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# Effect of Body Mass Index (BMI) On the Levels of Spexin Hormone, Growth Hormone, And Leptin Hormone in Some Infertile Women in Mosul City

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**KEYWORDS**
BMI, Obesity, Spexin, Leptin, Growth

**ABSTRACT:**
This study was conducted to determine the extent of the impact of body mass index (BMI) on certain biochemical variables in obese women suffering from infertility. A total of 30 blood samples were collected from women diagnosed with primary and secondary infertility, along with 10 blood samples from healthy women without any fertility issues, serving as the control group. The samples were divided into three groups based on body mass index (BMI): BMI 1 (19-24) kg/m², BMI 2 (25-30) kg/m², and BMI 3 (32) kg/m² or higher. The results of the study, following statistical analysis, demonstrated a significant decrease in the levels of Spexin hormone at a probability level ($P \leq 0.01$) in obese women suffering from infertility. The most noticeable decrease was observed within the BMI 3 group compared to the Control group. Similarly, the results indicated a significant reduction in the concentration of Growth hormone at a probability level ($P \leq 0.01$) in obese women, with the highest decrease seen in the BMI 3 group compared to the Control group. On the other hand, the results showed a significant increase in the concentration of Leptin hormone at a probability level ($P \leq 0.01$) as body mass index (BMI) increased. The highest increase in hormone concentration was observed in the BMI 3 group. These findings clearly demonstrate an inverse relationship between BMI and Spexin hormone, as well as BMI and Growth hormone, while indicating a positive correlation between BMI and Leptin hormone levels in the bodies of obese, infertile women.

## Introduction

One in every ten couples worldwide suffers from infertility issues, as indicated by statistics from the World Health Organization (WHO), which reported that the percentage of infertile women in the world ranges between (10-8) %. Approximately (80 – 50) million individuals face difficulties conceiving and achieving family stability (1) . Infertility is defined as the failure to achieve a successful pregnancy after one year of marriage without using any contraceptive methods. The couple begins to search for the causes of infertility after a year for women under 35 and six months if the woman is over 35 (2). In terms of female infertility, there are two types: primary infertility, which is the inability to conceive at all, and secondary infertility, which is the difficulty in achieving conception after at least one previous pregnancy, whether it ended in a healthy or stillborn baby, miscarriage, followed by the inability to conceive within a year (3). The causes of infertility in females can be attributed to a diverse range of underlying disorders, such as ovulation disorders, damage to the fallopian tubes, cervical disorders (benign tumours and cervical stenosis), and hormonal imbalances. These hormonal disorders include Polycystic Ovary Syndrome (PCOS), Endometriosis, Premature Ovarian Failure (POF), Hypothalamic Dysfunction, Hyperprolactinemia (HP), Uterine Fibroids, and Pelvic Inflammatory Disease. Additionally, obesity is associated with numerous hormonal implications, including Spexin, Leptin, and Resistin (4)(5) . It has been established that the risk of

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infertility among overweight women due to ovulation disorders is approximately 2.7%. However, several studies have shown that obesity negatively impacts fertility in both males and females (6). Spexin hormone, a recently discovered hormone, plays a crucial role in regulating various physiological functions in the body, including digestive system motility, fat storage, obesity, the secretion of luteinising hormone (LH), cardiovascular functions, and many others (7). Studies have confirmed that a significant decrease in Spexin hormone concentration occurs in patients with Polycystic Ovary Syndrome (PCOS) and is inversely related to insulin resistance, BMI, and androgens. This underscores the relationship between Spexin hormone levels in the blood, reduced fertility, increased body mass, and metabolic disorders (8). Studies reveal that growth hormone positively impacts ovarian stimulation during the in vitro fertilisation (IVF) process. Growth hormone stimulates egg quality (9). Additionally, it plays a positive role in the uterine environment by enhancing endometrial receptivity, especially in cases of infertility due to recurrent implantation failure or thin endometrium (10). Research by (11) has also demonstrated these effects. Conversely, the negative impact of growth hormone deficiency or disruption on women with Polycystic Ovary Syndrome (PCOS) has been highlighted. It is crucial to conduct intensive research into the mechanisms linking obesity and infertility to develop treatments. These mechanisms aim to manage and prevent the negative effects of obesity on the reproductive system (12). Indeed, the study by (13) demonstrates that weight loss of more than 10% in overweight, infertile women can reduce the required dose of gonadotropins during in vitro fertilisation (IVF), potentially improving clinical pregnancy rates and increasing live birth rates. This study aims to clarify the impact of Spexin, growth, and leptin hormones on the reproductive function of overweight, infertile women.

