Original Article

Sertoli Cell Function in Young Males with Metabolic Syndrome

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Abstract

Context: The last few decades have witnessed an alarming increase in the prevalence of the metabolic syndrome (MetS) worldwide including India. Apart from the known risks of MetS in terms of cardiovascular risk and mortality, there is increasing evidence that it also leads to alteration in testicular function and fertility. **Aims:** To assess the presence of hypogonadism and Sertoli cell dysfunction in young adult males with MetS and correlate these parameters with different components of the MetS. **Settings and Design:** Cross-sectional study conducted in the Department of Endocrinology, Gauhati Medical College, a tertiary care hospital in North East India. **Subjects and Methods:** Young adult males with MetS aged 20–40 years and age-matched healthy males who served as controls were examined clinically. Laboratory investigations done in the fasting state included blood glucose, lipid profile, serum follicle-stimulating hormone (FSH), inhibin B and total testosterone (Te). Semen was collected after 3 days abstinence and analysis done. **Statistical Analysis:** Baseline parameters were presented as median and 'Kruskal–Wallis' test was used to compare them. Pearson test and multiple regression analysis were used to assess the correlation and association between variables. **Results:** Fifty cases with MetS and 30 controls were included in the study. Subjects with MetS had significantly lower levels of total Te, FSH and inhibin B. They also had significantly lower semen volume, sperm count and total as well as progressive motility. There was a significant negative correlation of waist circumference and positive correlation of inhibin B with total sperm count. A significant negative association of serum triglycerides with semen volume was also found. **Conclusion:** MetS is a state of hypogonadotropic hypogonadism as reflected by low total Te, FSH and inhibin B levels with semen abnormalities reflecting Sertoli cell dysfunction.

Keywords: Hypogonadism, metabolic syndrome, Sertoli cell, sperm abnormalities

Introduction

The last few decades have witnessed an alarming increase in the prevalence of metabolic syndrome (MetS) worldwide including India. A recent study in urban Eastern India of 1178 adults has shown a prevalence of 24.9% in males and 42.3% in females.[1] Another recent study from Dibrugarh town of Assam in North Eastern India found a prevalence of MetS of 47.6% in an urban population of 1700 subjects.[2] Apart from the known risks of MetS in terms of cardiovascular risk and mortality, there is increasing evidence that it also leads to alteration in testicular function and fertility. Various studies have focused on the association of MetS with suppression of Leydig cell function as reflected by low serum testosterone levels. Recent studies have also highlighted the occurrence of Sertoli cell dysfunction in subjects with MetS. The Sertoli cells provide developing germ cells with structural and hormonal support.[3] Inhibin B is a dimeric peptide produced in the testis by the Sertoli cells and is emerging as a marker of Sertoli cell function. Animal studies have shown that the neonatal and pubertal period witness an increase in the number of Sertoli cells along with a rise of circulating inhibin B levels.[4] In the adult testis the Sertoli cells occupy around 25% of the volume of the seminiferous tubules and each Sertoli cell surrounds several germ cells providing structural and biochemical support.[5]

Inhibin B levels have been found to decline with increasing obesity in young adult males possibly indicating that obese men have fewer Sertoli cells than normal weight men.[4] Defects in spermatogenesis have also been described in men with obesity and MetS including low ejaculatory volume, sperm count, sperm concentration and defects in motility. Abnormal spermatozoal mitochondrial membrane potential (MMP) and sperm with high DNA fragmentation have also been reported in men with MetS.[6,7] Hypogonadism with low testosterone and

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low sex hormone-binding globulin (SHBG) levels in young adults with MetS have been reported previously from our centre.[8] Data on the defects in spermatogenesis in adult males with the MetS are lacking from North East India. The present study was designed to assess the presence of hypogonadism and Sertoli cell dysfunction in young adult males with MetS.

