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ASSOCIATION BETWEEN SERUM TESTOSTERONE-ESTRADIOL RATIO AND BODY MASS INDEX IN OBESE IRAQI MEN

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ABSTRACT

The obesity epidemic has grown to alarming rates in recent years, and a decrease in male fertility has been observed in parallel with obesity. **Objective:** To evaluate relationship between serum testosterone/estradiol ratioand body mass index BMI in obese Iraqi men. **Material & Methods**: The subjects of this study were 72 obese males, ageing 22-51 years, they were selected after a detailed medical history taken with physical exam including BMI with a body mass ≥ 30kg/m^2.Blood sampling was carried out to measure serum estradiol (E2), total testosterone (Tes), insulin level (Ins) and thyroid stimulation hormone (TSH) using Chemiluminescence assay analyzer (Tosoh AIA-600).Data distribution was evaluated. Variables displaying a normal distribution were expressed as mean ± SD. ANOVA were used for the comparison of variables. **Results & Discussion**: In this study Pearson correlation coefficients were calculated. Mean (± SD) age of the subjects included in this study was 35.4 (± 7.7) years mean (± SD) Estradiol, total testosterone, Insulin were 44.1(±13.4)pg/ml, 359.1(±6730)ng/dL and 17.0(±8.1)µU/ml respectively. Statistically significant differences were observed in the mean values of BMI between three IBM classgroups ($p<0.001$). Significant direct correlation of BMI with estradiol and insulin level ($r=0.388$, $p<0.01$ and $r=0.386$ $p<0.01$ respectively), whileinverse correlation with serum total testosterone($r = -0.413$, $p < 0.001$) was recorded in this study. The prime hormonal defect in obese men is (Tes/E2) ratio, which have a negative significant correlation with obese males.

Keywords: Esrtadiol, Total Testosteron, Insulin, BMI, Tes/E2 Ratio, IR, HOMA-β

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INTRODUCTION

Obesity linked to inflammation is a major concern, not only for the increasingof incidence this diseases, but also because inflammation linked to obesity can be an important trigger of metabolic disorders associated with obesity.

Obesity, defined by the World Health Organization "WHO" as a body mass index (BMI) ≥ 30 kg/m^2, is a disease with excess body fat which negatively affects morbidity and mortality due to the risk of noncommunicable diseases[1].Obesity is associated with various hormonal disorders and deregulation of insulin activity / insulin-like growth factors activity[2,3].Insulin resistance (IR) has long been associated with being overweight and sex hormone disorders.IR and compensatory hyperinsulinemia stimulate increased androgen synthesis at the expense of reduced estrogen production. Likewise, a moderate or significant decrease in estrogen levels increases the prevalence of IR conditions[4].

The relationship between elevated estradiol (E2) levels and obesity in men is relatively understandable. In men, about 15% of the circulating estrogen is obtained directly from testicular production with the remaining androgens due to the aromatase enzyme activity[5].The dominant estrogen circulating in men is 17β-estradiol, which is produced by aromatization of testosterone (Tes)[6].Several studies have clearly established that an increased activity of aromatase, the enzyme converting Tes into Estrogen, in adipose tissue may explain the rise of Estrogen levels in obese men[7].Other studies postulate that obese men have defective estrogen receptors, which leads to a decrease in estrogen-binding globulin, increased clearance of androgenic hormones, and elevated E2 production rates[8].

The objective of the study is to correlate the relationship within serum testosterone-estradiolratio dueto BMI, which may provide further clues to investigate the potential regulation and biological mechanism of obesity.

MATERIAL AND METHODS

This open label, non-randomized clinical trial was performed in the College of Medicine, University of Anbar from July to November 2019. The subjects recruited are from thosewho attended Ramadi Teaching hospital in Anbar Governorate, Iraq. The subjects of this study were 72 males ageing 22-51 years. The criteria of containment were obese subjects with a body mass index ≥ 30kg/m^{2}according to the WHO classification in absence of co-morbidities of obesity. Criteria of exclusion were diabetes mellitus, familial hyperlipidemia, hypothyroidism, renal and hepatic diseases.