**The Aim** is to study the effect of Body Mass Index (BMI) On the Levels of Spexin Hormone, Growth Hormone, And Leptin Hormone in Some Obese Infertile Women in Mosul City.

## Materials and Methods

### Blood Sample Collection

Blood samples were taken from both healthy and infertile women using a sterile syringe from the antecubital vein. This was performed by specialised personnel on days 2-5 of the menstrual cycle after a continuous 12-hour fast to ensure the accuracy and success of the test results. The collected samples were placed into clot activator gel tubes (Gell Tubes) and left for 15 minutes at room temperature or 5 minutes in a water bath. Subsequently, they were centrifuged at 5000 revolutions per minute for 10 minutes in a centrifuge to ensure complete separation of the serum, obtaining a pure serum. The serum was transferred using a sterile micropipette and placed in sterilised Eppendorf tubes. It was stored by freezing at -20 degrees Celsius until the required tests were conducted.

The blood samples were collected from various hospitals in Nineveh Province, including Al-Batoul Teaching Hospital, Al-Salam Teaching Hospital, and Al-Khansa Women's and Maternity Hospital, within the scheduled period. The collection process was carried out under the supervision of specialised gynaecologists and laboratory personnel. The samples were then divided into groups based on the Body Mass Index (BMI), which is calculated using the formula:

$$\textbf{BMI (kg/m}^2\textbf{) = weight (kg) / (height)}^2\textbf{ (m}^2\textbf{)}$$

### Serum hormonal tests

### Determination of Spexin (SPX) Hormone Concentration in Serum

The concentration of Spexin hormone was determined using several ready-made assays manufactured by BT LAB (Bioassay Technology Laboratory). These assays are based on competitive binding analysis using the Enzyme-Linked Immunosorbent Assay (ELISA) technique.

### Determination of Growth Hormone Concentration in Blood Serum

The effective concentration of Growth hormone was determined using several ready-made assays manufactured by DRG International Inc., a U.S.-based company, through the Enzyme-Linked Immunosorbent Assay (ELISA) method. This method relies on a Double-Antibody Sandwich Enzyme immune system.

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**Determination of Leptin Hormone Concentration in Blood Serum**

The effective concentration of Leptin hormone was determined using several ready-made assays of Chinese origin manufactured by BT LAB (Bioassay Technology Laboratory) through the Enzyme-Linked Immunosorbent Assay (ELISA) method. This method is based on a Double-Antibody Sandwich Enzyme immune system.

**Statistical Analysis**

The data analysis was conducted using the Simple Experiments design in the SPSS software, version 16. This analysis aimed to calculate the mean and standard error. A completely random method was employed. Different letters were used to denote significant differences among the variables at the 1% and 5% significance levels based on the Duncan test, a multiple-range test (14).

**Results and Discussion**

Figure 1 illustrates the impact of Body Mass Index (BMI) on the concentration of Spexin hormone. The results show a significant decrease in hormone concentration at a probability level of ($P \leq 0.01$) in the BMI 3 group (127.02 ± 2.9 ng/L) compared to the Control group (431.74 ± 4.9 ng/L). Similarly, the results indicate a significant decrease in the BMI 2 group (217.85 ± 4.1 ng/L) and the BMI 1 group (316.09 ± 3.7 ng/L) compared to the Control group.

The values are expressed as the mean (±) standard deviation, with sample sizes of 10 in each group. Different letters associated with the figures indicate statistically significant differences at a probability level of ($P \leq 0.01$).