Subjects and Methods

This study was conducted in the Department of Endocrinology, Gauhati Medical College which is a tertiary care hospital in North East India. A total of 50 subjects in the age group of 20–40 years who fulfilled the International Diabetes Federation (IDF) 2005 criteria for the diagnosis of MetS were included. Thirty age-matched men without MetS were taken as controls. Subjects having a known genetic disorder causing hypogonadism, a history of pituitary disease or any central nervous system (CNS) lesion, any testicular pathology like testicular tumours, genital tract infection, varicocele or undescended testis, mumps or orchitis, testicular trauma, radiation or reproductive organ surgery, any medication known to affect testicular function, thyroid disease or any major systemic illness were excluded from the study. The study was approved by the institutional ethics committee and informed consent was taken from the participants.

A thorough clinical evaluation of the subjects was done including body mass index (BMI), waist circumference (WC), blood pressure (BP) and genital examination. When measuring the WC the recommendation made by the National Heart, Lung, and Blood Institute (NHBLI)[9] was followed. Blood samples were collected from the subjects in the fasting state for glucose and lipid profile. Pooled samples were collected for follicle-stimulating hormone (FSH), total testosterone (Te) and inhibin B in the fasting state and stored at −20°C. Plasma glucose and lipid profile estimation were done by the auto analyzer Vitros 5600. The assays for FSH and Te were performed by radioimmunoassay. The normal range of Te was taken as 2.5–8.5 ng/ml with an intra- and interassay coefficient of variation (CV) of 6.15% and 5.8%, respectively. Normal range of FSH was 1.3–11.5 IU/L and intra- and interassay CV was 4.2% and 4.6%, respectively. Inhibin B was measured by the enzyme-linked immunosorbant assay (ELISA). The normal range was 25–325 pg/ml and intra- and interassay CV was <10% and <12%, respectively.

Semen was collected for analysis after 3 days of abstinence in a wide mouth sterile container. The analysis was performed according to the World Health Organisation (WHO) 2010 guidelines[10] and appearance, volume, count, morphology and motility noted.

Statistical analysis was performed by the use of the Statistical Analysis Software (SAS) 9.3. Baseline parameters were presented as median and 'Kruskal–Wallis' test was used to compare the median values. Pearson correlation was done to find out the pattern of correlation between the independent variables. Multiple regression analysis was carried out to see the association between different variables. Statistical significance was set at P value of ≤ 0.05.

Results

The baseline characteristics of the cases and controls are shown in Table 1. As expected subjects with MetS had significantly higher WC, BMI, systolic and diastolic blood pressure (SBP and DBP), fasting blood glucose (FBG), triglyceride (TG) and lower high-density lipoprotein (HDL) levels as compared to the controls. The serum levels of total Te, FSH and iInhibin B were significantly lower than the controls in subjects of MetS.

Comparison of semen parameters in subjects of MetS with that of controls showed significantly lower total sperm count, volume and lower total as well as progressive motility in the MetS group [Table 2]. No difference was found regarding sperm morphology between the two groups.

When the correlation of different variables with semen parameters was analysed in the subjects of MetS, it was seen

Table 1: The comparison of clinical, biochemical and hormonal parameters of cases and controls

Parameters	Cases (n=50) Median (range)	Controls (n=30) Median (range)	P
Age (years)	29.00 (21-35)	29.00 (22.00-35.00)	1.00
WC (cm)	96.50 (91-104)	71.40 (68.50-80.20)	<0.001*
BMI (kg/m^2)	29.98 (27.60-32.35)	21.24 (19.86-23.30)	<0.001*
SBP (mmHg)	143.00 (110.00-166.00)	100.00 (92.00-106.00)	<0.001*
DBP (mmHg)	85.00 (70.00-100.00)	70.00 (68.00-72.00)	<0.001*
FBG (mg/dl)	138.00 (70.00-297.00)	78.00 (66.00-97.00)	<0.001*
HDL (mg/dl)	39.00 (25.00-69.00)	52.00 (36.00-69.00)	<0.001*
TG (mg/dl)	173.00 (85.00-600.00)	100.00 (78.00-156.00)	<0.001*
FSH (IU/l)	0.97 (0.76-1.10)	3.80 (3.00-4.20)	<0.001*
Te (ng/ml)	2.32 (1.50-4.50)	4.04 (1.98-5.98)	<0.001*
Inhibin B (pg/ml)	22.25 (14.42-36.00)	124.43 (88.84-198.94)	<0.001*

WC: Waist circumference; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglyceride; FSH: Follicle-stimulating hormone; Te: Total testosterone

