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ORIGINAL RESEARCH

Hemodilution and Serum Progesterone Regulation in Males with Obesity

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Objective: This study aimed to examine the correlation between serum progesterone levels, body mass index (BMI), and hemodilution in males, with an emphasis on the potential influence of lymphocyte counts.

Methods: A retrospective analysis was conducted on two cohorts comprising of 83 and 139 participants, respectively. Data collected included age, BMI, plasma volume, and serum progesterone levels. Plasma volume was estimated using a standardized formula, and multivariate regression models calibrated for age were used to assess the effects of BMI on plasma volume, progesterone levels, and lymphocyte counts.

Results: An inverse association was identified between BMI and serum progesterone concentrations, likely attributable to hemodilution, while systemic progesterone load remained consistent across BMI categories. A positive correlation was observed between lymphocyte counts and serum progesterone levels, suggesting an inflammatory component influencing progesterone regulation.

Conclusion: These findings suggest that hemodilution and inflammation (the latter indicated by lymphocyte counts) may modulate serum progesterone levels in obese males. These observations could have potential clinical implications for hormonal health and highlight the need for further research into the underlying mechanisms.

Keywords: cross-sectional study, hemodilution, lymphocyte counts, obesity, progesterone

Introduction

Obesity is a major global public health concern, strongly linked to an elevated risk of various chronic diseases. The mechanisms contributing to obesity are multifaceted, with hormonal regulation playing a critical role in its onset and progression.[1] Among these hormones, progesterone—primarily studied for its physiological roles in females—has been implicated in adipose tissue accumulation and distribution in both males and females. However, the correlation between obesity and plasma progesterone levels in males remains poorly understood, with existing research presenting conflicting evidence.

Blanchette et al reported reduced progesterone levels in males with obesity, suggesting a potential reduction in adrenal cortical steroid production.[2] Conversely, Nie et al identified a positive correlation between serum progesterone and obesity, suggesting that high-sensitivity C-reactive protein (hsCRP) may partially mediate this correlation.[3] These findings highlight the potential role of systemic inflammation in linking progesterone levels with obesity. Despite these insights, research on this topic remains limited, with critical factors such as hemodilution often neglected. Previous studies have demonstrated that while the concentrations of certain serum biomarkers decrease with increasing body mass index (BMI), their total amounts remain unchanged.[4,5] This phenomenon, likely due to plasma volume expansion, suggests that hormonal alterations in males with obesity may be influenced by hemodilution.

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To address these knowledge gaps, this study aimed to further investigate the relationship between serum progesterone levels and BMI in males, with a particular focus on the roles of hemodilution and lymphocyte counts in mediating this association. Understanding these mechanisms may provide valuable insights into the complex interplay between progesterone and obesity in males.

Participants and Methods

Participant Selection

This retrospective study analyzed data from participants who underwent health examinations at the health management center of Taihu Rehabilitation Hospital of Jiangsu Province. Two datasets were utilized for this study. Dataset 1 was derived from a prior study, comprising retrospective records of 2359 healthy males who underwent health management between October 2012 and December 2012 at Taihu Rehabilitation Hospital of Jiangsu Province (formerly known as Taihu Cadre's Sanatorium of Jiangsu Province). From this cohort, 139 individuals with comprehensive progesterone data were included in the analysis.[5] Dataset 2, was based on an unpublished study scheduled for future publication. This dataset comprised of health examination data collected between March 2021 and August 2023, at Taihu Rehabilitation Hospital of Jiangsu Province. A total of 2873 individuals with detailed information on lymphocyte subgroups, body weight and height were included. Among these, 83 individuals had serum progesterone levels assessed as part of routine health examinations.

Access to the anonymized datasets was granted for research purposes on January 06, 2024, ensuring that no identifiable participant information was available to researchers during or after data collection.

Both datasets included comprehensive records of BMI and serum progesterone levels for all participants, with progesterone levels ranging from 0.14 to 2.06 ng/mL. The age of the participants ranged from 33 to 75 years in Dataset 1 and from 20 to 68 years in Dataset 2. None of the participants were using medications known to affect progesterone levels. All participants were deemed to be in apparent good health based on their medical history and physical examinations.

