Relationship between Testosterone, Insulin Resistance, Inflammatory Markers and Obesity Parameters in Overweight and Obese Adolescents and Adult Males - A Cross-Sectional Study

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ABSTRACT

BACKGROUND

Obesity is a global pandemic in adolescent and adult population. Although changes in hypothalamic-pituitary-gonadal (HPG) axis with obesity is well known, there is dearth of literature from Eastern India especially with its relationship to obesity parameters, insulin resistance (IR) & inflammatory markers. We wanted to study the changes in total testosterone (TT), sex hormone binding globulin (SHBG) and calculated free testosterone (cFT) with parameters of obesity [body mass index (BMI), waist, hip, neck, wrist circumference and waist-hip ratio], insulin resistance [homeostatic model assessment (HOMA) – insulin resistance (HOMA-IR) and (HOMA2-IR) and inflammation (adiponectin and high sensitivity C-reactive protein, hs-CRP)] in overweight and obese (OWOB) adolescent and adult males.

METHODS

An institution based cross-sectional study was done from January 2018 to January 2020 consisting of 323 male participants including adolescent and adults presenting to or being referred for overweight or obesity to the Department of Endocrinology and non-obese volunteers.

RESULTS

TT was lower in OWOB groups (adolescents - 216.6 ± 82.2 vs. 259.0 ± 111.1 ng / dl; P = < 0.0001, adults - 392.3 ± 131.4 vs. 500.24 ± 137.8 ng / dl; P = < 0.0001) compared to nonobese. Luteinizing hormone (LH), SHBG and cFT was also significantly lower in OWOB groups. Obesity parameters (except waist-hip ratio), HOMA-IR, HOMA2-IR and adiponectin correlated with TT, SHBG and cFT in OWOB adults and only TT in OWOB adolescents. Hs-CRP correlated with TT, SHBG and cFT in OWOB adults.

CONCLUSIONS

Testosterone was found to have a significant correlation with parameters of obesity, insulin resistance, and inflammation in overweight and obese adolescent and adult males.

KEYWORDS

Overweight, Obesity, Insulin Resistance, Testosterone, Hypogonadism

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BACKGROUND

Obesity has now reached epidemic proportions according to the World Health Organization (WHO). Over 1.9 billion adults are overweight (39 % men and 40 % women) out of whom 650 million are obese (11 % men and 15 % women).[1] Among children and adolescents aged between 5 - 19 years, over 340 million are overweight or obese. The rise has occurred similarly among both boys and girls.[2] The rise in the prevalence of obesity in India has been attributed to increased westernisation and urbanisation, increased consumption of processed and fast foods which are less in nutrients and high in energy and sedentary lifestyle.[3-5]

The bidirectional relationship between obesity and its relationship with low testosterone is known.[6] Despite this, there is still insufficient data from India regarding the changes of testosterone with parameters of obesity, insulin resistance and inflammatory markers. We intended to study the changes of testosterone with obesity parameters, insulin resistance and inflammatory markers in overweight and obese adolescent and adult males. Compare them to healthy individuals with normal BMI. We wanted to study the changes in total testosterone, sex hormone binding globulin and calculated free testosterone with parameters of obesity (BMI, waist, hip, neck, wrist circumference and waist-hip ratio), insulin resistance (HOMA, HOMA-IR and HOMA2-IR) and inflammation (serum adiponectin and high sensitivity C-reactive protein) in overweight and obese adolescent and adult males.

METHODS

Our study was an institution based cross-sectional study consisting of 323 participants in the Department of Endocrinology, Nilratan Sircar Medical College & Hospital, Kolkata for a period of 2 years from January 2018 - January 2020. Adolescent and adult individuals presenting to or being referred for overweight or obesity to the outdoor / indoor of the Department of Endocrinology and non-obese volunteers were recruited by convenience sampling and a greater number of patients were included in the overweight and obese groups while there were fewer patients in the normal body mass index groups.

Inclusion Criteria

1. Adolescent males aged between 12 - 18 years who were overweight or obese measured according to 2015 revised Indian Academy of Paediatrics (IAP) BMI chart for boys.
2. Adult males above 18 years who were overweight (BMI between 23.0 – 24.9 Kg / m^2) or obese (more than or equal to 25 Kg / m^2).
3. Healthy adolescents and adult males with normal BMI who gave consent.

Exclusion Criteria

1. Female sex / disorders of sexual dysfunction / gender dysphoria.
2. Age > 65 years.
3. Patients with known diabetes mellitus.
4. Patients with known hypothyroidism.
5. Patients with known hypopituitarism, primary / secondary hypogonadism, Cushing's syndrome and other endocrine / genetic disorders leading to weight gain.
6. Prior exposure to drugs causing weight gain (corticosteroids, antiepileptic, antipsychotics, antidepressants) or endocrine dysfunction.
7. Patients with acute inflammation / infections or chronic systemic illness (malignancy, rheumatic disease, human immunodeficiency virus-HIV, chronic hepatitis) or chronic organ failure (chronic liver disease, chronic kidney disease, restrictive or obstructive pulmonary disease, heart failure).
8. Patients exposed to chemotherapy or ionising radiation.
9. Patients with h / o head injury. Pituitary surgery, snake bite.

