IMPACT OF METABOLIC SYNDROME ON ANDROGEN/ ESTRADIOL RATIO, SEMEN PARAMETERS AND TESTICULAR VOLUME IN ADULTS

By

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ABSTRACT

Background: Metabolic syndrome and the related co-morbidities can lead to impaired male reproductive function, including adverse effects on spermatogenesis and steroidogenesis as illustrated by reduced sperm number and quality, decreased testosterone levels and elevated inflammatory markers.

Objective: To evaluate the impact of metabolic syndrome on androgen / estradiol ratio, semen parameters and testicular volume in adults.

Patients and methods: This study was carried out on 60 adult males recruited from Al-Azhar University Hospitals outpatient clinics during the period between November 2016 and February 2021, divided into two equal groups: Group A: Males with the criteria of metabolic syndrome, and Group B: Males without the criteria of metabolic syndrome. All patients were subjected to: complete history taking, general and local examination, laboratory investigations (including total and free testosterone, serum estradiol, lipid profile, fasting blood glucose and Semen analysis) and scrotal duplex.

Results: Significant decrease in both free and total testosterone in the metabolic group than the nonmetabolic group. Significant inverse correlation between free testosterone / estadiol ratio and BMI, and an inverse but non statically significant correlation between free testosterone / estadiol ratio and waist circumference. Significant decrease was in both semen volume and total motility in the metabolic group than the non-metabolic group, with no statically significant difference in total sperm count, Sperm concentration, progressive motility or abnormal forms between both groups. Significant inverse correlation was found between semen volumes with BMI. Significant inverse correlation between total sperm count and sperm concentration with BMI. Significant inverse correlation was found between testicular volume on one side, and both BMI and waist circumference (WC) on the other side.

Conclusion: Metabolic syndrome is directly related to a decrease in both free and total testosterone levels. Higher BMI is associated with decreased free testosterone/ estadiol ratio.

Keywords: Metabolic Syndrome, Androgen/Estradiol Ratio, Semen Parameters, Testicular.

INTRODUCTION

Metabolic syndrome has become a major public health challenge worldwide. Key components of this syndrome include: central obesity, dyslipidemia, high blood pressure and impaired glucose metabolism (*Kusuma and Siregar, 2018*).

In men, aging is associated with a decrease in testosterone level, in contrast to the sudden decrease in estrogen levels associated with menopause in women, This decrease accompanies changes in body composition, including increases in fat mass and decreases in lean body mass, disorders of insulin and glucose metabolism and dyslipidemia (*Feldman et al., 2010*).

Some studies showed decrease in androgen level in young men with metabolic syndrome rather than healthy men (Corona et al., 2011). Intervention trials have demonstrated that exogenous testosterone supplementation in young men lowers high-density lipoprotein. In contrast, testosterone replacement in older men with low serum testosterone compared with young healthy men, increases lean body mass and decreases fat mass, total cholesterol, and lowdensity lipoprotein without affecting high density lipoprotein (Page et al., 2010).

The age-related increasing prevalence of MS has been linked with the parallel decline in testosterone levels, perhaps due to increased conversion of testosterone into estradiol (E2) in obese individuals. It has been proposed that the relative increase of circulating levels of E2 derived from conversion of testosterone in adipose the tissue inhibits the hypothalamic-pituitary unit resulting in a reduction of testosterone/estradiol ratio and leading to the vicious cycle of "obese estrogenic hypogonadism" (Mah and Wittert, 2010).

Nearly 70% of conditions causing infertility in men can be diagnosed by history, physical examination, testicular volume estimation, hormonal and semen analysis, scrotal ultrasound (Singh et al., 2014).

Since the seminiferous tubules comprise 70% to 80% of the testicular mass, testicular volume is likely to reflect spermatogenesis and semen profile in infertile men. Testicular volume (TV) is proposed to be a positive predictor of male fertility status, because of the relation known between the TV and the seminiferous tubule content (*Spaggiari et al.*, 2020).

