International Journal of Biological and Pharmaceutical Sciences Archive

ISSN: 0799-6616 (Online)

Journal homepage: https://ijbpsa.com/

(RESEARCH ARTICLE)

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MULTI-HORMONAL DYSREGULATION IN OBESITY: ASSOCIATIONS WITH INSULIN RESISTANCE AND METABOLIC RISK MARKERS

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International Journal of Biological and Pharmaceutical Sciences Archive, 2026, 12(01), 118–130

Publication history: Received on 14 July 2026; revised on 20 August 2026; accepted on 22 August 2026

Article DOI: https://doi.org/10.53771/ijbpsa.2026.12.1.0078

ABSTRACT

This study systematically evaluated the profiles of ten key endocrine, adipokine, and metabolic hormones across individuals with obesity and healthy controls to determine if obesity-induced metabolic stress overrides baseline variations governed by biological sex, age, as well as the 3-way interaction of age x gender x health status. Serum concentrations of ten hormones (insulin, IGF-1, resistin, adiponectin, leptin, cortisol, Ghrelin, TSH, T3, and T4) were quantified. Statistical analysis was performed using a three-way analysis of variance followed by multiple pairwise comparisons. The three-way ANOVA revealed that obesity was the dominant factor driving systemic endocrine dysregulation. Obesity explained the vast majority of total variance in insulin (91.91%), leptin (91.91%), TSH (91.73%), ghrelin (90.89%), adiponectin (88.65%), resistin (81.04%), cortisol (80.13%), and T3 (72.57%) ($p < 0.0001$). Multiple comparisons confirmed significant elevations in circulating insulin, leptin, resistin, cortisol, and TSH, alongside marked reductions in adiponectin and ghrelin across all obese subgroups ($p < 0.0001$). Conversely, IGF-1 variation was predominantly driven by age (33.30%, $p < 0.0001$), while T4 showed a lower variance explained by obesity (57.31%). Crucially, biological sex and demographic interaction terms failed to reach statistical significance across the majority of the master metabolic hormones ($p > 0.05$). Advanced obesity functions as a universal endocrine equalizer, leading to significant metabolic syndrome and peripheral thyroid hormone resistance. Metabolic and inflammatory stress caused by excessive adiposity can surpass normal physiological variations related to age and gender. Consequently, therapeutic approaches should address the underlying mechanisms of adipose tissue dysfunction rather than relying on management strategies.

Keywords: Three-Way ANOVA; Obesity; Adipokines; Endocrine Dysregulation; Metabolic Syndrome

1 INTRODUCTION

Fast food recipes have become an inseparable part of our daily lives, and a significant portion of the population is currently suffering from obesity due to various factors, including economic reasons and recent developments in our country [1]. Most diseases that affect humans may have weight gain as a secondary cause because adipose tissue enlarges in many organs of the body where fat should not be present [2]. Because of people's ignorance of their culture and the detrimental habits they've picked up over the years, fats are divided into gel tubes, which will provide serum

for analyzing all hormones except for ghrelin to determine if they are harmful and beneficial. This ignorance has led people to consume large amounts of food of unknown hygiene and source, under the mistaken belief that it is healthy. Therefore, the environment around us affects our body and is the leading cause of weight gain and body imbalance. Recent developments in our country have led to physical and physiological changes in our bodies due to a lack of movement and an increased reliance on food from outside our homes. Thus, saturated and unsaturated fats build up in our organs, which further enhances the problem, and then we show symptoms of certain diseases like hypertension, arthritis, obesity, and glands not functioning properly [3]. Eating certain fast foods from unknown sources causes microbial masses to gather in our digestive tract, which can lead to reduced immunity and the development of various diseases [4]. Within the composition of adipose cells in our body, there are also substances known as "adipokines," which help with certain functions such as metabolism and the production of steroid hormones. When your adipocytes enlarge, the increase in these hormones will cause a hormonal imbalance in your body. For instance, pancreatic cells are significantly affected when certain fats in the blood increase, leading to an inability to secrete insulin, which is essential for regulating blood sugar levels. Therefore, the body will then develop the disease type 2 diabetes mellitus [6].

The aim of this study was to systematically review and compare the metabolic, adipokine, and endocrine profiles of 10 key hormones between individuals with obesity and healthy controls while considering the possible regulatory effect and interactions of biological sex and chronological age.

2 MATERIALS AND METHODS

2.1 Study population

Sixty Iraqi patients were chosen from the beginning of 2026, which included thirty healthy cases and thirty obese ones. Both patients and healthy controls were categorized into males and females, with each gender comprising fifteen patients and fifteen healthy controls. All participants were aged between 18 and 60 years old, diagnosed with obesity using the body mass index (BMI), and had signed the consent form to join the study. Exclusion criteria were applied to rule out cases with pre-existing thyroid problems, chronic severe diseases, or cancerous tumors [7]. Pregnancy or the use of medication containing hormones that might interfere with the results of our study were also exclusion criteria.

2.2 Classification of cases based on age.

All cases were categorized into three main groups according to their age as shown in table 1.

2.3 Calculation of BMI.

BMI was calculated as follows: BMI= Weight (kg)/ Height $(m)^2$

2.4 Collection of blood samples.

Approximately five milliliters of blood from a vein were collected from all samples, whether patients or healthy controls, in the morning because some tests require fasting for at least 8 hours. The samples were separated into two 4 ml aliquots and placed in the freezer until we completed the required number of gel tubes, which will provide serum for analyzing all hormones except for ghrelin gel tubes, which will give us serum that will be used to analyze all hormones except for the ghrelin hormone. The samples were placed in the freezer until we completed the requirement of 1 ml in an EDTA test for ghrelin hormone levels. Following this process, the serum will be put into white tubes, which will be placed in the freezer until we complete the required number of samples. All hormone measurements were done using an ELISA device except thyroid hormones and cortisol. For these two hormones, their measurement was done using Mini VIDAS (bioMérieux, France), which is based on enzyme-linked fluorescent assay (ELFA) technology. The tests were done in accordance with the manufacturer' instructions. The main idea behind using both devices is that they allow the hormone to interact with certain antibodies and then release a light signal that will be measured by the device used [8]. Every laboratory investigation was done at Alpha-Private Laboratory, located in Al-Anbar province, in accordance with routine quality assessment to ensure that the results are accurate. The difference between testing these ten hormones we chose for our study is the units in which they are measured. After correlating all the measurements with the devices we mentioned above, tables were created specifically for each hormone to make statistical analysis easier [9]. The program used detects if there is any difference between groups in the studied parameters and is called GraphPad Prism. Data were shown as mean ± standard error (SE). A three-way ANOVA followed by multiple comparisons was used to analyze differences between groups. P-values were reported as follows:

- $P < 0.05$: was considered statistically significant.
- $P < 0.01$: was considered highly statistically significant.
- $P < 0.001$: was considered very highly statistically significant.
- $P < 0.0001$: was considered extremely statistically significant.