The study protocol was reviewed and approved by the Institutional Review Board of Taihu Rehabilitation Hospital of Jiangsu Province prior to the commencement of the study. All procedures were performed in accordance with applicable guidelines and regulations.

BMI was calculated as weight in kilograms divided by height in meters squared. Participants were weighed with emptied pockets and without footwear. Height was measured with a fixed stadiometer with a vertical backboard and an adjustable headboard. Participants were categorized into two groups based on BMI, according to the new Asian classification standards: ≤ 22.9, 23−27.4, and ≥ 27.5.[6]

Serum progesterone levels were assessed using a Beckman Coulter DXI 800 Immunoassay Analyzer. Lymphocyte counts were routinely determined using a fully automated hematology analyzer. All assessments were conducted by qualified staff at the health management center. Plasma volumes (PVs) and progesterone masses were estimated using the following equations:[7–10]

$$\text{Body surface area}\,(\text{m}^2) = \text{body weight}\,(\text{kg})^{0.425} \times \text{height}\,(\text{m})^{0.725} \times 0.2025$$

$$\text{PV}\,(\text{L}) = \text{body surface area}\,(\text{m}^2) \times 1.670$$

$$\text{Systemic progesterone load}\,(\text{ug}) = \text{Serum progesterone level}\,(\text{ng/mL}) \times \text{PV}\,(\text{L})$$

Statistical Analyses

Statistical analyses were conducted using SPSS version 29.0, and the results were subsequently validated through R language scripting. A general linear model was applied to evaluate the relationships between PV, serum progesterone concentration, and serum progesterone load in relation to increasing BMI. Adjustments were made for potential confounding factors, such as age and BMI, to ensure the accuracy and reliability of the results. Statistical significance were defined as a p-value less than 0.05.

Results

Among the male participants, the prevalence of overweight and obesity was 22.143% and 32.53% respectively.

Characteristics of Study Population by Datasets

The mean (SD) age of participants in Dataset 1 and Dataset 2 was 47.26 (9.219) and 52.157 (8.929) years, respectively. Participants in Dataset 2 exhibited higher average BMI levels compared to those in Dataset 1.

Correlations between Progesterone Levels, Plasma Volume, Systemic Progesterone Load, and BMI

A comprehensive analysis of the relationships between serum progesterone levels, PV, serum progesterone load, and BMI are summarized in Table 1. In Dataset 1, a statistically significant correlation was observed between PV and BMI, while no significant correlations were found for other variables. In Dataset 2, the mean serum progesterone concentration was significantly higher in males of normal weight recorded at 0.804 ng/mL, compared to, 0.493 ng/mL in males with obesity. This difference was statistically significant ($p < 0.05$). Additionally, a significant increase in mean estimated PV was noted across rising BMI categories, ranging from 2.863 liters in males with normal weight to 3.384 liters in males with obesity. However, the estimated serum progesterone load did not demonstrate a significant association with BMI, as indicated by a p-value greater than 0.05.

Relationship between Progesterone and Lymphocytes

Linear regression analysis, as presented in Table 2, was used to elucidate the relationship between serum progesterone levels and lymphocyte counts. After accounting for age and BMI, an increase in lymphocyte count was associated with a corresponding increase in progesterone levels. Specifically, in Dataset 1, each unit increase in lymphocyte count was

Table 1 Progesterone Concentration and Mass According to BMI Category

Items	WHO Asian BMI Category, kg/m^2			P for Trend
	≤22.9	23–27.4	≥27.5	
Dataset 1				
No. men	24	84	31	
P4 Level(ng/mL)^, Mean*	0.681	0.591	0.619	0.584
Plasma Volume, Mean (L)	2.943	3.15	3.392	<0.001
P4 Mass(ng/mL)^, Mean*	2.019	1.881	2.1	0.679
Dataset 2				
No. men	8	48	27	
P4 Level(ng/mL)^, Mean*	0.804	0.682	0.493	0.029
Plasma Volume, Mean (L)	2.863	3.124	3.384	<0.001
P4 Mass(ng/mL)^, Mean*	2.309	2.141	1.664	0.141

Note: *Adjusted for age.
Abbreviations: CI, confidence interval; P4, Progesterone.