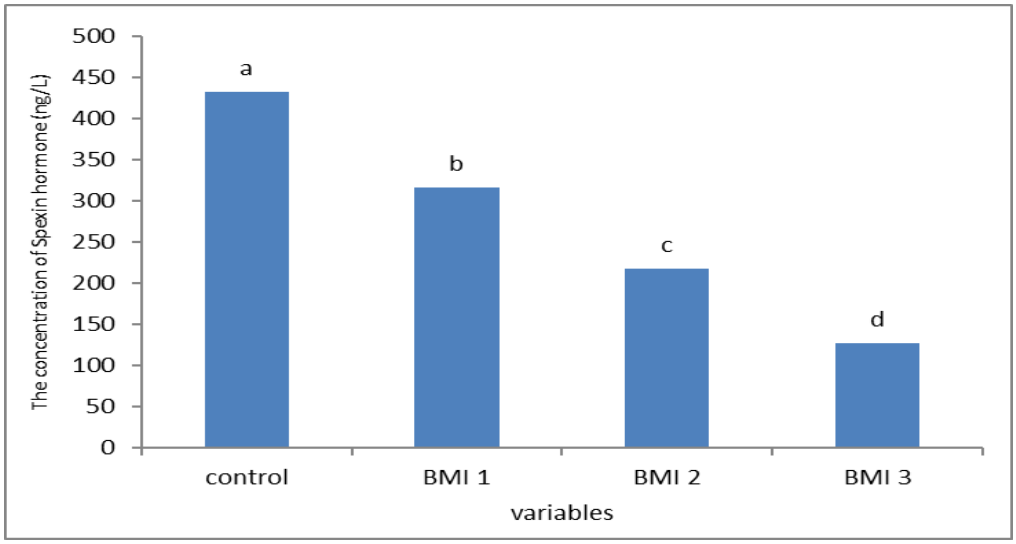


**Figure 1 illustrates the effect of Body Mass Index (BMI) on the concentration of Spexin hormone (ng/L) in the following groups: Control, BMI 1, BMI 2, and BMI 3.**

Upon analysing the results and conducting statistical assessments, a pronounced and statistically significant decrease in Spexin hormone concentration is evident with increasing body mass. This phenomenon underscores the adverse impact of weight gain on Spexin hormone concentration in infertile women when compared to the control group, which represents healthy women with normal weight and high fertility. The reason behind this decline in hormone concentration can be attributed to the inverse correlation between the Spexin hormone and the Leptin hormone. The latter is linked to elevated body mass index (BMI), increased triglycerides (T.G), blood glucose levels, diminished satiety, and reduced expression in adipose cells in obese women (15) (16) (17) . Numerous studies have concurred that the reduction in Spexin hormone

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concentration inhibits the secretion of LH hormone, presenting an additional barrier to female fertility, particularly among overweight women (18) (19).

Salah-Aldeen & Hameed (2023) have indicated the inverse relationship between the Spexin hormone and both body mass index (BMI), insulin resistance, luteinising hormone (LH), testosterone, and prolactin hormones in infertile women suffering from Polycystic Ovary Syndrome (PCOS) (20) . This association suggests the potential role of Spexin in the pathological physiology of the syndrome, making it a promising diagnostic indicator for infertility cases. Additionally, a study conducted by Hussein (2021) affirmed that treatment with Spexin or Metformin improves ovarian and hepatic dysfunctions in PCOS-afflicted mouse models. This improvement was correlated with a significant increase in insulin, low-density lipoprotein (LDL), glucose, total cholesterol (TC), and triglycerides (T.G) levels, along with a decrease in high-density lipoprotein (HDL) and estradiol hormone levels (21) . The reason behind the decrease in Spexin hormone can be attributed to its particular downregulation in adipose tissues, with varying levels in other organs and tissues in obese individuals. Consequently, this leads to disruptions in lipid metabolism and blood glucose balance, especially in patients with Type 2 Diabetes Mellitus (T2DM) and Type 1 Diabetes Mellitus (T1DM) (22)(23)(24).