Table 1: Division of sample study according to Gender and Age in healthy and patient groups

Factor		Healthy/ control No. (%)	Patients/ Obese No. (%)	P-value
Gender	Female	15 (50.00%)	15 (50.00%)	1.00 NS
	Male	15 (50.00%)	15 (50.00%)	
Age groups (year)	<18-30 yr.	10 (33.33%)	10 (33.33%)	1.00 NS
	31-45 yr.	10 (33.33%)	10 (33.33%)	
	>46-60 yr.	10 (33.33%)	10 (33.33%)	
	Means ±SE	37.86 ±2.47	39.03 ±2.32	0.7321 NS
Total No.		30	30	---
NS: Non-Significant.				

3 RESULTS AND DISCUSSION

To test the effects of age, gender, and health status on serum insulin levels, a three-way between-subject ANOVA was performed. The analysis showed the health status had a robust and very significant main effect, which explained 91.91% of the total variation ($p < 0.05$). The complete set of ANOVA parameters is summarized in Table 2. The initial multiple comparisons indicate that serum insulin concentrations were significantly higher in obese patients from each of the groups compared to their healthy controls. Importantly, the very high increases ($p < 0.0001$) were noted for patient males compared with control males as well as for patient females compared with control females among all 3 separate age groups: 18–30, 31–45, and 46–60 years as shown in Figure 1.

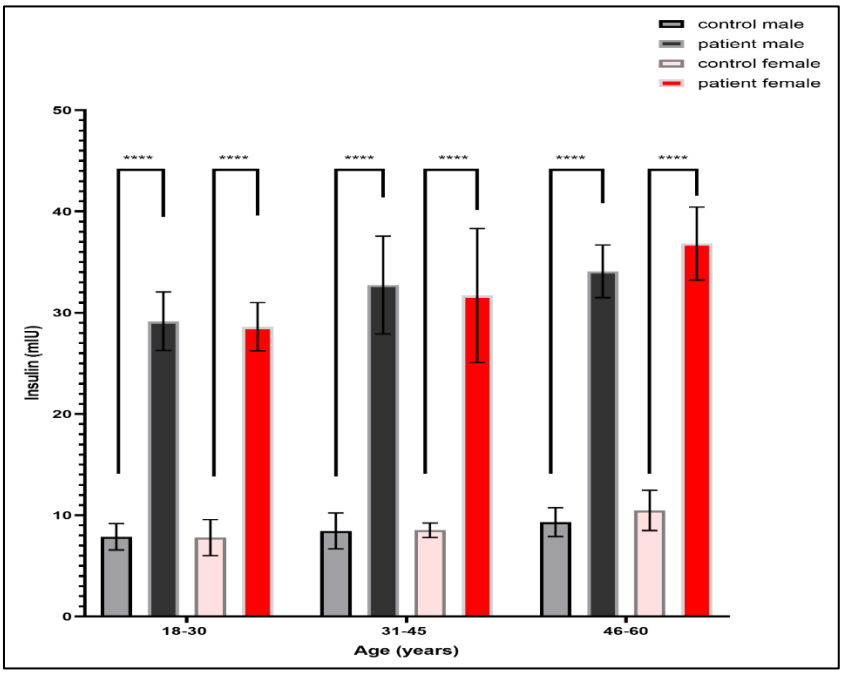

Figure 1: Serum insulin levels across different age, gender, and health status groups

From a physiological perspective, the exaggerated increase in serum insulin concentration seen in obese groups is due to the onset of extreme whole-body insulin resistance, one of many metabolic derangements caused by morbid adiposity [9]. Obesity causes an increase in fatty-acid circulation and causes systemic low-grade inflammation [10]. This inflammation inhibits post-receptor insulin signaling through inflammatory kinase activation [9, 11]. To compensate for this stress on insulin signaling, pancreatic beta cells increase basal insulin secretion, leading to severe hyperinsulinemia [11].

A complete lack of statistical significance of the gender effect and both interaction terms ($p > 0.05$) confirms that severe metabolic stress/disturbance and down-regulation of key metabolic pathways provoked by morbid obesity blunt/bypass much more subtle physiologic differences seen in normal individuals that are determined by

sex/biological gender or age group. Therefore, these data further confirm what is currently accepted as fact: morbid obesity serves to level the metabolic "playing field" between different population subsets [12]. Serum levels of IGF-1 were then assessed by three-way ANOVA for significance of main effects and interactions with regard to age, gender, and health (normal vs. obese). A significant and substantial main effect for age was observed (33.30% of variance, $p < 0.0001$) as well as a small but significant main effect for health status (4.795% of variance, $p = 0.0398$). For the interaction terms, only the two-way Gender × Health interaction was statistically significant (4.368%, $p = 0.0493$). The main effect for gender as well as the two-way interactions for age × gender and age × health and the three-way interaction for age × gender × health were all not significant ($p > 0.05$). See Table 2 for full ANOVA parameters. Post hoc multiple comparisons demonstrated that although overall differences between the groups were mild, there were no statistically significant differences ($p > 0.05$) when directly comparing obese patients to their respective healthy controls within any given age category (ages 18–30, 31–45, and 46–60 y). Figure 2.

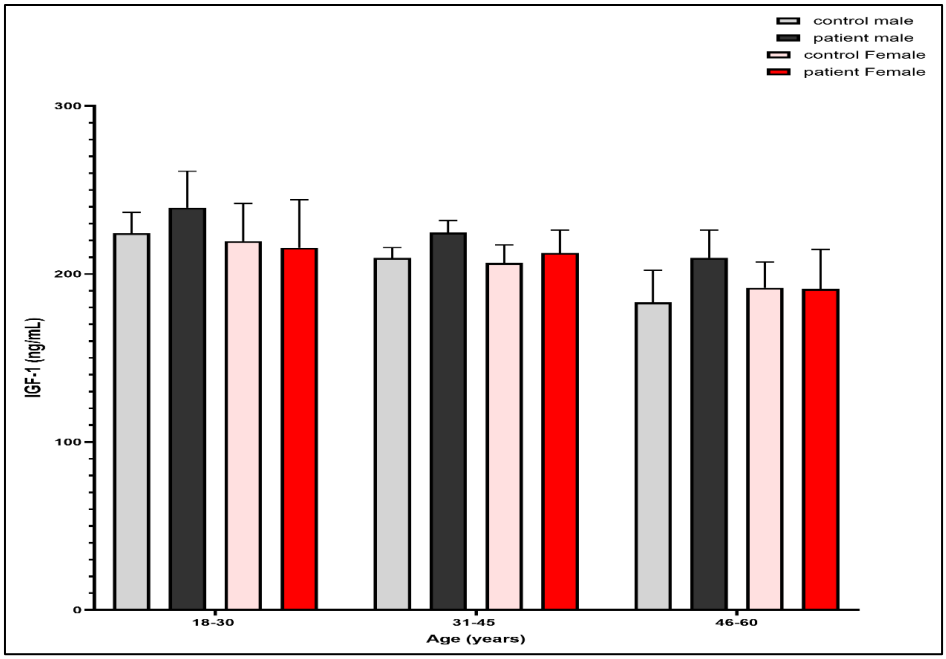

Figure 2: Serum IGF-1 levels across different age, gender, and health status groups

The IGF-1 profile was distinct from that of the other measured adipokines in that chronological age was the primary source of variance rather than health status or sex. Physiologically, the observed precipitous drop in IGF-1 levels between age groups can be attributed to somatopause: an age-related decrement in the amplitude and frequency of GH pulsatile release from the anterior pituitary, which negatively regulates hepatic IGF-1 production [13].