Each patient was physically examined by a consultant of internal medicine at the time of admission into the study. The anthropometric determinants included weight (kg), and height (m) measuring and the body mass index (BMI) measurement using Quetlet's equation:

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

Venous blood samples (fasting) obtained from subjects and collected in test tubes without anticoagulant.The serum was separated by centrifugation (3000rpm/min) for biochemical and hormonal assays: Insulin (Ins), E2, Tes& thyroid stimulation hormone (TSH)using Chemiluminescence assay analyzer (Tosoh AIA-600).

The IBM SPSS Statistics (version 23.0) was performed for statistical analysis. Mean ± SD express a normal distribution. ANOVA used to compare between obese males. For this whole study Pearson correlation coefficients were calculated. Significant statistics were considered when P values less than 0.05.

RESULTS

Table 1: Parameter levels among men of different age groups

	20-29 years	**30-39 years**	**40+ years**	**Total**	*p*	*N.V.*
Age number (%)	18 (25.0)	38 (52.8)	16 (22.2)	72 (100)		
Age mean (±SD)	25.83(2.43)	25.13(2.97)	46.69(2.58)	35.38(7.71)	0.001	
BMI	34.35(2.17)	34.88(2.16)	36.52(4.68)	35.09(2.93)	0.082	
IR	3.31(2.05)	3.67(1.56)	6.21(1.75)	4.14(2.05)	0.001	(1-17) µU/ml
E2	40.19(13.14)	41.32(11.85)	55.14(11.75)	44.11(13.39)	0.001	(10-40) pg/ml
Tes	387.0(71.2)	359.8(50.5)	326.2(84.4)	359.1(67.0)	0.028	(250-950)ng/dL
Ratio (Tes/E2)	99.92(31.13)	91.72(35.50)	60.17(23.99)	86.76(35.03)	0.001	

ANOVA test was used to calculate f & p-value

N.V: Normal value.

The patients were sub-grouped according to the WHO classification of obesity. The frequency distribution is shown in table 2, and their mean laboratory data comparison shown in table-3.

Table 2: Frequency distribution of different BMI among men of different age groups

Age group (in years)	**BMI Class 'I' (30.00-34.99)**		**BMI Class 'II' (35.00-39.99)**		**BMI Class 'III' (≥40.00)**	
Group	n	(%)	n	(%)	n	(%)
20-29	9	(25)	9	(30)	0	(0)
30-39	20	(55.6)	16	(53.3)	2	(33.3)
40+	7	(19.4)	5	(16.7)	4	(66.7)
Total	36	(50)	30	(41.7)	6	(8.3)

Table 3: Mean comparison by ANOVA depending on BMI classes.

	BMI Class 'I' (30.00-34.99)	BMI Class 'II' (35.00-39.99)	BMI Class 'III' (≥40.00)	**Total**	*p*
BMI number (%)	36 (50.0)	30 (41.7)	6 (8.3)	72 (100)	
BMI mean (±SD)	33.10(1.48)	34.80(7.55)	42.17(9.20)	35.38(7.71)	0.001
Age	34.72(7.25)	36.70(6.48)	28.50(1.87)	35.13(6.35)	0.077
E2	38.15(8.51)	47.71(15.11)	61.87(0.99)	44.11(13.39)	0.001
Tes	384.4(51.9)	340.5(72.9)	300.3(56.9)	359.1(67.0)	0.002
Ratio (Tes/E2)	101.4(30.1)	77.4(34.5)	45.9(9.4)	86.8(35.0)	0.001
Ins	14.71(6.42)	17.16(7.97)	29.80(5.40)	16.99(8.05)	0.001
IR	3.52(1.53)	4.11(1.85)	8.03(1.48)	4.14(2.05)	0.001
HOMAβ	160.7(73.6)	205.3(152.5)	233.7(45.0)	185.4(113.9)	0.159

Measurement the linear relationship between BMI and laboratory parameters by Pearson Correlation was applied as shown in Table-4.