The results are in agreement with Al-Daghri et al. (2018a), as observed in a study that included both men and women. The study noted a decrease in Spexin hormone levels in the blood of women afflicted with Metabolic Syndrome (MetS), a group of risk factors associated with cardiovascular diseases, vascular conditions, and Type 2 Diabetes, when compared to the Non-MetS group (25).

Moreover (26) discovered that the reduction in Spexin hormone was associated with Metabolic Syndrome (MetS) in women exclusively. This association may be attributed to gender-related differences in glucose metabolism and insulin sensitivity due to the influence of sex steroids. The researchers stressed that the Spexin hormone should be regarded as a vital biomarker for Metabolic Syndrome and its related factors. This underscores the pressing need for further research to elucidate the clinical significance of this hormone and its relationship with Mets. Additionally, multiple studies have confirmed a decline in the hormone's expression in adipocytes and its inverse relationship with the Leptin hormone, which is linked to increased body weight (27)(28)(29). The researchers also emphasised the direct impact of reduced Spexin hormone levels in diminishing the sensation of satiety, considering it the novel peptide responsible for appetite, acting as an appetite suppressant and contributing to weight loss. Spexin plays a pivotal role in regulating feeding behaviour, facilitating the absorption of long-chain fatty acids into adipocytes, energy utilisation, metabolism, and body weight (30)(31).

The study results are consistent with (32)(33). A comparison conducted between overweight children and those with normal weight revealed a significant reduction in Spexin hormone levels among overweight children compared to their counterparts with normal weight. Similarly, a related study in overweight children indicated an inverse relationship between Spexin hormone levels and TG (34). Furthermore, in a study conducted on adipose tissue in obese individuals, researchers affirmed that the decline in Spexin hormone concentration might be attributed to genetic factors related to decreased gene expression of the hormone in adipose tissues of overweight individuals compared to those with normal weight (15). In a study conducted on severely obese adolescents, serum Spexin hormone levels were inversely associated with Leptin hormone (35). Additionally,(18) indicated that Spexin levels were negatively correlated with body mass index (BMI), fasting glucose, and age, suggesting the potential role of this peptide in functions and age-related disorders.

Other studies have highlighted the role of the Spexin hormone in various physiological functions due to its widespread presence in both central and peripheral tissues of many living organisms, including mammals and non-mammals. It plays a role in the pathophysiology of the reproductive system, digestive system, cardiovascular system, endocrine glands, and particularly in food intake and energy metabolism, including carbohydrates and fats (36).

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Figure 2 illustrates the effect of Body Mass Index (BMI) on the concentration of the growth hormone. The results clearly indicate a significant decrease in hormone concentration at a probability level of $P \leq 0.01$ in the BMI 3 group (0.44 ± 0.09 ng/ml) compared to the Control group (2.92 ± 0.04 ng/ml). Furthermore, the results show a significant decrease in hormone concentration in the BMI 2 group (0.71 ± 0.01 ng/ml), followed by the BMI 1 group (1.35 ± 0.06 ng/ml) in comparison to the Control group.

The values are expressed as the mean (±) standard deviation, and the sample size is 10. Different letters associated with figures indicate statistically significant differences at a significance level of $p \leq 0.01$.