Perhaps surprisingly, the relative paucity of robust pairwise differences between patient groups and their healthy controls may indicate that obesity's effect on total IGF-1 can be quite heterogeneous. Although severe accumulation of visceral adipose tissue typically suppresses GH production and alters IGFBP expression, consequential hyperinsulinemia directly induces hepatic IGF-1 production by up-regulating liver GH receptors [14]. This phenomenon may blunt obesity's otherwise inhibitory downstream effects on total IGF-1 output, creating only a mild main effect of health status that borders on insignificance and instead driving only an overall baseline shift rather than drastic pairwise dysregulation between each age, as well as the 3-way interaction of age x gender x health status group. A statistically significant main effect of health status was seen in resistin levels, with serum obtained from patients exhibiting dramatically higher amounts than healthy controls. Three-way ANOVA showed that health status was the source of 81.04% of the variation ($p < 0.0001$), while the main effects of age group and sex, as well as all 2-way and 3-way interaction effects, were not ($p < 0.0001$). Although age had a statistically significant main effect on resistin levels, it explained a very small amount of variance (2.260%) ($P = 0.0381$). Gender had no significant main effect on resistin levels, and neither did any of the two-way or three-way interactions ($P>0.05$). Table 2 shows parameters of the resistin ANOVA. "Parameters of Serum Resistin ANOVA.

Supporting this, multiple comparisons revealed a clear trend of significantly increased serum resistin concentrations in all patients when compared to their appropriate healthy controls. Patient males exhibited highly significant ($p < 0.0001$) increases over control males, and patient females exhibited highly significant ($p < 0.0001$) increases over control females in each of the three age groups: 18–30, 31–45, and 46–60 years. Figure 3.

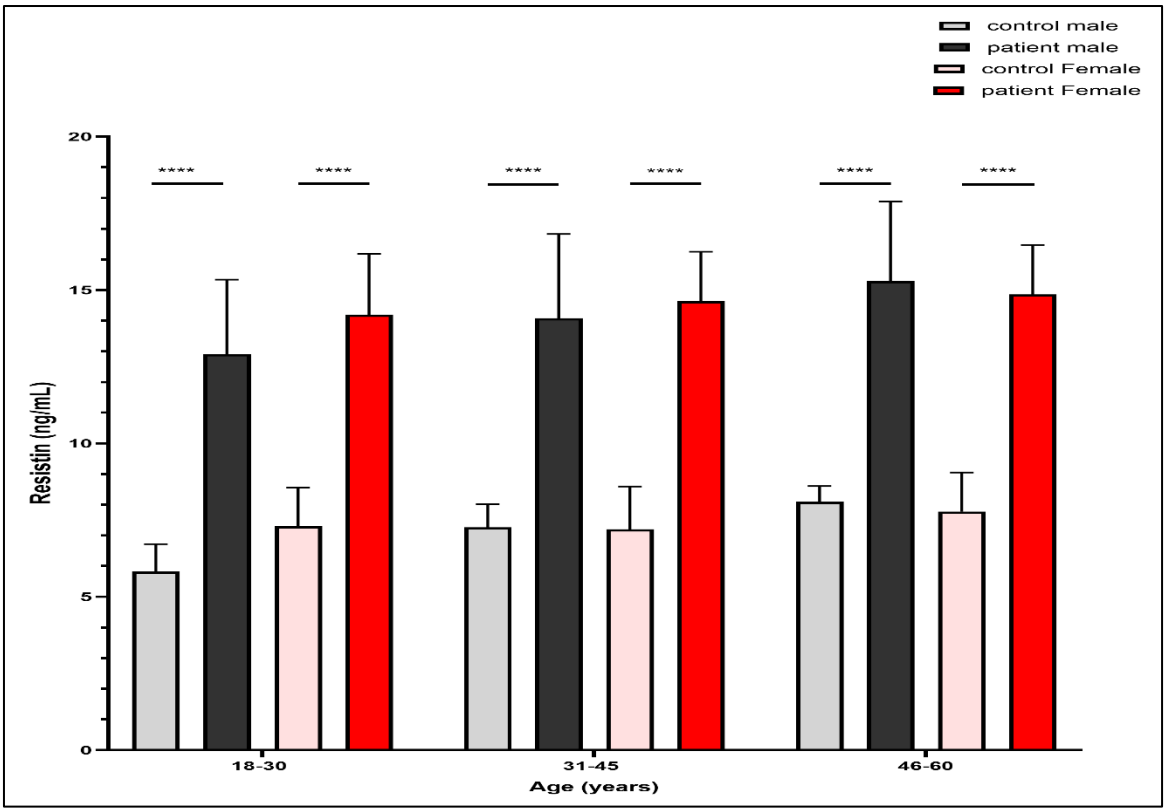

Figure 3: Serum resistin levels across different age, gender, and health status groups

Resistin provides a direct connection between obesity, systemic insulin resistance, and cardiovascular risk [15]. Resistin secretion in humans occurs primarily from infiltrating monocytes and macrophages within hypertrophic visceral adipose tissue, not from adipocytes themselves [16]. The significant elevation we observed circulating resistin across our entire obese group represents this chronic innate inflammatory response to increased adiposity. Expansion of adipose promotes infiltration of pro-inflammatory M1 macrophages that vigorously release resistin into circulation [15, 16].

Persistent elevation of resistin also directly contributes to inhibition of glucose transport into skeletal muscle and liver as previously described [9, 16]. Although age had a slight significant effect on baseline resistin levels, no interactions were significant, leading me to conclude that once macrophage infiltration occurs in obesity, a similar pathophysiology occurs despite minor age or gender baseline differences. Next, a three-way ANOVA was performed to evaluate the influence of age groups, gender, and health status on serum adiponectin levels. The analysis showed a very large and highly significant main effect due to health status, which explained 88.65% of the total variance ($p < 0.0001$). The main effect due to gender was statistically significant but small, accounting for 0.8735% of the total variance ($p = 0.0114$). With respect to the interaction between variables, all three 2-way interactions were statistically significant. These included Gender x Health status (1.909%, $p = 0.0003$), Age x Health status (1.034%, $p = 0.0228$), and Age x Gender (0.8789%, $p = 0.0388$). The main effect due to age as well as the 3-way interaction of age x gender x health status was not significant ($p > 0.05$). Table 2 describes these ANOVA parameters.

