Original Article

BMI-Driven Variations in Testosterone, Luteinizing Hormone, Follicle-Stimulating Hormone and Sex Hormone-Binding Globulin in Males

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Abstract

Objective: To explore the association of luteinizing hormone (LH), follicle-stimulating hormone (FSH), total (TT), free (FT), and bioavailable testosterone (BAT), and sex hormone-binding globulin (SHBG) in relation to body mass index (BMI), in middle aged males recognizing its pivotal role in modulating homeostasis.

Material and Methods: Ninety-eight participants, aged between 48 and 56 years, were categorized into three distinct groups based on their BMI: those with a BMI less than 25 (normal), BMI ranging from 25 to 30 (overweight), and BMI exceeding 30 (obese). Rigorous analysis of serum samples enabled the quantification of luteinizing hormone, follicle-stimulating hormone, total testosterone, free testosterone, bioavailable testosterone, and sex hormone-binding globulin, with standard procedures employed for body weight and height measurement.

Results: Statistical comparisons using a one-way analysis of variance (ANOVA) discerned significant variations across these BMI groups (p-value = 0.001). It revealed significant differences in luteinizing hormone, follicle-stimulating hormone, total testosterone, and sex hormone-binding globulin concerning BMI across the three delineated groups. Further reinforcing a negative correlation between testosterone and BMI, a p-value of 0.005 underscores the impact of BMI on testosterone dynamics.

Conclusions: This study highlights a noticeable decline in luteinizing hormone, follicle-stimulating hormone, total testosterone, and sex hormone-binding globulin with increasing BMI.

Keywords: Follicle stimulating hormone, luteinizing hormone, free testosterone, bioavailable testosterone, sex hormone binding globulin.

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Introduction

About 60% of testosterone binds tightly to SHBG, 38% to albumin, and 2% remains free and biologically active. Since SHBG levels vary with factors like age, weight, and health, bioavailable testosterone (free and albumin-bound) is a better marker of active hormone levels than total testosterone, especially as aging increases, SHBG reduces bioavailable testosterone.[1] Obesity is linked to lower levels of testosterone, LH and SHBG[2], particularly due to visceral fat, which may trigger inflammation and affect the hypothalamic-pituitary-gonadal axis. SHBG, regulating testosterone concentrations, is also associated with risks like insulin resistance and metabolic syndrome in men, though obesity may affect its levels bidirectionally through adipocytokines like TNF-a.[3] Obese males show lower total and bioavailable testosterone, decreased inhibin-B, and diminished LH pulse amplitude, alongside increased peripheral conversion of testosterone to estrogen.[4] The primary laboratory assessments employed to verify a diagnosis of late-onset hypogonadism (LOH) consist of total testosterone (TT) and free testosterone (FT) levels in serum, with

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the former being the most commonly utilized worldwide.[5] The primary objective of this study is to elucidate the impact of BMI on hormonal dynamics in middle-aged men which is a critical transitional phase where hormonal levels begin to decline more rapidly, and also there is heightened risk metabolic syndrome, cardiovascular disease, and other BMI-associated conditions in this demographic variant. This involves a comprehensive examination of the relationship between BMI and total testosterone, free testosterone, bioavailable testosterone, luteinizing hormone, follicle stimulating hormone considering the three distinct BMI groups. The secondary objectives were to identify specific patterns or trends in levels across different BMI categories, to explore potential confounding factors. While previous studies have hinted at a negative correlation between testosterone and BMI, a comprehensive exploration within a middle-aged cohort is warranted. This study aims to bridge these gaps by offering a more nuanced understanding of how BMI influences testosterone dynamics, providing insights that could have implications for male health and future interventions.

Materials and Methods

This comparative cross-sectional study was conducted from September 2018 to December 2020. The Institutional Review Board of the University of Lahore approved the study (reference number: UOL/IMBB/Sample/ 19/ 106 on February 11, 2019), following the Helsinki Declaration. Permission for sample collection was granted by the Principal of Gujranwala Medical College and the DHQ Hospital Gujranwala, affiliated with the college.