Table 4: Pearson Correlations

Parameters	INS	R (TES/E2)	TES	E2	IR	BMI
Age	0.096	0.108	-0.013	-0.143	0.065	0.141
BMI	**0.386****	**-0.352****	**-0.413****	**0.388****	**0.441****	
IR	**0.974****	**-0.290***	**-0.245***	**0.257***		
E2	**0.267***	**-0.935****	**-0.790****			
TES	**-0.264***	**0.827****				
R (TES/E2)	**-0.280***					

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

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

DISCUSSION

Ageing is commonly accompanies loss of muscle mass and increased body fat, especially in the abdomen; each of these changes can accretion insulin resistance(9).Therefore, ages were chosen in a period of 22 to 51 years, as the aging of people can be considered a cause of increased insulin resistance per se.

The present study confirmed previous studies that showed that estradiol level in obese males is significantly elevated[10,11]. As the class of obesity increased, serum estradiol (E2) were noted to be elevated then serum testosterone was decreased as shown in table (3). The positive correlation between serum estradiol and BMI for male recorded in our study was ($r=+0.388, p<0.01$). Previously Grantham and Henneberg, found ($r=+0.4, p<0.01$)[12].

The estradiol level is largely dependent on testosterone concentration as a precursor. In general, testosterone synthesis is stimulated by Leyding cells by luteinizing hormone (LH) together with follicle stimulating hormone (FSH) from the anterior pituitary are necessary for Sertoli cells to transduce signals and produce factors that nurture germ cells. Estradiol is known to regulate testosterone levels by decreasingthe release of these hormonesfrom the pituitary gland[13,14].

This clarifywhy in most cross-sectional studies testosterone and estradiol levelsare found invers correlation between E2 and Tes.In our study E2 was observed strongly negative associated with testosterone ($r=-0.790, p<0.001$).

Osuna and his colleagues studied the relationship of BMI and Tes in 77 men aged between 20 to 60 years in a cross sectional study.They were found significant negative correlation of Tes with BMI in the obese males [15]. Compatible with Stewart *etal*. study, they findings similar to the currentstudy results ($r=-0.413, p<0.001$)(1)

So it is observed serum testosterone (Tes) concentrations were reduced in obese males, averaging 359 ng/dl (±67), this finding is in agreement with Schneider *etal*. who found 348 (±35) vs. 519 (±42) in thin controls[8].

A correlation analysis was performed to identify the mechanisms underlying the increase estrogen and decrease testosterone levels in obese males. In contrast, HOMA-β was positive associated with E2, but

negative with Tes and Tes/E2 ratio (r = +0.315, p<0.007,r=-0.347, p<0.003 andr=-0.272, p<0.022 respectively).

There is an inverse association between testosterone levels vs insulin resistance and insulin level markers (r=0.33, P <0.0001)(16) and (r=-0.31, p<0.01)(17) respectively. The results of this study are in agreement with a previous studies (r=-0.245, p< 0.05) and (r=-264, p<0.05) respectively.

The testosterone (TES)/estradiol (E2) ratio may be low due to the low testosterone levels and increase estradiol levels. In people witha low in TES/E2 ratio has been shown to be associated with infertility[18]. Our study appropriate these relationship, a negative significant correlation between (Tes/E2) ratio with BMI (r=-0.352, p<0.05)

Formally (Bekaert et al., 2015) study on adult obese males report a strong negative significant relationship between HOMA-IR and (Tes/E2) ratio (r=-0.606, p<0.001).In our study (r=-0.290, p<0.05).

LIMITATION

Further studies with larger sample size and age-matched control group are required to validate our findings and to improve the diagnostic performance of leptin and ghrelinthat related to obesity, while examining the correlations between sex hormones and BMI on infertile obese males.

CONCLUSION

The relationship between obesity and inflammation is a topic a major concern, not only for the increasing incidence may this diseases but also due to obesity-driven inflammation be an important factor of the metabolic abnormalities that accompany the obesity.

The prime hormonal defect in obese men is (Tes/E2) ratio, which have a negative significant correlation with obese males.

ETHICAL CLEARANCE

The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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