Multiple comparisons further validated these results, showing a significant decrease in serum adiponectin from obese patients when compared to healthy controls within each group. Specifically, there was a highly significant decrease ($p < 0.0001$) in patient males when compared to control males AND patient females when compared to control females within all age groups (18–30, 31–45, and 46–60 years). Figure 4.

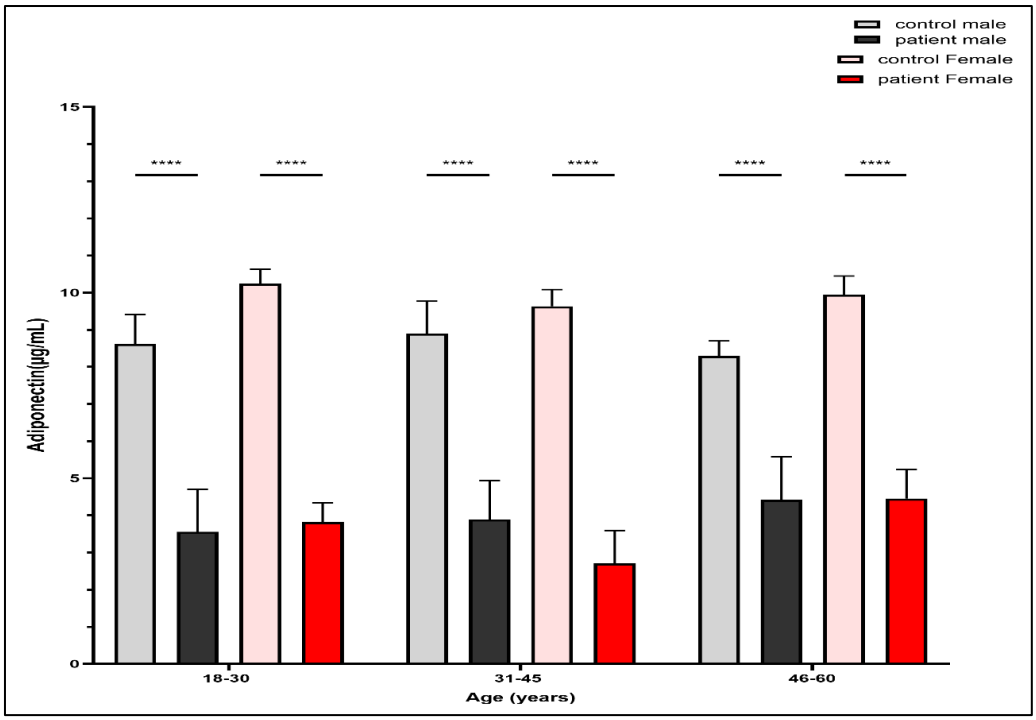

Figure 4: Serum adiponectin levels across different age, gender, and health status groups

Adiponectin is unique from most other adipokines due to its paradoxical down-regulation observed in obesity [17]. In a healthy metabolic state, adiponectin is a strong anti-inflammatory, anti-atherogenic, and insulin-sensitizing hormone [18]. In our patients, the dramatic decrease in circulating levels of adiponectin is a result of visceral adipocyte dysfunction and hypertrophic stress. Due to hypoxia and oxidative stress that occurs locally within enlarged adipocytes of obesity, there is a resulting increase in pro-inflammatory cytokines (TNF-alpha and IL-6), which actively inhibit adiponectin gene transcription and subsequent secretion. While the small but significant main effect of gender and presence of multi-directional two-way interactions suggests that sex hormones (especially testosterone, which has been shown to have inhibitory effects on adiponectin) and age-related body fat distribution have secondary roles in the regulation of baseline adiponectin secretion [18], the overwhelming influence of health status (88.65%) implies that once pathological conditions of obesity are present, the unhealthy microenvironment is what ultimately drives the extreme hypoadiponectinemia observed across all populations, promoting insulin resistance and metabolic CAD.

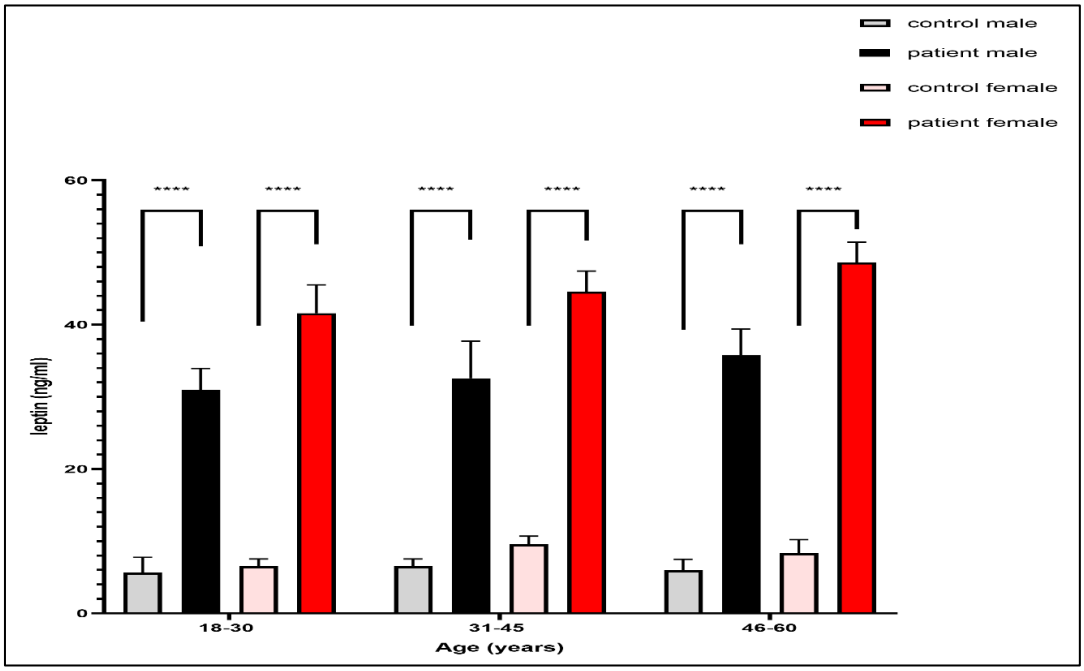

Figure 5: Serum leptin levels across different age, gender, and health status groups

Leptin was also analyzed using a three-way ANOVA to test for main effects and interactions based on age, gender, and health status. There was a profound main effect of health status on serum leptin levels that was highly significant ($p < 0.0001$), accounting for 91.91% of total variance. A significant main effect of age was observed but had a minimal effect size, only accounting for 2.084% of total variance ($p = 0.0003$). A main effect of gender was not observed ($p > 0.05$). No two-way interactions or three-way interactions were significant ($p > 0.05$). Table 2 shows the parameters of the ANOVA. Multiple comparisons further confirmed these results. In each group, obese patients' serum leptin levels were significantly higher than their respective healthy controls'. Leptin was significantly higher ($p < 0.0001$) in patient males when compared to control males AND patient females when compared to control females within all age groups (18-30, 31-45, and 46-60 years). Figure 5.