Table 2: Comparison of semen parameters between cases and controls

Parameters	Cases (n=50) median (range)	Controls (n=30) median (range)	P
Total sperm count (million/ml)	14.00 (10.0022.00)	70.00 (50.00-78.00)	<0.001*
Total sperm volume (ml)	3.15 (2.40-4.20)	3.45 (2.50-4.20)	0.03*
Total sperm motility (TM) (%)	69.50 (58.00-82.00)	79.50 (70.00-86.00)	<0.001*
Progressive motility (PR) (%)	36.00 (32.00-45.00)	54.00 (50.00-59.00)	<0.001*
Normal morphology (%)	82.00 (64.00-90.00)	80.00 (70.00-85.00)	0.24

*P: Significant

that the WC has a significant negative correlation with the total sperm count. No correlation with the other parameters of semen was observed. Among the hormones a significant positive correlation of inhibin B was found with total count while the correlation of the other hormones and semen parameters were not significant [Table 3].

Multiple regression analysis in the subjects with MetS showed WC and inhibin B to have a significant negative and positive association with total sperm count, respectively. The other parameters did not have any significant association with the sperm count [Table 4]. No significant association of any of the parameters with total motility, progressive motility or sperm morphology was seen.

In the control group the correlation analysis did not show any relation of WC to semen parameters [Table 5]. However, there was a significant negative correlation of age with volume and total motility of semen. Multiple regression analysis showed a significant negative association of serum TG with semen volume in cases [Table 6].

Discussion

Hypogonadism is a feature of MetS and is postulated to be multifactorial. One of the principal mechanisms is a state of hyperestrogenic hypogonadotropic hypogonadism induced by excess aromatase activity in MetS patients because of obesity, which results in both lower total and free Te levels.[11] The resulting low Te increases lipoprotein lipase activity and TG uptake leading to increased obesity and insulin resistance and further androgen deficiency. High leptin levels in obese men have also been postulated to play a role in reduced androgen levels in obese men.[12] MetS is considered to be a state of low-grade inflammation. High levels of inflammatory cytokines have been found in seminal fluid of patients with MetS[6] reflecting a local reproductive tract inflammatory state which may have direct detrimental effect on the hypothalamo-pituitary-testicular axis, negatively modulating male reproductive function. In the present study serum total Te, inhibin B and FSH levels were significantly lower in subjects with MetS as compared to controls possibly reflecting a state of impaired Sertoli and Leydig cell function combined with an inadequate gonadotropin response due to obesity. Gonadotropin release from the pituitary could be suppressed due to estrogen and proinflammatory cytokines released due to increased adiposity creating a state of secondary hypogonadism.[13] Our findings are in concordance with the study of Robeva *et al.*[14] of 20 men with MetS and 20 age-matched non-obese men who also documented significantly lower levels of Te and SHBG and has also been seen in meta-analysis of various studies.[15,16] An inverse relation between inhibin B levels and BMI has been found in a cross-sectional study of 1558 young men.[17] Declining levels of inhibin B with increasing obesity with 26% lower levels in obese men have also been reported.[4] Which of the two hormones FSH or inhibin B better reflects Sertoli cell dysfunction of MetS? For answering this question linear regression analysis was carried out and it was found that only inhibin B had a significant positive relationship with the total

Table 3: Correlation of different variables with semen parameters in cases (n=50)

PARAMETERS	COUNT	VOLUME	TOTAL MOTILITY	PROGRESSIVE MOTILITY	MORPHOLOGY
AGE CC	0.01	0.03	−0.05	−0.08	−0.03
P	0.97	0.83	0.74	0.58	0.83
WC CC	−0.43	−0.09	−0.20	0.04	−0.22
P	0.00*	0.53	0.17	0.81	0.14
BMI CC	−0.05	−0.18	−0.02	0.06	−0.22
P	0.75	0.23	0.90	0.70	0.14
SBP CC	0.19	−0.06	0.07	0.07	0.03
P	0.20	0.70	0.62	0.64	0.82
DBP CC	0.16	−0.14	0.03	−0.01	0.09
P	0.27	0.35	0.85	0.93	0.54
FBG CC	−0.15	−0.02	0.32	0.32	−0.07
P	0.31	0.89	0.08	0.12	0.61
HDL CC	0.07	−0.08	0.11	0.11	−0.14
P	0.66	0.58	0.44	0.46	0.34
TG CC	0.02	−0.26	0.13	0.23	0.22
P	0.89	0.08	0.38	0.11	0.13
FSH CC	0.17	0.05	−0.29	−0.13	−0.18
P	0.26	0.75	0.08	0.38	0.23
Te CC	−0.27	−0.12	−0.04	−0.12	−0.16
P	0.07	0.42	0.77	0.41	0.27
Inhibin B CC	0.45	−0.10	0.09	−0.01	0.04
P	0.00*	0.52	0.55	0.96	0.80