Table 2 Associations of Serum Progesterone Levels with Lymphocyte by Datasets

Outcomes	Subjects	Linear Regression β Coefficients (β, 95% CI)	
		Unadjusted Model	Adjusted Model
Dataset 1	139	0.176 (0.06–0.291)	0.151 (0.036–0.267)
Dataset 2	83	0.126 (0.008–0.244)	0.112 (−0.002–0.226)

Notes: Unadjusted Model: No covariates were included for adjustment. Adjusted Model: The model was adjusted for age and BMI as covariates.

associated with a 0.151 ng/mL increase in progesterone levels, while in Dataset 2, the increase was 0.112 ng/mL. These findings indicate a positive association between higher lymphocyte counts and higher serum progesterone levels across the analyzed datasets.

Discussion

Multifaceted Mechanisms of Hemodilution and Inflammation in the Progesterone-Obesity Relationship

Hemodilution as a Contributor to Lower Progesterone Levels

The findings suggest the significance of hemodilution as a key mechanism contributing to lower progesterone concentrations observed in males with obesity. A significant positive correlation between BMI and PV was observed across both datasets ($p < 0.001$), confirming the association between obesity and PV expansion. In Dataset 2, males with obesity exhibited a 38.7% reduction in mean serum progesterone concentration compared to those with normal weight (0.493 ng/mL vs 0.804 ng/mL). This reduction occurred despite no significant differences in systemic progesterone load across BMI categories ($p > 0.05$). These results indicates that the observed decline in serum progesterone levels are primarily attributable to hemodilution rather than reduced hormone production, consistent with prior research on the effects of obesity-induced hemodilution on the concentration of various serum biomarkers.[4,5,11,12]

However, in Dataset 1, no significant correlation was found between BMI and progesterone concentration, despite the positive association between BMI and PV. This discrepancy may reflect variability in the impact of hemodilution based on factors such as the extent and duration of PV expansion, inflammation, and metabolic dysregulation.[13] The interplay of these mechanisms may explain the heterogeneity in findings across studies examining obesity and progesterone levels.[2,3]

Role of Inflammation and Immunity in Progesterone Regulation

Chronic low-grade inflammation, a characteristic feature of obesity, significantly influences progesterone regulation. Elevated levels of pro-inflammatory cytokines, such as tumor-necrosis-factor-alpha (TNF-α) and interleukin-6 (IL-6), along with immune dysregulation can impair the expression and function of progesterone receptors.[14] These cytokines interfere with progesterone signaling pathways, reducing its anti-inflammatory effects. Furthermore, adipose tissue dysfunction in obesity exacerbates immune cell activation and adipokine imbalances, characterized by increased leptin and decreased adiponectin levels. These changes exacerbate inflammation and reduce the regulatory role of progesterone.[15]

Inflammatory markers, such as C-reactive protein (CRP) and IL-6 are frequently elevated in obesity and inflammation-associated states and may also be linked to changes in progesterone levels. These markers can affect the hypothalamic-pituitary-gonadal axis, potentially altering progesterone secretion indirectly by modulating the release of gonadotropin-releasing hormone and luteinizing hormone.[16] This suggests that systemic inflammation may impair the normal endocrine regulation of progesterone, complicating its interactions with metabolic and immune factors in obesity.

Progesterone may also function as a regulator of inflammation and metabolic dysfunction in obesity. Its anti-inflammatory properties, which include suppression of pro-inflammatory cytokines (TNF-α, IL-6), and the promotion of IL-10, highlight its protective role in reducing obesity-related chronic inflammation.[17] Moreover, progesterone influences adipocyte differentiation and lipid metabolism through receptor-mediated pathways, potentially mitigating metabolic dysregulation.[14] However, the reduced serum progesterone levels observed due to hemodilution may limit these protective effects, thereby exacerbating inflammation and metabolic dysfunction in obesity.

The datasets further elucidate the relationship between immune factors and progesterone. In Dataset 1, a positive association between lymphocyte counts and progesterone concentrations ($\beta = 0.151$, $p < 0.05$) suggests an adaptive immune response to obesity-related inflammation. However, this association became non-significant in Dataset 2 after adjusting for BMI and age, indicating the presence of potential confounding factors. These findings underscore the complex interplay between inflammation, immunity, and progesterone regulation, which may vary depending on metabolic and inflammatory conditions.