The collective up-regulation of circulating leptin amongst all obese subjects can be directly attributed to leptin resistance [19]. Secreted by white adipocytes proportional to total-body adiposity, leptin typically acts to feedback negatively to the hypothalamus, inhibiting hunger and promoting thermogenesis [20]. Constantly high leptin levels associated with obesity cause adaptations in the form of down-regulation and saturation of blood-brain barrier transporters and leptin receptors (Ob-Rb) in the CNS. In doing so, leptin receptor desensitivity inhibits the audiovisual signaling cascade causing further hyperphagia and fat deposition. As was seen with insulin, biological sex and age group being statistically insignificant indicates that the severity of adiposity expansion in obesity has an independent and equal effect on endocrine dysfunction, hindering normal hormone function in all age and sex groups studied. The serum cortisol levels were then evaluated based on age, gender, and health condition using three-way ANOVA. There was a significant and strong main effect for health condition, which contributed 80.13% of the total variance ($p < 0.0001$). There were also significant main effects for age (7.235%, $p < 0.0001$) and gender (2.244%, $p = 0.0005$). In terms of interaction effects, there was a significant interaction between gender and healthy status (1.170%, $p = 0.0100$). The age x gender interaction and age x healthy status interaction were not significant. ($p > 0.05$). As well as the three-way interaction between Age x Gender x Healthy status ($p > 0.05$). See Table 2 for ANOVA values. Once again, when looking at multiple comparisons, there was a significant increase in serum cortisol levels in all obese patients when compared to their respective control group within the same sex. Specifically, there was a highly significant increase ($p < 0.0001$) in patient males when compared to control males and patient females when compared to control females in each of the three age groups: 18–30, 31–45, and 46–60 years. Figure 6.

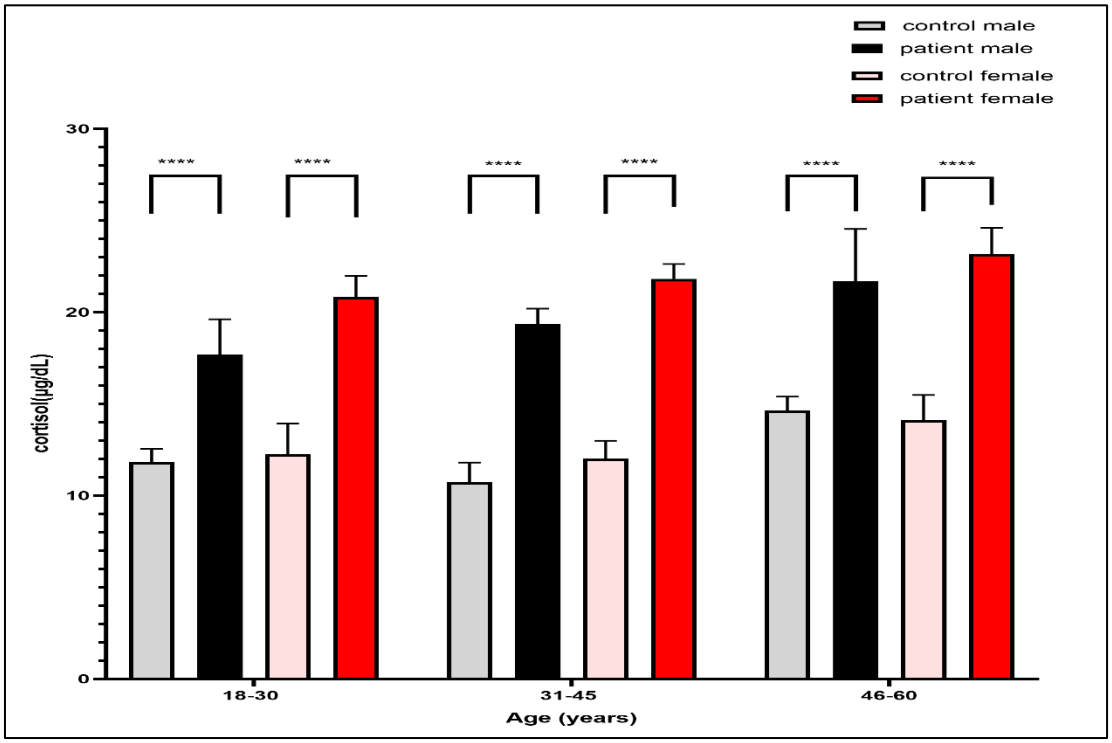

Figure 6: Serum cortisol levels across different age, gender, and health status groups

The increase seen in serum cortisol levels among our obese patients is indicative of hyperactivity of the hypothalamus-pituitary-adrenal (HPA) axis related to obesity [21]. Total cortisol levels may be relatively normal or even lower than normal in obesity due to increased clearance of cortisol from circulation; however, metabolic syndrome and visceral obesity have been linked to increased tissue cortisol activity. This effect appears to be dependent on increased expression of 11beta-hydroxysteroid dehydrogenase type 1 (11b-HSD1) in mesenteric fat. 11b-HSD1 is the enzyme responsible for reconverting inactive cortisone into active cortisol, locally within adipose tissue (an important driver of

further visceral accumulation of cortisol). The highly significant main effect we observed for age groups and sex, as well as a significant sex × health status interaction, likely relates to the normal age-dependent variation in HPA axis regulation (alterations in central sensitivity to feedback inhibition) and the effect of sex hormones on HPA axis hyperactivity (estrogen is known to increase cortisol binding globulin levels, whereas testosterone inhibits HPA axis activity) [22]. However, despite these secondary effects, the overriding significance of health status as a determinant of serum cortisol levels suggests that the metabolic inflammatory state associated with obesity is the major factor contributing to HPA axis overactivity in these patients. Serum ghrelin levels were also assessed using a three-way ANOVA. Once again we saw a very strong and significant main effect for health status, which accounted for 90.89% of total variance ($p < 0.0001$). A smaller but still significant main effect for age was also observed, which accounted for 1.737% of total variance ($p = 0.0015$). In terms of interaction effects, only the two-way interaction between Age × Sex was significant (1.099%, $P = 0.0133$). The main effect for sex and both two-way interactions between age × healthy status and sex × healthy status as well as the three-way interaction were all nonsignificant ($P > 0.05$). Parameters of the ANOVA are depicted in Table 2.

However, when we performed multiple comparisons, we saw data that confirms our initial results. In each of the groups studied, serum ghrelin was significantly lower in patients when compared to healthy controls. We see highly significant decreases ($P < 0.0001$) in males of the patient group when compared to male controls and females of the patient group when compared to female controls within all age groups (18–30, 31–45, 46–60 years). Figure 7.