Ninety-eight male participants, aged 48 to 56 years, were selected using a convenient sampling technique. Cochran's equation6 determined the sample size, considering the population of Punjab[7] which was 110 million in 2020. This method, suitable for small populations with known sizes, incorporates a population correction factor. A precision level of ±5% and a confidence level of 95% were chosen, ensuring a margin of error within 5 percentage points of the true population value.

The Cochran formula is:

$$n = \frac{n_o}{1 + \frac{(n_0 - 1)}{N}}$$

The estimated proportion was set to 0.5 to account for maximum variability, resulting in a calculated sample size of 86.

The study included male participants aged between 48 and 56 years, with Body Mass Index (BMI) classified into three categories: normal weight (< 25 kg/m²), overweight (25-30 kg/m²), and obese (> 30 kg/m²). Participants had no history of chronic diseases, long-term medication use, or hormonal disorders. Informed written consent was obtained from all participants, ensuring they were fully aware of the study's aims and procedures. The mean age of each group was maintained within the range of 48-56 years to minimize confounding factors and ensure age-related uniformity across groups, providing more reliable results. Individuals were excluded from the study if they had any chronic or infectious diseases, used long-term medication (including steroids), or had severe communication problems or intellectual disabilities that could interfere with participation or data collection.

Clinical and anthropometric measurements, demographic information, and risk factors were collected using standard methods. Six milliliters of blood were taken before noon, because hormones typically peaks in the early morning and declines throughout the day. Collecting samples before noon ensures consistency by capturing hormone levels during their peak phase, reducing variability due to time of day, then centrifuged at 4000 rpm for 10 minutes to separate serum.

Hormonal assays employed ABBOTT kits for testosterone analysis, identified by specific lot and reference numbers. For LH, FSH, and SHBG, similar ABBOTT kits with corresponding lot and reference numbers were used. Competitive chemiluminescence enzyme immunoassays using the Alinity Ci analyzer quantified levels of Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), Testosterone, and Sex Hormone-Binding Globulin (SHBG). This method involved mixing samples with reagents containing antibodies specific to each hormone. The Alinity Ci analyzer then used chemiluminescence technology to detect and quantify hormone concentrations based on the emitted light's intensity. The competitive nature of the assay meant that the light produced was inversely proportional to the concentration of the target hormone in the sample. Testosterone binds to sex hormone-binding globulin and albumin to form combinations. When total testosterone is low or there are changes in sex hormone-binding globulin levels, measuring free testosterone is advised. Bioavailable testosterone, which consists of free testo-

sterone and testosterone bound to albumin, is linked to free testosterone levels. Costly and not widely available methods, such as equilibrium dialysis and ammonium sulfate precipitation, can measure free and bioavailable testosterone. Alternatively, algorithms can calculate free and bioavailable testosterone levels.[8] The Vermeulen formula is often used as a more accessible alternative. To utilize the Vermeulen formula, testosterone values were initially transformed from ng/ml to nmol/L using an online conversion tool. The algorithm was then applied, assuming albumin as a fixed value of 4.3 g/dL. For the calculated free testosterone (FT), standard ranges were applied, with levels considered normal if greater than 0.225 nmol/L (greater than 64.9 pg/ml) for males and less than 0.039 nmol/L (less than 11.25 pg/ml) for females.[9] The data was analyzed using SPSS version 25, with normality tested by the Shapiro-Wilk test, and ANOVA used to compare means across BMI groups, while Pearson's correlation coefficient examined relationships between BMI and hormones, with statistical significance set at a p-value ≤0.05.