Ultrasound (US) is generally recognized the accurate as most noninvasive primary modality in the evaluation of testicular function (Paltiel et al., 2010). While the semen analysis appears to be important in the evaluation of testicular function, the testicular volume has long been associated with testicular function (Singh et al., 2014).

The aim of this study was to clarify the correlation between metabolic syndrome and male factor infertility, showing its effect on androgen / estradiol ratio, seminal parameters and testicular volume measured by scrotal duplex.

PATIENTS AND METHODS

This study was carried out on 60 adult males recruited from Al-Azhar University Hospitals outpatient clinics during the period between November 2016 and February 2021, divided into two equal groups: Group A: Males with the criteria of metabolic syndrome, and Group B: Males without the criteria of metabolic syndrome.

Exclusion criteria: Men with varicocele, men with azoospermia, men with cryptorchidism, a known case of primary hypogonadism, men receiving medications affecting fertility or hormonal status, men with chronic systemic disease as liver cell failure, chronic renal failure,etc, and primary scrotal disease identified by ultrasound evaluation as hydrocele.

All subjects were subjected to the following:

- I. Complete History taking: (a) Personal history (b) Medical history: Hypertension treatment, diabetes treatment, dyslipidemia treatment, infertility treatment and any treatment affecting fertility or hormonal state.
- **II. Examination:** (a) General body examination including: Mean arterial blood pressure, weight, height, BMI, waist circumference, and secondary sexual characters: were inspected. (b) Local genital examination: Testicular examination, vas palpation, spermatic cord inspection and palpation, and pubic area inspection.
- **III. Laboratory investigations:** (a) Fasting blood Glucose level (b) Lipid profile (c) Hormonal assay (d) Semen analysis.
- **IV.Imaging:** Scrotal duplex to assess the testicular volume, and to exclude varicocele or any other abnormalities.

High frequency US was performed by using 7.5 MHZ transducers (Mindray Z5) with subjects in a supine position, and the penis displaced over the pubis, covered and held by the patient. The scrotum was supported over the thighs of the patient that were drawn together with an amount of acoustic gel the temperature of which is the same as room temperature. Examination started by gray scale system of the scrotal contents, then Color Doppler was used to examine the testis. Ultrasonic Testicular volumes were calculated using the prolate spheroid formula: volume= length× width 2×0.52 (*Lasiene et al.*, 2020).

Statistical analysis:

Data were collected, revised, coded and entered to the Statistical Package for the Social Science (IBM SPSS) version 23 to find the Impact of Metabolic Syndrome on Androgen / Estradiol Ratio, Semen Parameters and Testicular Volume. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IOR) when data found nonparametric. Also qualitative variables number were presented as and percentages. The comparison between both groups regarding quantitative data and parametric distribution was done by using Independent t-test while with nonparametric distribution was done by using Mann-Whitney test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. The confidence interval was set to 95% and the margin of error accepted was set to 5%. P value < 0.05 was considered significant.

RESULTS

The mean and standard deviation of age in group A was 39.50 ± 8.24 and in group B was 33.53 ± 6.36 with a statistically significant increase in age in group A than group B.

The mean and standard deviation of weight in group A was 105.00 ± 22.85 and in group B was 75.27 ± 9.83 with statistically significant increase in weight in group A than group B. The mean and standard deviation of height in group A was 167.70 ± 18.19 and in group B was 172.70 ± 6.28 with no statistically significant difference between both groups. The mean and standard deviation of BMI in group A was 38.66 ± 12.32 and in group B was 25.20 ± 2.60 with a statistically increase in BMI in group A than group B. The mean and standard deviation of waist circumference in group A was 114.60 ± 14.94 and in group B was 89.17 ± 9.16 with statistically significant increase in waist circumference in group A than group B.

The mean and standard deviation of fasting blood glucose in group A was 110.30 ± 39.99 and in group B was 86.73 ± 11.60 with a statistically significant increase in fasting blood glucose in group A than group B.