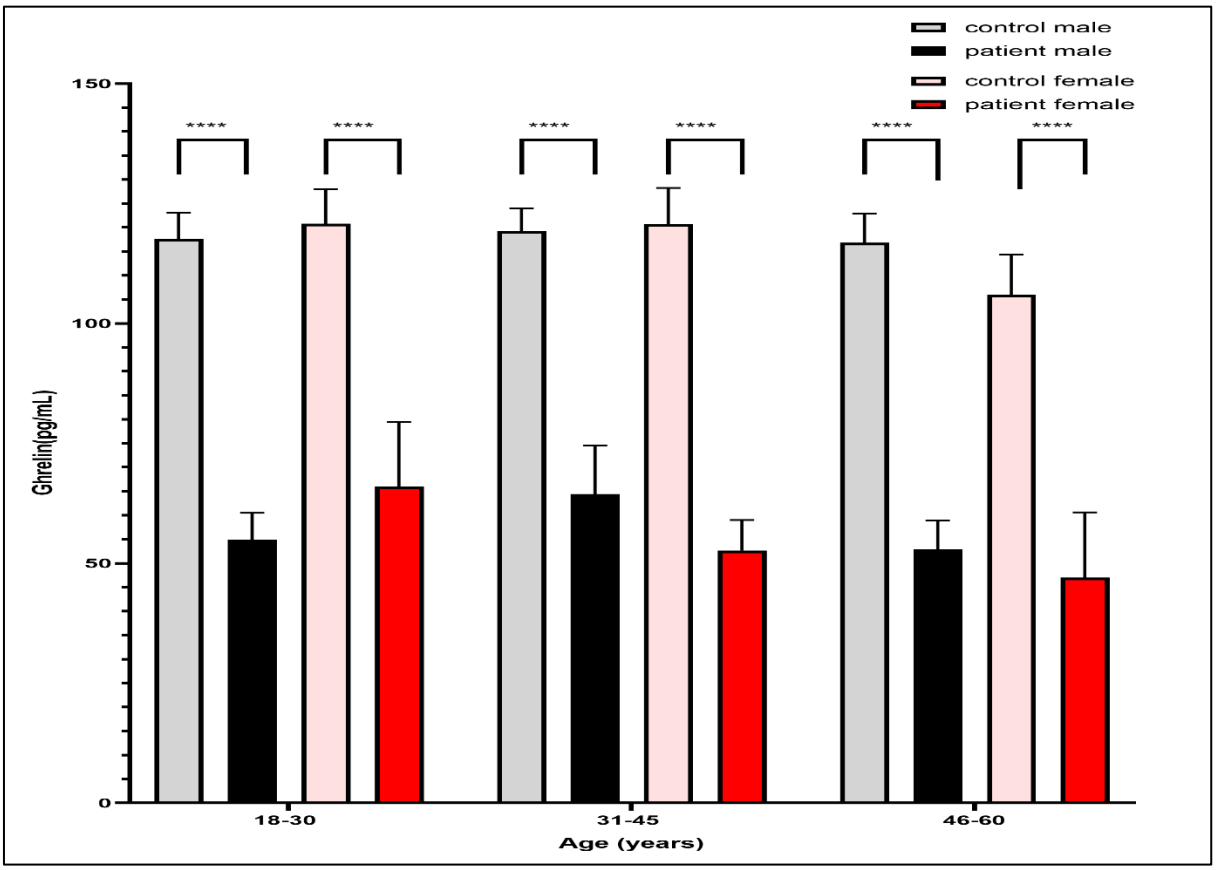

Figure 7: Serum ghrelin levels across different age, gender, and health status groups

Serum ghrelin concentrations were significantly down-regulated in every patient group. This observation can be expected as a physiological response to prolonged positive energy balance [23]. Ghrelin is produced mainly by the oxyntic gastric mucosa and is an orexigenic hormone that reaches its peak during fasting and diminishes after feeding [24]. Overnutrition causes persistently high amounts of nutrients to be delivered to the gastric mucosa, as well as high serum concentrations of insulin and leptin. Both of these factors strongly inhibit baseline synthesis and release of ghrelin in obese individuals [25].

The overall age factor had a small main effect, and age × gender had a small interaction effect, which can most probably be attributed to age-associated gastric mucosal adaptation and gender-associated (sex hormone-associated) differences in body fat distribution. However, health status as the overwhelming predictor (90.89%) signifies that redundant fat masses extensively inhibit gastric secretion to physiologically decrease food intake [24]. Figure 7 depicts serum TSH concentrations grouped according to health status, age group, and gender.

ANOVA was performed for age group (factor 1), gender (factor 2), and health status (factor 3) as main effects on serum TSH concentrations. A highly significant and overwhelming main effect of factor 3 (health status) was found to be the only statistical predictor for serum TSH concentrations, which amounted to 91.73% of the total variance ($p < 0.0001$). Main effects of factors 1 (age group) and 2 (gender) as well as all two-way and three-way interaction effects did not reach statistical significance ($p > 0.05$). Parameters of the ANOVA are displayed in Table 2.

Post hoc multiple comparisons confirmed the assumptions, as serum TSH levels were significantly higher in every patient group when compared to the matched healthy controls. The group-specific student's t-tests for assessing differences between patient males and control males, as well as patient females and control females, were highly significant ($p < 0.0001$) in each age group (18–30 years, 31–45 years, and 46–60 years). Figure 8 portrays this finding.