Results

The physical characteristics and random blood levels in three different groups of subjects are summarized in Table 1. The mean age in Groups I, II, and III was 48-56 years. On comparison, it was noticed that with advancing BMI, the total testosterone was significantly declined with a p value of 0.0001 as shown in figure 1. Same was the case with SHBG, FT, LH and FSH. However, bioavail-able testosterone showed a falling trend but it was non-significant. Pearson's correlation of BMI was made with anthropo-metric and biochemical parameters of our

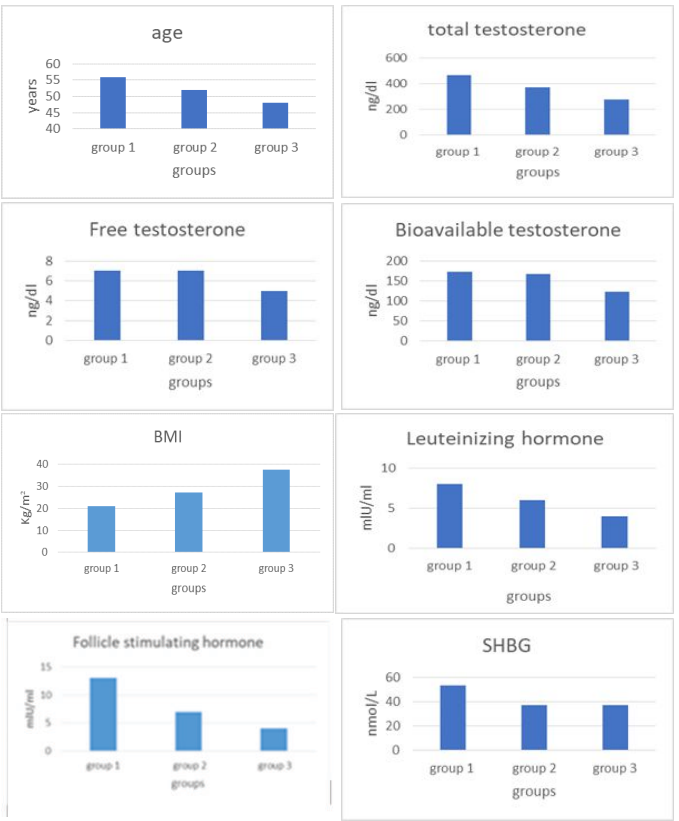

Figure 1: *Comparison of BAT: bioavailable testosterone; FSH: follicle stimulating hormone; FT: free testosterone; SHBG: sex hormone binding globulin; TT; total testosterone among different BMI groups*

study. BMI showed a significant negative correlation with total testosterone (r = -0.3, n=98, p= 0.05), SHBG (r=-0.34, n=98, p=0.001), LH(r=- 0.22, n=98, p=0.02) and FSH (r=-0.27, n=80, p=< 0.06). This represents that elevated BMI results in decline of TT, SHBG, FT, BAT, LH, and FSH as depicted in Table 2.

Table 1: *Physical and Biochemical Parameters across Different BMI Groups*

Parameter	Normal Value	Group I (BMI < 25 kg/m², n = 56)	Group II (BMI 25–30 kg/m², n = 28)	Group III (BMI > 30 kg/m², n = 14)	p-value
Age (years)		56 ± 21	52 ± 23	48 ± 12	0.34
BMI (kg/m²)		21 ± 2	27 ± 1	37 ± 8	0.01*
TT (ng/dl)	264–916	467 ± 241	370 ± 187	279 ± 184	0.0001*
BAT (ng/dl)	10–575	173 ± 92	167 ± 76	123 ± 51	0.14
SHBG (nmol/L)	19–76	53 ± 23	37 ± 21	37 ± 24	0.003*
FT (ng/dl)	5–21	7.3 ± 3.9	7.1 ± 3.2	5.2 ± 2.1	0.14
LH (IU/L)	1.5–8.6	8.3 ± 5.7	5.9 ± 4	4.4 ± 2.5	0.01*
FSH (IU/L)	1.5–12.4	13.8 ± 15	7.6 ± 5.9	4.3 ± 2.4	0.01*

Note: Data presented as mean ± standard deviation. Asterisks (*) indicate statistically significant differences (p < 0.05). "n" represents the number of cases in each group .BMI: body mass index, BAT: bioavailable testosterone; FSH: follicle stimulating hormone; FT: free testosterone; SHBG: sex hormone binding globulin; TT; total testosterone. p*=<0.05 is taken as significant.