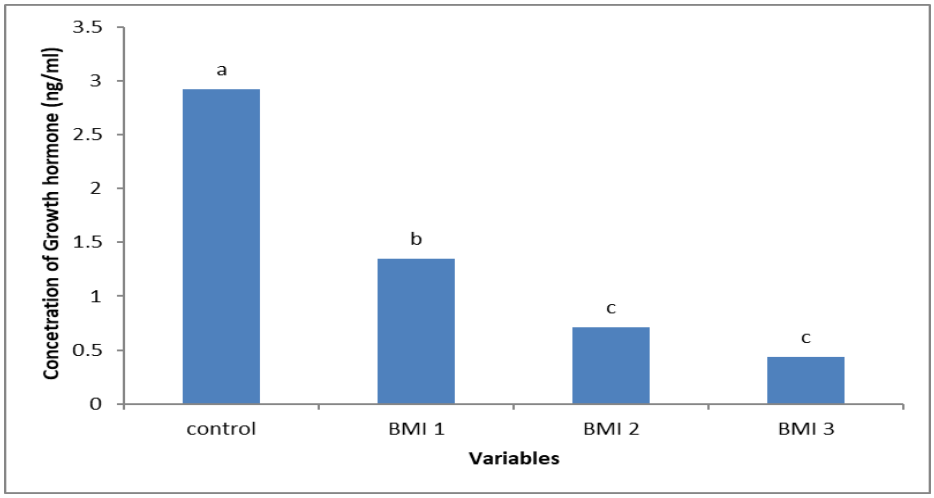


**Figure 2 illustrates the impact of the body mass index (BMI) on the concentration of growth hormone (ng/ml) in the Control, BMI 1, BMI 2, and BMI 3 groups.**

The results demonstrate the relationship between body mass and the concentration of growth hormone in the studied groups of women with infertility who are overweight compared to women of normal weight. After statistical analysis, a significant decrease in the concentration of growth hormone within the overweight groups of women with fertility issues was observed compared to the control group. The reason for the decrease in hormone concentration is attributed to the increase in the number of fat cells, which indirectly leads to the suppression of growth hormone secretion by elevating somatostatin levels through leptin. The increase in BMI in women with infertility affected by PCOS is often associated with insulin resistance (37). This is the condition in which the body's cells become less responsive to insulin, and insulin and IR can interact with GH production. Elevated insulin levels are associated with decreased growth hormone and lead to an increase in fat mass (38). The results are consistent with (39) , who emphasised that the cause of the decrease in hormone concentration is related to obesity in women with what is known as leptin resistance, which is secreted from fat cells and helps regulate appetite and metabolism. In cases of extreme obesity, leptin resistance develops, weakening the natural feedback control of growth hormone production and secretion.

Studies have confirmed that overweight women experience sleep disturbances such as sleep apnea, a serious syndrome associated with extreme obesity. Sleep apnea causes hormonal disturbances and affects the GH/IGF-1 axis, leading to decreased production and secretion of growth hormone from the pituitary gland (40) (41). Additionally, the results align with studies that have noted a decrease in growth hormone concentration with increased body mass in short-statured children and in adults who are overweight due to elevated levels of free fatty acids (FFA). FFA can inhibit the secretion of growth hormone. This

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phenomenon has also been observed in older adults who are overweight (42) (43) (44). The decrease in growth hormone (GH) is associated with insulin-like growth factor 1 (IGF-1), which is linked to elevated blood insulin, increased blood glucose, elevated triglycerides, and increased insulin resistance. This condition can lead to higher levels of glucose and unesterified fatty acids in the blood, possibly due to increased dietary intake and white adipose tissue availability, along with muscle insulin resistance (IR). Another study has shown that treatment with growth hormone supplements in patients with growth hormone deficiency stimulates continuous fat breakdown and a gradual reduction in fat mass towards normal levels (45).

Figure 3 illustrates the impact of body mass index (BMI) on leptin hormone concentration. The results reveal a significant increase in hormone concentration at a probability level of ( $P \leq 0.01$) in BMI group 3 (19.9 ± 1.6 ng/ml) compared to the Control group (5.6 ± 1.0 ng/ml). Additionally, the results also indicate a significant increase in hormone concentration in BMI group 2 (15.8 ± 0.3 ng/ml) and BMI group 1 (8.4 ± 0.3 ng/ml) compared to the Control group.

The values are expressed as the mean (±) standard deviation, and the sample size is 10. Different letters associated with figures indicate statistically significant differences at a significance level of $p \leq 0.01$.