Interplay between Hemodilution and Inflammation in Progesterone Regulation

The regulation of progesterone levels in individuals with obesity reflects a dynamic interplay between hemodilution and inflammatory processes. Hemodilution contributes to reduced serum progesterone concentrations, while inflammation

and immune activation may modulate its production and function. The relative impact of these mechanisms likely vary among individuals, depending on factors such as metabolic state, inflammatory burden, and progesterone sensitivity.

Discrepancies in findings across studies, including the datasets analyzed in this study, highlight this complexity. For instance, the observation of lower progesterone levels in individuals with obesity in Dataset 2 is consistent with prior research,[2] whereas other studies have reported a positive association between BMI and progesterone.[3] These variations emphasize the need to consider both hemodilution and inflammation in future research to clarify the underlying mechanisms and address inconsistencies in the literature.

Study Strengths and Limitations

This study represents one of the first systemic evaluations of the dual roles of hemodilution and inflammation in the association between obesity and serum progesterone levels. Utilizing two independent datasets, the analysis confirmed the role of hemodilution while also investigating the potential contributions of inflammation and immune regulation. These findings contribute to an in-depth understanding of the multifactorial mechanisms underlying obesity-induced changes in hormone levels and highlight the importance of considering hemodilution as a potential confounding factor in clinical assessments of hormonal health.

Several limitations of this study must be acknowledged. First, the cross-sectional nature of this study precludes causal inferences, highlighting the need for longitudinal studies to clarify the temporal relationships between obesity, inflammation, and progesterone levels. Second, while lymphocyte counts were used as an inflammatory marker, the absence of other key inflammatory and metabolic markers such as CRP and TNF-α, limits the comprehensiveness of the evaluation of inflammatory pathways. Third, PV was estimated using a reputable formula based on body surface area rather than direct measurement, which may introduce potential inaccuracies in the calculation of systemic progesterone load. Finally, the relatively small sample size, particularly in Dataset 2, may limit the generalizability of the findings, highlighting the need for future studies with larger and more diverse populations.

Clinical Implications and Future Directions

The findings of this study may carry potential clinical implications. Recognizing hemodilution as a possible key factor contributing to low progesterone levels in males with obesity could help prevent potential misinterpretation of hormonal function. Additionally, the role of chronic inflammation and immune regulation in modulating progesterone levels suggests that targeted interventions—aimed at reducing inflammation and restoring hormonal balance in obese individuals—warrant further investigation. Weight management strategies and anti-inflammatory therapies might help mitigate the endocrine and metabolic consequences associated with obesity. Future studies should ideally incorporate longitudinal designs and more comprehensive inflammatory and metabolic profiling to further elucidate the complex interplay between obesity, progesterone, and immune regulation, with a view to informing the development of personalized treatment approaches.

Conclusion

This study suggests that hemodilution may be an important contributor to reduced serum progesterone levels observed in obese men. The expansion of plasma volume associated with higher BMI could lower progesterone concentrations, even when systemic progesterone load appears unchanged. The observed positive link between lymphocyte counts and progesterone levels further supports a possible role for systemic inflammation in regulating progesterone. Together, these findings underscore the need to consider both hemodilution and inflammatory processes when interpreting serum progesterone levels in clinical settings. Future studies should aim to further elucidate these mechanisms and their potential clinical implications.

Abbreviations

BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; PVs, Plasma volumes; SD, mean; TNF-α, tumor-necrosis-factor-alpha; IL-6, interleukin-6; CRP, C-reactive protein.

Data Sharing Statement

The data supporting this study's findings are available from the corresponding author (Feng Li) upon reasonable request.

Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of Taihu Rehabilitation Hospital of Jiangsu Province (SGLL-2024015). This study was conducted in accordance with the declaration of Helsinki. Informed consent is not required for this study because it is a retrospective study. However, anonymized data analysis was conducted for the article only with good confidentiality.

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Disclosure

The authors declare that they have no competing interests in this work.

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