Nevertheless, SHBG, FT, BAT, LH and FSH were significantly correlated with age (p=0.0001). Likewise, total testosterone was positively correlated with SHBG, FT, BAT significantly (p=0.0001) but not with LH and FSH.

LH and FSH were significantly correlated (p= 0.0001) with each other and so with BMI.

Discussion

Obesity significantly contributes to the prevalence of hypogonadism in men, a condition that further accelerates its progression.[10] While the association between obesity and hormonal imbalances has been explored in numerous studies, and it remains a subject of ongoing scrutiny. In the present study, hormone levels across three distinct BMI categories (18–24, 25–29, and 30–39), revealing significant associations between elevated BMI and reductions in total testosterone, sex hormone-binding globulin (SHBG), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were examined. Furthermore, age emerged as a significant factor influencing hormonal dynamics, with certain hormones exhibiting a gradual decline as age progressed, a well-documented phenomenon in the male population.

This study corroborates existing literature that BMI significantly impacts testosterone levels in middle-aged men, particularly through a negative correlation with total testosterone levels. This finding links with previous research, that higher BMI is linked with reduced testosterone and altered reproductive function, such as impaired sperm motility and lower sperm concentration.[11] Similarly, a decline in serum testosterone levels was demonstrated in adolescent and adult males, reinforcing the notion that obesity-related hormonal disruptions are pervasive across age groups.[12]

Furthermore, this investigation highlights that rising BMI correlates with lower levels of SHBG, consistent with studies that have found that a decline in SHBG levels in obese individuals are often a predictor of metabolic syndrome and diabetes, which further complicates the hormonal balance.[13] This suggests that BMI, through its effect on SHBG, could act as a mediator between obesity and androgen-related dysfunction, such as lower testosterone levels. However, the present study

Table 2: *Pearson's Correlations between Hormones and BMI*

Table 2: Pearson's Correlations										
		Height	**Weight**	**BMI**	**TT**	**SHBG**	**FT**	**BAT**	**LH**	**FSH**
Age	r	-0.11	-0.18	-0.15	-0.15	0.432	-0.5	-0.49	0.421	0.328
	p	0.26	0.07	0.13	0.12	0.0001**	0.0001**	0.0001**	0.0001**	0.001*
Height	r		0.3	-0.37	1.75	0.03	0.17	0.18	-0.005	-0.02
	p		0.003	0.0001**	0.08	0.7	0.08	0.07	0.5	0.8
Weight	r			0.75	-0.2	-0.3	-0.05	-0.05	-0.2	-0.2
	p			0.0001**	0.05*	0.001*	0.5	0.5	0.001**	0.001**
BMI	r				-0.3	-0.34	-0.15	-0.152	-0.22	-0.27
	p				0.05*	0.001*	0.31	0.31	0.02*	0.006*
TT	r					0.51	0.8	0.8	0.1	0.1
	p					0.0001**	0.0001**	0.0001**	0.23	0.29
SHBG	r						-0.04	-0.04	0.12	0.18
	p						0.6	0.6	0.28	0.07
FT	r							1	-0.26	-0.24
	p							0.0001**	0.008*	0.01
BAT	r								-0.26	-0.24
	p								0.008*	0.01
LH	r									0.78
	p									0.0001**

****. Correlation is significant at the 0.01 level (2-tailed).**

***. Correlation is significant at the 0.05 level (2-tailed).**

BMI: body mass index, BAT: bioavailable testosterone; FSH: follicle stimulating hormone; FT: free testosterone; SHBG: sex hormone binding globulin; TT; total testosterone. LH; luteinizing hormone p=<0.05 is taken as significant.*

extends the current understanding by examining not only the average effects of BMI on hormonal dynamics but also the variability across different percentiles of hormone distributions. A Quantile regression analysis revealed that BMI has a consistently negative association with testosterone across all quantiles, supporting earlier conclusions that higher BMI is a robust predictor of lower testosterone levels. Additionally, quantile regression showed a positive association with estradiol levels, particularly up to the 80th percentile. This suggests that BMI may have a more complex relationship with estradiol.[14]