The mean and standard deviation of cholesterol in group A was 217.00 ± 37.82 and in group B was 171.60 ± 28.68 with a statistically significant increase in cholesterol in group A than group B. The

mean and standard deviation of TG in group A was 226.00 ± 87.71 and in group B was 91.67 ± 37.47 with a statistically significant increase in TG in group A than group B. The mean and standard deviation of HDL in group A was 50.49 ± 7.35 and in group B was 66.84 ± 12.89 with a statistically significant decrease in HDL in group A than group B. The mean and standard deviation of LDL in group A was 134.17 ± 38.61 and in group B was 96.28 ± 25.55 with a statistically significant increase in LDL in group A than group B.

The mean and standard deviation of free testosterone in group A was $10.73 \pm$ 4.17 and in group B was 15.79 ± 8.13 with a statistically significant decrease in free testosterone in group A than group B. The mean and standard deviation of total testosterone in group A was 4.15 ± 1.89 and in group B was 5.60 ± 1.63 with a statistically significant decrease in total testosterone in group A than group B. The mean and standard deviation of estradiol in group A was 34.65 ± 8.65 and in group B was 38.51 ± 13.04 with no statistically significant difference in estradiol between both groups.

The median (IQR) of free testosterone / estradiol ratio in group A was 0.31 (0.22 - 0.4) and in group B was 0.38 (0.26 - 0.52) with no statistically significant difference in free testosterone/ estradiol ratio between both groups (**Table 1**).

	Groups	Group A	Group B	D -volveo
Parameters		No. = 30	No. = 30	P-value
1.00	Mean \pm SD	39.50 ± 8.24	33.53 ± 6.36	0.002
Age	Range	25 - 52	25 - 46	0.003
Weight	Mean \pm SD	105.00 ± 22.85	75.27 ± 9.83	0.000
	Range	84 - 155	62-95	
Unight	Mean \pm SD	167.70 ± 18.19	172.70 ± 6.28	0.160
neight	Range	115 - 178	161 - 182	0.100
$\mathbf{DMI}(l_{ra}/m2)$	Mean \pm SD	38.66 ± 12.32	25.20 ± 2.60	0.000
Diviti (Kg/1112)	Range	28.08 - 68.05	20.53 - 31.02	0.000
Waist	Mean \pm SD	114.60 ± 14.94	89.17 ± 9.16	0.000
circumference	Range	104 - 148	70 - 107	0.000
Facting blood Chases	Mean \pm SD	110.30 ± 39.99	86.73 ± 11.60	0.003
r asung blood Glucose	Range	79 - 214	79 - 127	
Cholostorol	Mean \pm SD	217.00 ± 37.82	171.60 ± 28.68	0.000
Cnoiesteroi	Range	142 - 304	120 - 222	
Trialvooridos	Mean \pm SD	226.00 ± 87.71	91.67 ± 37.47	0.000
rigiyceriaes	Range	96-365	40 - 145	0.000
UDI	Mean \pm SD	50.49 ± 7.35	66.84 ± 12.89	0.000
IIDL	Range	40 - 62	48 - 94	
IDI	Mean \pm SD	134.17 ± 38.61	96.28 ± 25.55	0.000
	Range	78.4 - 210	54.3 - 131	0.000
Free Testesterone	Mean \pm SD	10.73 ± 4.17	15.79 ± 8.13	0.004
Free Testosterone	Range	6.6 - 20.88	5.77 - 33.57	
Total Testestarana	Mean \pm SD	4.15 ± 1.89	5.60 ± 1.63	0.002
	Range	1.9 - 8.2	2.79 - 8.96	
Fetradial	Mean \pm SD	34.65 ± 8.65	38.51 ± 13.04	0.182
L'SU AUIVI	Range	21.2 - 51.9	21.6 - 72.2	
Free Testosterone /	Median (IQR)	0.31 (0.22 – 0.4)	0.38 (0.26 - 0.52)	0.214
Estradiol ratio	Range	0.16 - 0.58	0.11 - 1.55	0.214

 Table (1): Age, body measurements, fasting blood glucose, lipid profile, hormonal assay, and free testosterone / estradiol ratio distribution in both groups

There was a statistically significant inverse correlation between free testosterone and BMI. There was a statistically significant inverse correlation between total testosterone and BMI. There was statistically significant inverse correlation between free testosterone / estadiol ratio and BMI (**Table 2**).