CC: Correlation coefficient, *P: Significant, WC: Waist circumference; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglyceride; FSH: Follicle-stimulating hormone; Te: Total testosterone, FBG: Fasting blood glucose; HDL: High-density lipoprotein

sperm count even after adjusting for age. Neither FSH nor total Te showed any significant relationship with any of the semen parameters. The superiority of inhibin B as a better marker of spermatogenesis than FSH has also been demonstrated in previous studies.[18,19]

The pattern of semen abnormalities observed among the cases in the present study, is consistent with several studies done on semen abnormalities of subjects with higher BMI. Jensen *et al.*[17] in their study of 1558 Danish men observed a lower sperm concentration and total count in men with BMI >25 kg/m^2. Stewart *et al.*[20] examined the semen quality in fertile Australian men and demonstrated that BMI was an independent factor related to total sperm count. There was a significant lower total sperm count in obese men with BMI of >30 kg/m^2. A recent Iranian study by Hajshafiha *et al.*[21] done on 159 male patients who attended an infertility clinic concluded that at higher BMI values the likelihood of oligospermia increased. Obese men were found to be 3.5 times more likely to have oligospermia as compared to normal counterparts.

As regards motility, the findings of decreased total and progressive motility of sperms in the subjects with MetS corroborates with the results of two previously published studies. Kort *et al.*[22] in their study of 520 men demonstrated that in those with BMI >25 kg/m^2 there was decreased total motility of sperms per ejaculate. It was also observed in the study that BMI had a significant negative relationship with sperm motility. La Vignera *et al.*[23] observed that in overweight and obese men there was a significantly lower progressive motility of sperms along with significantly more sperms with abnormal morphology. An additional finding of our study, which was not seen in several earlier studies, is the lower semen volume in subjects of MetS. However a recent study of 32 men with MetS[6] found significantly reduced levels for ejaculate volume, sperm concentration, total sperm count, sperm vitality and total and progressive motility as

Table 4: Multiple regression analysis of variables in relation to sperm count in cases (*n*=50)

Independent variables	Parameter estimate	Standard error	*P*
Intercept	16.9993	17.9108	0.3489
Age	0.0934	0.1180	0.4337
WC	−0.4292	0.1575	0.0098*
BMI	0.6571	0.3822	0.0942
SBP	−0.0022	0.0330	0.9477
DBP	0.0572	0.0606	0.3512
FBG	−0.0093	0.0072	0.2051
HDL	0.0220	0.0435	0.6166
TG	−0.0010	0.0045	0.8215
FSH	8.7745	5.1056	0.0943
Te	−0.7872	0.4563	0.0931
Inhibin B	0.2714	0.0918	0.0054*

**P*: Significant. WC: Waist circumference; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglyceride; FSH: Follicle-stimulating hormone; Te: Total testosterone, FBG: Fasting blood glucose; HDL: High-density lipoprotein

Table 5: Correlation of different variables with semen parameters in controls (*n*=30)

