relationships with BMI, and the direction of the correlation depended on the specific groups.

Discussion

Obesity is a growing health concern worldwide and has been linked to numerous reproductive dysfunctions in men including erectile dysfunction, decreased libido, and abnormal sperm parameters [26]. Exercise interventions have been shown to improve erectile dysfunction and sperm quality in obese men [27]. Irisin, a myokine secreted by skeletal muscle, has emerged as a potential player in male reproduction [28]. Studies suggest that irisin may influence the hypothalamic-pituitary-gonadal (HPG) axis and spermatogenesis [29]. This study investigated the relationships between irisin, leptin, testosterone, FSH, and LH serum levels and semen parameters in obese sub-fertile men with different sperm pathologies.

The results of this research showed significantly lower serum irisin levels in obese sub-fertile men with oligoasthenozoospermia compared to that in the control group and normozoospermic sub-fertile men, which suggested a potential role for irisin in spermatogenesis similar to previous report [30], demonstrating a correlation between circulating irisin levels and reproductive health. Hoffmann and Weigert proposed that irisin might enhance FSH, LH, and testosterone levels, thereby promoting spermatogenesis [31]. Interestingly, the correlation analysis in this study showed a negative correlation between irisin and BMI in the fertile control group, which aligned with the established role of irisin in inducing brown adipose tissue formation and increasing thermogenesis [32]. Conversely, the overweight oligozoospermia group displayed a positive correlation between irisin and BMI, which might be attributed to a compensatory response to obesity-induced metabolic dysfunction *via* irisin resistance as suggested by Ulker *et al.* [33]. Further investigation is needed to elucidate the complex interplay between irisin, BMI, and spermatogenesis. Serum leptin levels were significantly higher in all obese sub-fertile men groups compared to that in the control group. The results aligned with previous studies demonstrating a positive correlation between leptin and abnormal sperm morphology and motility. Elevated leptin levels may suppress testosterone production by Leydig cells, thus disrupting spermatogenesis [34]. Serum testosterone levels were significantly lower in fertile men but in normal range compared with infertile groups. These findings were consistent with the results of Jiang *et al*. who reported no change in testosterone levels despite increased LH and FSH levels in obese male rats [35]. Testosterone plays a critical role in regulating gonadotropin secretion *via* a feedback loop. Estradiol, a metabolite of testosterone, also contributes to this feedback mechanism [36]. Possible explanations for the observed increase in gonadotropin levels in some infertile men include estradiol resistance, estradiol receptor mutations, or aromatase deficiency, which can lead to increased FSH and LH secretion [37].

The correlation analysis revealed a positive correlation between testosterone, FSH, and LH levels with BMI, particularly in the obese oligoasthenozoospermia group. This result aligned with previous studies suggesting a dose-response relationship between high BMI and subfertility in men [38]. The mechanisms underlying the detrimental effects of obesity on male fertility are likely multifactorial and involve abnormal semen quality, endocrine alterations, sexual dysfunction, and co-morbidities [39]. Increased oxidative stress, decreased mitochondrial activity, and epigenetic changes have been proposed as potential mechanisms by which obesity impairs sperm function [40]. Furthermore, obesity can negatively impact testicular morphology, leading to disrupted germ cell arrangement, reduced sperm production, and thinning of the germinal epithelium [41]. Kim *et al*. demonstrated severe histological damage in the testes of obese mice including reduced seminiferous tubule area and disruption of spermatogenesis [42]. These detrimental changes can impair sperm membrane integrity and motility, ultimately leading to increased numbers of defective sperm. Alves *et al*. highlighted the role of apoptosis, a programmed cell death process, in maintaining normal testicular function and eliminating abnormal sperm. Obesity had been linked to increased apoptosis in the testes, further contributing to sperm dysfunction [43].

One limitation of this study was the relatively small sample size, which warranted further research with larger cohorts. Additionally, the study was cross-sectional, and causal relationships between the investigated parameters could not be established. Future longitudinal studies with detailed clinical evaluations are needed to gain a more comprehensive understanding of the complex interactions between obesity, irisin, and male reproductive health.

Conclusion

The findings of this study suggested that irisin might play a role in spermatogenesis with lower levels observed in obese sub-fertile men with oligoasthenozoospermia. Elevated leptin levels were associated with obesity and potentially contribute to impaired spermatogenesis through suppression of testosterone production. The observed alterations in gonadotropin and testosterone levels in some infertile men might be due to complex feedback mechanisms involving estradiol and its receptors. The positive correlation between BMI and testosterone, FSH, and LH levels in the obese oligoasthenozoospermia group highlighted the detrimental effects of obesity on male reproductive health. Further research is needed to elucidate the precise mechanisms by which irisin and other factors interact to influence spermatogenesis in obese men. Longitudinal studies with larger sample sizes and detailed clinical evaluations are crucial for developing effective therapeutic strategies to improve male fertility in the context of obesity.

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