 Table (2):
 Correlation between free and total testosterone, free testosterone / estadiol ratio with BMI in all patients

BMI (kg/m2		
Parameters	R	P-value
Free Testosterone	-0.367**	0.004
Total Testosterone	-0.596**	0.000
Free Testosterone / estadiol ratio	-0.302*	0.019

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There was a statistically significant inverse correlation between semen volume and BMI. There was a statistically significant inverse correlation between total sperm count and BMI. There was a statistically significant inverse correlation between sperm concentration and BMI. There was a non-statistically significant correlation between total motility and BMI. There was a non-statistically significant correlation between progressive motility and BMI. There was a nonstatically significant correlation between abnormal forms and BMI (**Table 3**).

BMI (kg/m2)		
Semen analysis	r	P-value
Volume (ml)	-0.258*	0.046
Total sperm count	-0.366**	0.004
Sperm concentration	-0.338**	0.008
Total motility	0.232	0.075
Progressive motility	0.035	0.790
Abnormal forms	0.184	0.159

Table (3): Correlation between semen analysis and BMI in all patients

There was a statistically significant inverse correlation between semen volume and waist circumference. There was a statistically significant inverse correlation between total sperm count and waist circumference. There was a statistically significant inverse correlation between concentration sperm and waist circumference. There was а nonstatistically significant correlation between motility and waist total There was circumference. а nonstatistically significant inverse correlation between progressive motility and waist circumference. There was а nonstatistically significant correlation between abnormal forms and waist circumference (Table 4).

 Table (4):
 Correlation between semen analysis and waist circumference in all patients

Waist circumference		
Semen analysis	r	P-value
Volume (ml)	-0.370**	0.004
Total sperm count	-0.383**	0.003
Sperm concentration	-0.274*	0.034
Total motility	0.156	0.234
Progressive motility	-0.073	0.579
Abnormal forms	0.182	0.165

There was a statistically significant inverse correlation between right testicular volumes with BMI. There was a statistically significant inverse correlation between left testicular volumes with BMI. There was a statistically significant inverse correlation between right testicular volume with waist circumference. There was a statistically significant inverse correlation between left testicular volumes with waist circumference (**Table 5**).

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Table (5):	Correlation between right and left testicular volume with BMI an	nd waist
	circumference in all patients	

		r	P-value
BMI	Right testicular volume (L*W^2*0.52)	-0.360**	0.005
(kg/m2)	Left testicular volume (L*W^2*0.52)	-0.539**	0.000
Waist	Right testicular volume (L*W^2*0.52)	-0.299*	0.020
circumference	Left testicular volume (L*W^2*0.52)	-0.447**	0.000

DISCUSSION

According to the results obtained the mean and standard deviation of free testosterone showed a statistically significant decrease in both free and total testosterone in the metabolic group than the non-metabolic group.

This was in agreement with Kaplan et al. (2010) who demonstrated that the effect combined of parameters of metabolic syndrome resulted in а reduction in mean total serum T levels of approximately 150 ng/dl relative to that of middle aged lean men who did not have the metabolic syndrome. Also. approximately 70% of men, in the obese metabolic syndrome cohort had a total serum T of 400ng/dl or less.

These results were corroborated also by a study by *Muller et al. (2010)* who demonstrated that total testosterone, bioavailable testosterone, and SHBG were inversely related to several of the risk factors of MetS as defined by the National Cholesterol Education Program.

In another study of middle-aged men who had neither diabetes nor the metabolic syndrome, after 11 years of follow-up had a severalfold increased risk of developing the metabolic syndrome and diabetes (*Laaksonen et al.*, 2010).

In a study of males with Metabolic Syndrome, total and calculated FT and SHBG were significantly lower in cases with MetS than controls. Hypogonadism was seen in 30% cases with MetS compared to 3.1% in controls (*Singh et al.*, 2011).

Makhside (2010) suggested the hypogonadism addition of to the constellation of aberrations seen in MetS. The author points to observational studies reporting that low levels of testosterone and SHBG are significantly correlated with MetS and its associated components (including measures of BMI, waist circumference, and waist-height ratio).