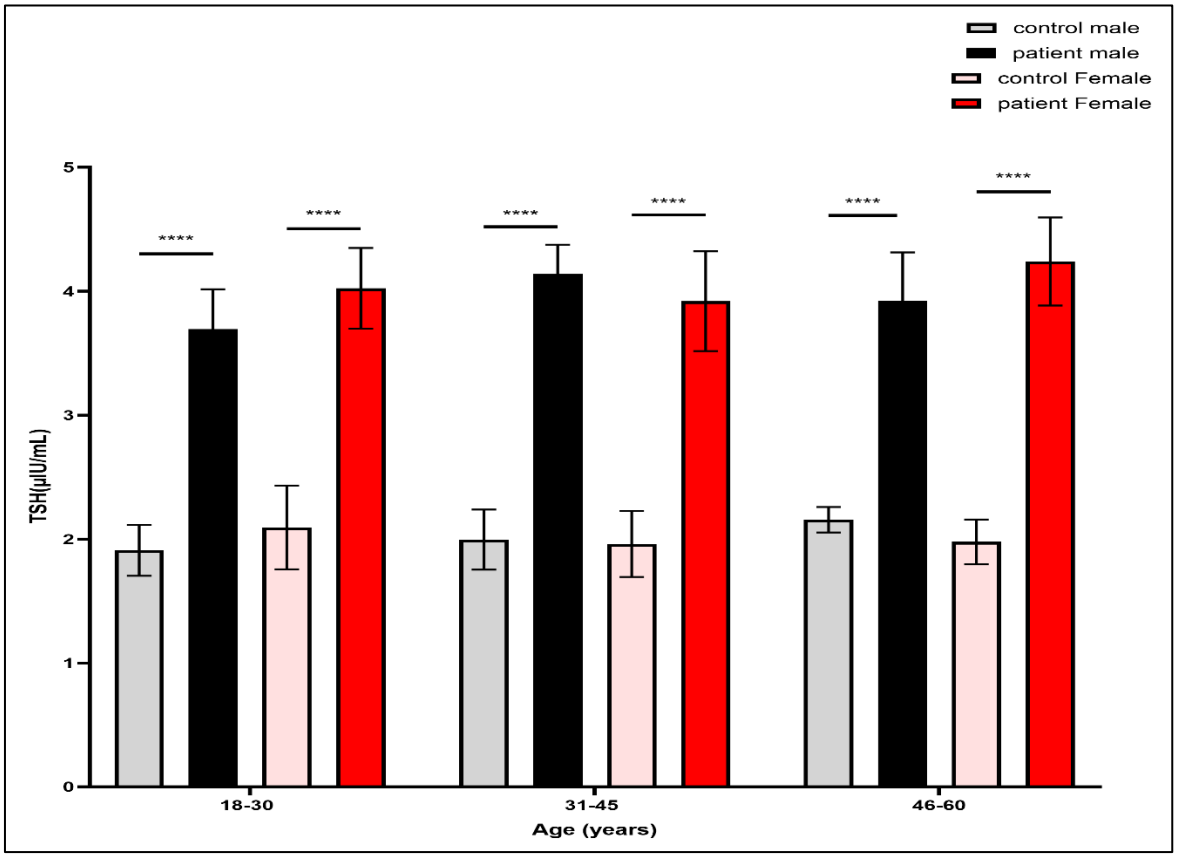

Figure 8: Serum TSH levels across different age, gender, and health status groups

TSH was the only hormone for which health status was the only main effect that significantly affected it. TSH levels were highly significantly increased throughout the obese patients with age, sex, and their interaction failing to reach significance. This hyperthyrotropinemia seen in obesity does not always suggest primary failure of the thyroid gland itself but may be a functional reversible response from the neuroendocrine system [26]. Increased circulating leptin due to increased adiposity is thought to be the major causative factor for increased TSH, as leptin stimulates TRH gene transcription directly via the paraventricular nucleus of the hypothalamus, increasing pituitary TSH expression [27]. TRH/TSH stimulation in this case is the body's physiological response to increase thyroid axis activity, thus ramping up the basal metabolic rate and energy consumption to try and limit fat deposition [24]. The complete lack of age or sex differences suggests that stimulation of central TRH/TSH by leptin acts the same way through all ages and both sexes in morbid obesity. Upon running a three-way ANOVA to determine the effects of age, sex, and health status on serum T3 levels. We found a very highly significant main effect of health status, which was the only main effect that reached significance and accounted for 72.57% of the total variability ($p < 0.0001$). While main effects of age and sex and all two-way and three-way interactions did not reach significance ($p > 0.05$). Table 2 shows parameters of ANOVA. Multiple comparisons further confirmed this, as they found that obese patients had significantly lower T3 levels when compared to their matched healthy controls within all groups. Significant decreases were seen when compared within patient males to control males and patient females to control females in all age groups. (18–30 $p < 0.01$; 31–45 (male) $p < 0.0001$, female $p < 0.001$); and 46–60 (male) $p < 0.01$, female $p < 0.001$. Figure 9.

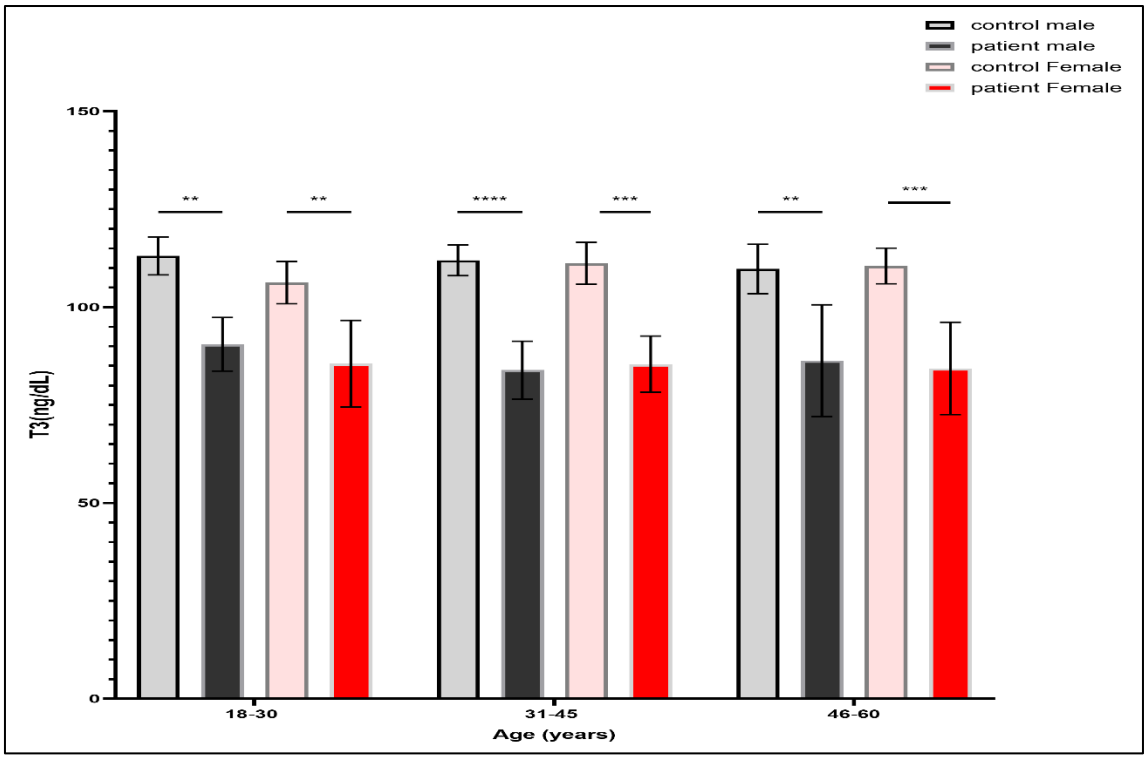

Figure 9: Serum T3 levels across different age, gender, and health status groups

Opposite the raised TSH phenotype, circulating T3 was significantly decreased in our obese patient population, suggesting a potential active thyroid hormone resistance (THR) or peripheral conversion derangement in the tissue microenvironment. T3 is considered the active form of thyroid hormone and is produced through conversion from T4 in peripheral tissues by type 2 deiodinase (DIO2) enzymes [28]. Obesity, characterized by chronic low-grade inflammation and excess circulating free fatty acids, negatively affects peripheral deiodinase activity, shifting T4 conversion away from active T3 and towards inactive rT3 [29]. This process is considered a form of functional down-regulation causing adaptive metabolic braking, thus decreasing energy expenditure and resting metabolic rate, further driving weight insensitivity [30]. Since health status was the only significant predictor, it can be concluded that obesity-induced inflammation and metabolic dysregulation directly cause this decrease in active thyroid hormones independent of sex or age. A three-way ANOVA was performed for age group, sex, and health status as main factors affecting serum T4 levels. Our results demonstrated a very highly significant main effect for health status as the only predictor (accounting for 57.31% of the variation, $p<0.0001$), while the main effects of age group and sex, as well as all 2-way and 3-way interaction effects, did not meet statistical significance ($p>0.05$). See Table 2 for full ANOVA parameters. Pairwise multiple comparisons showed a significantly decreased serum T4 level in patients vs. healthy controls in several subgroups. For the age group 18–30, there was a very highly significant decrease in patient males vs. control males ($p < 0.0001$) and a significant decrease in patient females vs. control females ($p < 0.05$). Similarly, for age group 46–60 only, there was a significant decrease in patient females vs. control females ($p < 0.01$). No significant pairwise differences ($p>0.05$) were found between patients and controls in age group 31–45 or male sex in age group 46–60. Figure 10.