Parameters	Count	Volume	Total motility	Progressive motility	Morphology
AGE CC	0.01	−0.46	−0.38	0.06	−0.19
p	0.94	0.01*	0.05*	0.75	0.32
WC CC	0.14	0.16	0.00	−0.2	0.11
p	0.49	0.41	0.98	0.32	0.56
BMI CC	0.24	0.23	−0.16	−0.03	0.17
p	0.22	0.23	0.42	0.89	0.40
SBP CC	0.05	0.11	0.36	−0.11	−0.10
p	0.81	0.57	0.06	0.59	0.62
DBP CC	0.14	0.10	0.23	−0.22	−0.06
p	0.49	0.60	0.23	0.26	0.76
FBG CC	0.21	0.14	0.09	−0.01	0.00
p	0.28	0.47	0.65	0.98	0.99
HDL CC	−0.12	0.16	0.01	−0.03	0.53
p	0.53	0.43	0.97	0.90	0.08
TG CC	−0.01	0.00	0.05	0.26	0.12
p	0.98	0.99	0.80	0.90	0.55
FSH CC	0.21	0.10	−0.40	−0.09	−0.35
p	0.29	0.60	0.06	0.63	0.07
Te CC	−0.07	0.20	−0.12	0.23	0.19
p	0.71	0.31	0.53	0.24	0.32
Inhibin B CC	−0.07	0.20	−0.12	0.23	0.19
p	0.71	0.31	0.53	0.24	0.32

CC: Correlation coefficient,**P*: SignificantWC: Waist circumference; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglyceride; FSH: Follicle-stimulating hormone; Te: Total testosterone, FBG: Fasting blood glucose; HDL: High-density lipoprotein

Table 6: Multiple regression analysis of variables in relation to semen volume in cases (n=50)

Independent variables	Parameter estimate	Standard error	*P*
Intercept	7.7784	2.6106	0.0051
Age	0.0040	0.0172	0.8187
WC	0.0000	0.0230	0.9999
BMI	−0.0915	0.0557	0.1091
SBP	−0.0019	0.0048	0.6940
DBP	−0.0094	0.0088	0.2921
FBS	−0.0005	0.0011	0.6529
HDL	−0.0061	0.0064	0.3471
TG	−0.0014	0.0007	0.0374*
FSH	−0.0922	0.7442	0.9021
Te	−0.0765	0.0665	0.2579
Inhibin B	−0.0042	0.0134	0.7546

**P*: Significant. WC: Waist circumference; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglyceride; FSH: Follicle-stimulating hormone; Te: Total testosterone, FBG: Fasting blood glucose; HDL: High-density lipoprotein

compared to the control group. The percentages of sperm with abnormal MMP and DNA fragmentation were also found to be significantly increased.

Correlation analysis of the present study showing a significant negative correlation of WC but not BMI with total sperm count could be explained in two ways. Firstly, the cases were selected based on the WC primarily and not on BMI. Second, the disparity observed with these two closely related parameters could be due to statistical analysis of a small number of cohorts. Nevertheless, this does not alter the conclusion that obesity which is a part of MetS has significant correlation with the decreased total sperm count.

The other parameters of semen analysis – motility, morphology and volume did not show any significant correlation with either BMI or WC and is in accordance with the correlation analysis of the aforementioned studies. We found a significant negative association of serum TG levels with semen volume. A potential link between lipids and sperm parameters has been suggested by previous animal and human studies. In the Longitudinal Investigation of Fertility and Environment (LIFE) study a significant negative association was observed between total cholesterol and semen volume while free cholesterol was negatively associated with percent sperm head with acrosome, sperm head area and sperm head perimeter.[24] Another study has shown that increased TGs correlate with significantly reduced sperm motility in a group of infertile men.[25] The mechanism is not clear but hormone sensitive lipase (HSL) which liberates free fatty acids from TGs may play a key role. Fatty acids are important for spermatogenesis.

The limitation of the study is a small sample size of the study cohort. Another limitation is that it was total Te that was measured without estimation of SHBG or free Te levels and hence this should be kept in mind while interpreting Te levels.

Conclusion

MetS is a state of hypogonadotropic hypogonadism as reflected by low testosterone, FSH and inhibin B levels. The Sertoli cell dysfunction of MetS is evident in low total sperm count, volume, low total and progressive motility with normal sperm morphology as compared to healthy non-obese controls. There is a negative correlation of WC with total sperm count. TG levels have a significant negative association with semen volume. Among the hormones only inhibin B has a significant positive association with total sperm count, thus demonstrating its superiority over FSH as a marker of Sertoli cell function.

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Conflicts of interest

There are no conflicts of interest.

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