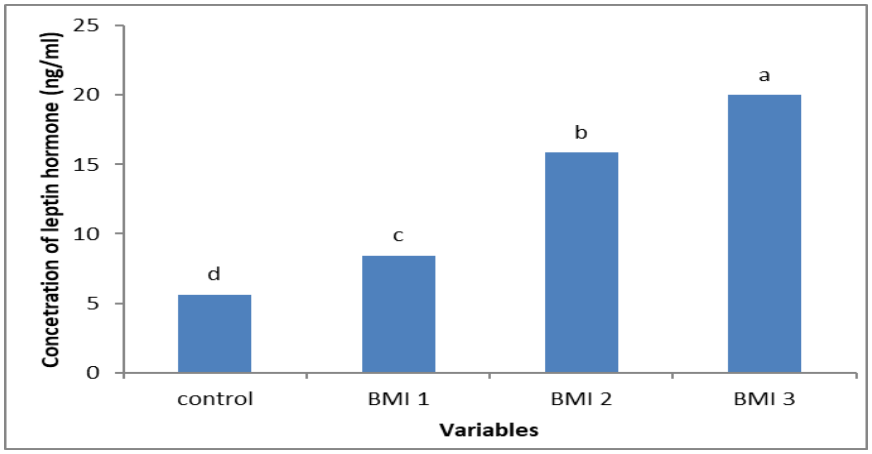


**Figure 3 illustrates the effect of body mass index (BMI) on leptin hormone concentration (ng/ml) in the Control, BMI 1, BMI 3, and BMI 2 groups.**

The results also indicate a positive relationship between leptin hormone concentration and body mass. The data shows a statistically significant increase in hormone concentration as body mass increases in the studied groups of women suffering from infertility and increased weight compared to the control group. This increase may be attributed to the role of leptin in the significant increase in the overall sympathetic nervous activity, which seems to be a result of the direct effects of sub-threshold, mediated by neuropeptides such as the Melanocortin System and the Corticotrophin-releasing Hormone. The maintenance of sympathetic activation by leptin hormone is achieved in the presence of obesity, which ultimately leads to leptin resistance, similar to insulin resistance (46). Additionally, the increased secretion of the leptin hormone in humans is associated with its inverse relationship with the hormone Somatostatin due to its direct impact on adipocytes (47). Studies have also confirmed an inverse relationship between growth hormone deficiency and elevated levels of leptin in adults with pituitary dysfunction and even in normal individuals, though the mechanism behind this relationship has not been fully elucidated (48). Leptin is considered the major mediator between a woman's nutritional status and reproductive health, as confirmed by a study involving women with Polycystic Ovary Syndrome (PCOS) and obesity. The study observed that leptin levels increased with higher

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body mass and elevated hormone levels in the blood serum were associated with an increased risk of developing PCOS. This is due to significant disruption of the Hypothalamus-Pituitary-Ovarian (H-P-O) axis in obese infertile women compared to women with normal weight. This disruption affects gonadotropin hormones, leading to reduced levels of Sex Hormone-Binding Globulin (SHBG), growth hormone, and insulin-like growth factor binding proteins (IGFBP) (49) (50). In another study involving women with Polycystic Ovary Syndrome (PCOS) and unexplained infertility, the results revealed a link between elevated leptin levels in the bloodstream and a chronic decrease in the regulation of leptin receptors (LEPR) in overweight women's brains. This elevation of leptin levels in relation to body mass index (BMI) may explain reduced pregnancy rates in women using in vitro fertilisation (IVF). These findings are consistent with studies conducted on a large group of overweight women in Denmark who had elevated leptin levels and experienced fertility problems, taking longer to achieve pregnancy. This confirms the inverse relationship between increased BMI and fertility. Furthermore, the results align with research conducted by (51) , which established a positive correlation between leptin hormone and increased BMI, considering this hormone a strong and accurate indicator of fertility in infertile women.

The study results are consistent with research conducted by (12), which explored the relationship between infertility and obesity and the likelihood of the pathophysiology of infertility in overweight men and women. The study demonstrated a positive correlation between elevated leptin levels and increased body weight in both genders. This relationship can be attributed to the excessive aromatisation of androgens to form estrogen, leading to higher androgen levels in the blood due to insulin resistance, hyperinsulinemia, and disruptions in the hypothalamic-pituitary-gonadal axis. These factors, coupled with reduced growth hormone and sex hormone-binding globulin and increased leptin secretion from adipocytes, collectively impede implantation and reduce pregnancy chances in overweight women.

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