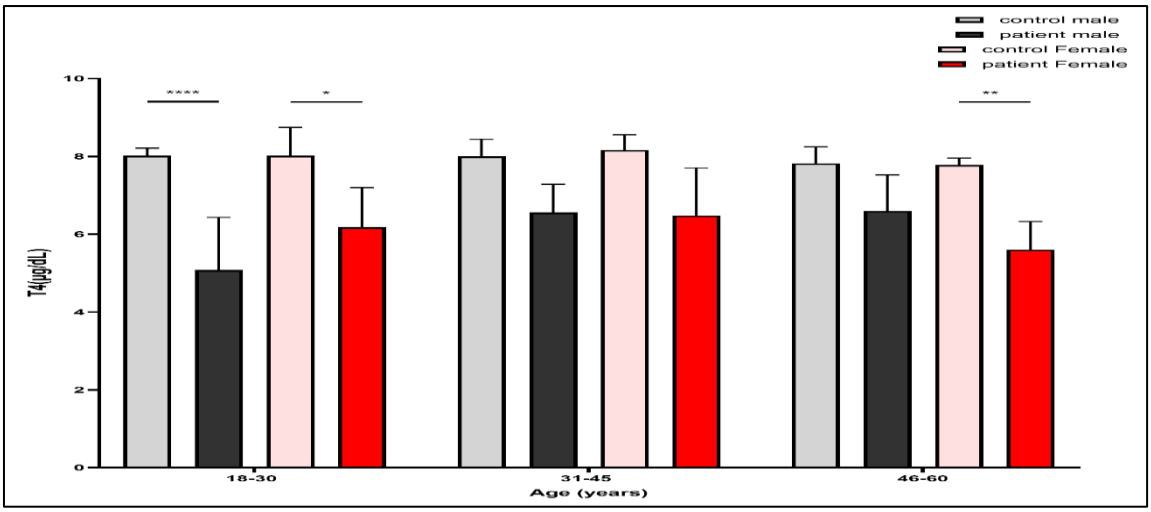

Figure 10: Serum T4 levels across different age, gender, and health status groups

Serum Thyroxine (T4) levels displayed similar down-regulation effects as T3 with a significant main effect of health status, BUT differed in that the pairwise drops were highly selective for only certain subcategories (pg/mL): significant for the youngest ages (18–30) and oldest ages (46–60) but statistically insignificant for those in middle age (31–45).

This discrepancy in statistical significance underscores the fact that although obesity down regulates the HPT axis through central and inflammatory pathways, basal production of the prohormone T4 by the thyroid gland itself can also experience mild sensitivity shifts with regard to thyroid age and TBG capacity [31]. T4's lower percent of total variance explained by health status (57.31%) when compared to other hormones also indicates that there are compensatory pituitary adaptations (revealed by high TSH) able to partially normalize baseline T4 levels in certain subcategories of patients but not enough to correct active T3.

Table 2: Comprehensive Summary of Three-Way ANOVA Results Across the Ten Studied Hormones

Source of Variation	parameters	Insulin	IGF-1	Resistin	Adiponectin	Leptin	Cortisol	Ghrelin	TSH	T3	T4
Age	% Var. *P*-value	2.084 0.0003	33.30 <0.0001	2.260 0.0381	0.5487 0.1250	2.084 0.0003	7.235 <0.0001	1.737 0.0015	0.3274 0.3074	0.1023 0.9072	2.612 0.1513
Gender	% Var. *P*-value	0.02456 0.6344	4.045 0.0581	0.2799 0.3565	0.8735 0.0114	4.287 <0.0001	2.244 0.0005	0.1107 0.3337	0.1035 0.3864	0.5074 0.3301	0.008797 0.9089
Health Status	% Var. *P*-value	91.91 <0.0001	4.795 0.0398	81.04 <0.0001	88.65 <0.0001	90.17 <0.0001	80.13 <0.0001	90.89 <0.0001	91.73 <0.0001	72.57 <0.0001	57.31 <0.0001
Age × Gender	% Var. *P*-value	0.2060 0.3899	0.8071 0.6886	0.8547 0.2757	0.8789 0.0388	0.06377 0.5044	0.4846 0.2356	1.099 0.0133	0.5841 0.1268	0.9237 0.4210	3.085 0.1091
Age × Health	% Var. *P*-value	0.5757 0.0785	0.4722 0.8034	0.006556 0.9899	1.034 0.0228	0.4353 0.0132	0.8146 0.0924	0.03959 0.8438	0.1663 0.5453	0.5672 0.5857	2.127 0.2125

Gender × Health	% Var.	1.857 e-006	4.368	0.0040 31	1.909	2.102	1.170	0.0001 587	0.134 6	0.0060 62	0.0044 88
	P-value	0.996 7	0.049 3	0.9115	0.0003	<0.000 1	0.010 0	0.9707	0.323 7	0.9148	0.9349
Age × Gen × Health	% Var.	0.054 57	0.688 6	0.0549 2	0.04226	0.0089 82	0.113 0	0.5445	0.450 6	0.1554	2.943
	P-value	0.776 4	0.727 2	0.9186	0.8464	0.9070	0.708 4	0.1068	0.200 1	0.8626	0.1203

Note: % Var. = Percentage of total variation explained by the source. Statistically significant P-values (P < 0.05) are highlighted in bold.

4 CONCLUSION

This research indicates that morbid obesity leads to significant endocrine and metabolic disruptions, creating a new state of homeostasis characterized by elevated insulin, leptin, resistin, and cortisol levels, alongside decreased adiponectin and ghrelin. Notably, metabolic inflammation from obesity surpasses age and sex differences, affecting all demographics. Evidence of thyroid axis suppression was found, indicated by high TSH and low active T_3/T_4, signifying metabolic damage and reduced energy output. The study concludes that morbid obesity results in a consistent state of metabolic syndrome and that treatment should focus on adipose dysfunction rather than being age or sex-dependent.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Statement of ethical approval

Ref.: CSEC/0326/0025, University of Baghdad, College of Science, Ethics Committee. csec@sc.uobaghdad.edu.iq

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

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