Regarding free testosterone / estradiol ratio, in the present study, we did not find a stastistically significant difference in the median (IQR) of free testosterone / estradiol ratio between the metabolic group than the non-metabolic group. This was in agreement with *Muller et al.* (2010), who revealed that the estradiol levels were not significantly associated with metabolic syndrome or its risk factors. Also, *Kusuma and Siregar* (2018) found that estradiol to testosterone ratio in aging metabolic syndrome men was increased, but insignificant compared to the nonmetabolic syndrome group.

In the present study, a significant inverse correlation was found between both total testosterone and free testosterone on one side and BMI on the other side. This result was parallel to *Kaplan et al. (2010)* who examined baseline total serum testosterone in men participating in 2 lipid treatment studies and demonstrated an inverse correlation between BMI and serum testosterone in men with and without MetS. Also this result was in accordance with *Zumoff et al.* (2010) who reported a negative correlation between free testosterone and body mass index (BMI).

Also, our study showed a statistically significant inverse correlation between free testosterone / estadiol ratio and BMI and an inverse but non statically significant correlation between free testosterone / estadiol ratio and waist circumference. This result was nearly parallel to Kusuma and Siregar (2018) who found that estradiol to testosterone ratio in metabolic syndrome men was increased, but insignificant compared to the nonmetabolic syndrome group.

As regard to semen parameters, there was a statistically significant decrease in both semen volume and total motility in the metabolic group than the nonmetabolic group with no statistically significant difference in total sperm count, Sperm concentration, progressive motility or abnormal forms between both groups. This was in agreement with Fejes et al. (2010) who studied the semen quality in a total of 81 males involved in the study during the 1 year. The mean age of the population was 32.2 study ± 5.6 years and they stated that there was a significant decrease in semen volume inversely to BMI. Also this result was in accordance with Bhattacharva et al. (2014) who stated that in addition to the negative effects on sperm count, motility, and DNA integrity, lower ejaculate volumes were also observed in diabetic men. This also was supported by

Leisegang et al. (2021) who stated that obesity and its underlying mediators result in a negative impact on semen parameters, including sperm concentration, motility, viability and normal morphology.

In the present study, a significant inverse correlation was found between semen volume with BMI, a significant inverse correlation between semen volume and waist circumference (WC). а statistically significant inverse correlation between total sperm count and sperm concentration with BMI, a significant inverse correlation between total sperm count and WC, and a significant inverse correlation between sperm concentration and WC. This result was parallel to Chavarro et al. (2010) who found that the ejaculate volume decreased steadily with increasing BMI levels. Our result was in contrast to MacDonald et al. (2010) who found no relationship between male BMI and semen parameters. Hammiche et al. (2012) found that waist circumference ≥102 cm, a measure for central adiposity, was inversely associated with with ejaculate volume, sperm concentration and total motile sperm count. Also, this result was in agreement with Eisenberg et al. (2014) who sated that the ejaculate volume showed a linear decline with increasing BMI and WC. Similarly, the total sperm count showed a negative linear association with WC.

In the present study, the relations analysis between semen with free total testosterone testosterone. and estradiol levels were analyzed. There was statistically significant correlation а between semen volume and a significant inverse correlation between abnormal forms with free testosterone. There was a statistically significant correlation between total sperm count and sperm concentration with total testosterone. This result was in agreement with *Tang et al.* (2012) who included 90 infertile men aged 25 - 40 years in their study and stated that the The percentage of morphologically normal sperm was positively correlated with the levels of serum FT.

A significant inverse correlation was found between testicular volume on one side and both BMI and WC on the other side. This result was in contrast to *Bahk et al.* (2010) who concluded that testicular volume is positively correlated with height, body weight and BMI. Also, this was in contrast to *Ku et al.* (2010) who found significant but weak correlations between testicular volumes and height, body weight and body mass index. This contrast could be due to ethnic variations or difference in the number of patients between our study and these studies.