The present study also reveals differential effects between BMI categories, with men in the obese group exhibiting significantly lower levels of both total testosterone and SHBG, in contrast to their normal-weight counterparts. This is in line with the findings of a study which demonstrated that obesity-related hormonal alterations are not merely due to body weight but also to adiposity distribution and other metabolic factors. The dysregulation of the hypothalamic-pituitary-gonadal (HPG) axis and elevated leptin levels in obese individuals may inhibit gonadotropin-releasing hormone (GnRH) secretion, which could subsequently decrease LH and FSH levels, both of which are integral to the proper functioning of the testes and the synthesis of testosterone.[15]

A Mendelian randomization study supports our findings, suggesting a negative relationship between genetically predicted body fat and testosterone levels, which implies that reducing fat mass could potentially restore testosterone to healthier levels.[16] This aligns with evidence indicating that weight stability plays a crucial role in maintaining hormonal balance. Specifically, a study of men over 40, particularly those who are overweight, non-smoking, and healthy, found that stable BMI was associated with consistent reproductive hormone levels.

Further, a study exploring the link between hypertension and testosterone levels revealed that hypertensive men exhibited significantly higher SHBG levels and lower free testosterone (FT) and bioavailable testosterone (BT) levels compared to their normotensive counterparts. More strikingly, both FT and BT were inversely associated with systolic and diastolic blood pressure, reinforcing the notion that obesity-related hypertension might exacerbate the decline in testosterone levels, independent of other confounding factors.[18]

In younger populations, specifically men aged 18–40 with erectile dysfunction (ED), a notable association between decreased FT and diminished erectile function scores was observed. This relationship remained significant even after adjusting for age and BMI. Interestingly, while total testosterone correlated with erection hardness in some males, free testosterone levels seemed to be a more reliable marker for ED severity. These findings suggest that low FT, even in the presence of normal total testosterone levels, may serve as a key indicator of ED in young men, highlighting the importance of free testosterone measurements in clinical evaluations.[19]

A study on youth revealed sex-specific disruptions in reproductive hormones, with obesity leading to lower testosterone and higher estradiol metabolites in boys, and higher free androgen index (FAI) in girls, alongside lower SHBG levels in both sexes.[20] In coherence with this, this study demonstrated a broader, generalized decline in testosterone, SHBG, LH, and FSH with increasing BMI, highlighting the detrimental impact of obesity on hormonal regulation across life stages.

In conclusion, testosterone deficiency is increasingly recognized as a major concern, particularly given its impact on male reproductive and overall health. The results from this study emphasize the importance of evaluating not only total testosterone but also free and bioavailable testosterone in clinical settings, as these hormones provide a more comprehensive picture of an individual's hormonal health.

This study has limitations, including insufficient consideration of confounding factors like lifestyle and health conditions, limiting generalizability. The lack of a longitudinal design prevents establishing causal relationships between BMI and hormonal changes.

Future studies should use longitudinal designs to explore the temporal relationship between BMI and hormonal changes, determining if BMI changes precede testosterone alterations. Additionally, randomized controlled trials with diverse populations and advanced techniques like metabolomics, transcriptomics, and proteomics could uncover the molecular pathways of obesity-related hormonal shifts. Combining multi-omics approaches would offer a comprehensive understanding of the mechanisms linking hormonal regulation and obesity.

Conclusions

This study reveals a significant decline in male sex hormones, including LH, FSH, total testosterone, free testosterone, and SHBG, with increasing BMI. These hor-

monal changes impact key physiological processes and negatively affect male physical, cognitive, and reproductive health. Addressing BMI-related hormonal imbalances is essential for improving men's overall health and quality of life, especially as they age.

Conflicts of Interest: *None*

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Authors Contribution

UY: Conceptualization of Project
UY: Data Collection
UY: Literature Search
SA: Statistical Analysis
SA, TS: Drafting, Revision
SA: Writing of Manuscript