CONCLUSION

Metabolic syndrome was directly related to a decrease in both free and total testosterone levels. Higher BMI was with decreased associated free testosterone/ estadiol ratio. Metabolic syndrome was strongly associated with a decrease in both semen volume and total motility Higher BMI and Waist circumference were closely related to poor semen quality. Low androgen level is significantly correlated with abnormal semen parameters. BMI and waist circumference were significant risk factors for lower testicular volume.

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IMPACT OF METABOLIC SYNDROME ON ANDROGEN/ ESTRADIOL...¹⁶⁰¹

تأثير متلازمة الأيض على نسبة هرمون الذكورة الى هرمون وحجم الخصية في البالغين الاستر اديول وتحليل السائل المنوي محمد عبدالشكور عبد الحفيظ، عمرو محمد زكي، أحمد رشاد الشاهد، محمد سعيد ابراهيم الشوربجي*

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خلفية البحث: أظهرت بعض الدراست ضعف مستوى الهرمون المذكرى فى المرضى المرمون المذكرى فى المرضى الذين يعانون من متلازمة الأيض عن غير هم من الأصحاء، كما أظهرت بعض الدراسات الأخرى أنه بإعطاء الهرمون المذكرى لهؤلاء المرضى الدراسات الوزن وتحسن مستوى الدهون فى الدم فى هؤلاء المرضى.

الهدف من البحث: تقييم تأثير متلازمة الأيض على نسبة هرمون الذكورة الى هرمون الاستراديول، وتحليل السائل المنوي وحجم الخصية في البالغين.

المرضى وطرق البحث: أجريت هذه الدراسة على 60 من الذكور البالغين المترددين على العيادات الخارجية بمستشفيات جامعة الأز هر خلال الفترة ما بين نوفمبر 2016 وفبراير 2021 ، مقسمين إلى مجموعتين متساويتين: المجموعة أ: ذكور لديهم معايير متلازمة التمثيل الغذائي، المجموعة ب: ذكور بدون معايير متلازمة التمثيل الغذائي. وقد خضع جميع المرضى إلى أخذ التاريخ الكامل، والفص العام والموضعي، والفحوصات المخبرية (بما في ذلك التستوستيرون الكلي والحر، واستراديول المصل، وتحليل الدهون، وصيام الجلوكوز في الدم وتحليل السائل المنوي) وكيس الصفن.

نتائج البحث: حدث إنخف اض كبير في كل من هرمون التستوستيرون الحر والكلي في المجموعة الأيضية مقارنة بالمجموعة غير الأيضية. وهناك علاقة عكسية كبيرة بين نسبة التستوستيرون / الاستاديول الحرة ومؤشر كتلة الجسم وعلاقة عكسية ولكن غير ذات دلالة إحصائية بين نسبة التستوستيرون / الاستاديول الحرة ومحيط الخصر. وقد حدث انخفاض كبير في كل من حجم السائل المنوي والحركة الكلية في المجموعة الأيضية مقارنة بالمجموعة غير الأيضية مع عدم وجود

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فروق ذات دلالة إحصائية في إجمالي عدد الحيوانات المنوية أو تركيز الحيوانات المنوية أو الحركة التقدمية أو الأشكال غير الطبيعية بين المجموعتين. وهناك علاقة عكسية معنوية بين حجم السائل المنوي مع مؤشر كتلة الجسم، وعلاقة عكسية ذات دلالة إحصائية بين مجموع الحيوانات المنوية وتركيز الحيوانات المنوية مع مؤشر كتلة الجسم. وقد تم العثور على علاقة عكسية ذات دلالة إحصائية بين حجم الخصية على جانب واحد وكلا من مؤشر كتلة الجسم ومحيط الخصر على الجانب الآخر.

الاستنتاج: ترتبط متلازمة التمثيل الغذائي إرتباطًا مباشرًا بانخفاض مستويات هرمون التستوستيرون الحرر والإجمالي. ويرتبط إرتفاع مؤشر كتلة الجسم بانخفاض نسبة هرمون التستوستيرون/ الاستاديول الحر.

الكلمات الدالة: متلازمة التمثيل الغذائي، نسبة الأندروجين/ الإستراديول، معاملات السائل المنوى، الخصية.