Adolescent (12 - 18 years) and adult (> 18 years) males were included in the study after taking an informed consent according to the above-mentioned inclusion / exclusion criteria. The recruitment into the study was done by convenience sampling. Institutional ethics committee clearance was taken prior to the start of this study. Diagnosis of overweight and obesity for adolescents and adults was done according to the 2015 Revised IAP BMI Chart and the BMI Consensus Statement by Misra et al. (2009), respectively.[7,8]

The subjects were divided into four arms.

1. Overweight and Obese adolescent males.
2. Overweight and Obese adult males.
3. Adolescent males with normal BMI.
4. Adult males with normal BMI.

Parameters Studied

Anthropometric Parameters

a. Height (in cm) - measured to the nearest 0.1 cm using a stadiometer. The patient stands with feet together with the heel, buttock, upper back and occiput touching the scale with head in the Frankfurt plane.
b. Weight (in kgs) - measured to the nearest 0.5 kg using a standard weighing scale.
c. Body mass index – weight (in kg) / height (in m^2)
d. Waist circumference (in cm) - measured at the end of expiration at the midpoint between the top of the iliac crest and the lower margin of the last palpable rib in midaxillary line
e. Hip circumference (in cms) – Hip circumference was measured around the widest portion of the buttocks, with the tape parallel to the floor with patient standing erect with feet together and wearing light clothing.
f. Waist to hip ratio
g. Neck circumference (in cm) - Taken in centimetres to the nearest 1 mm, using plastic tape measure. It was taken in a plane as horizontal as possible, at a point just below the larynx (thyroid cartilage) and perpendicular to the long axis of the neck (the tape line in front of the neck at the same height as the tape line in the back of the

neck). While taking this reading, the participant was asked to look straight ahead, with shoulders down, but not hunched.

h. Wrist circumference (in cm) - measured using an un-stretchable tape measure positioned over the Lister tubercle of the distal of radius and over the distal of ulna with participants in a sitting position.

Sexual Maturity Rating (Tanner Staging) and Stretched Penile Length [SPL] (in cm)

Testicular Volume [TV] (in ml) measured using Prader Orchidometer

Metabolic and Hormonal Profile

a. Fasting plasma glucose (FPG) and 2 hours post 75 gm glucose plasma glucose (75 gm OGTT 2 hour)
b. Fasting lipid profile [total cholesterol, triglycerides, HDL, LDL (calculated using Friedewald formula)]
c. Liver function test (AST and ALT)
d. Thyroid stimulating hormone (TSH), Free T4
e. Follicle stimulating hormone (FSH) / luteinizing hormone (LH) (3 pooled samples)
f. 8 am total testosterone
g. Sex hormone binding globulin – (CMIA by Abbott ARCHITECT)
h. Calculated free testosterone [using formula by Vermeulen et al. (1999)][9]
i. Fasting insulin levels (immunoassay)
j. HOMA-IR [fasting plasma glucose (mg / dl) x fasting insulin (mU / L) / 445]
k. HOMA2-IR (using HOMA2 calculator developed by the Diabetes Trials Unit, University of Oxford http://www.dtu.ox.ac.uk/homacalculator/index.php)[10]
l. Hs–CRP (high sensitivity-CRP) (Nephelometry method)
m. Serum adiponectin (ELISA method)

Hormonal investigations were done using Siemens IMMULITE 2000 immunoassay system.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 25. Descriptive statistics was expressed as mean ± SD or median. Normality of data was tested by Shapiro-Wilk test or Kolmogorov–Smirnov test. Student t-test was used to compare means between two groups. To find out correlation between two parameters, Pearson / Spearman Correlation Coefficient was used depending on data type (parametric or non-parametric). A P-value of < 0.05 was considered statistically significant.

RESULTS

This was a cross-sectional study conducted over 2 years which studied 323 individuals including 102 overweight and obese adolescents, 118 overweight and obese adults, 48 healthy adolescents and 55 healthy adults with normal BMI. Baseline characteristics are summarised in Table 1. In the adolescents groups the mean age was 14.3 ± 1.77 years (range = 12 - 18 years) in the OWOB individuals the mean age was 14.7 ± 1.59 years (range = 12 - 18 years) in the normal BMI volunteers (P = 0.319). In the adult groups the mean age was 37.2 ± 11.19 years (range = 19 - 60 years) in OWOB individuals mean age was 35.8 ± 11.8 years (range 19 - 60) in the normal BMI group (P = 0.852). The mean BMI was 28.5 ± 5.5 v / s 20.42 1.32 kg / m^2 (P = < 0.0001) in adolescent group and 29.15 ± 6.55 v / s 22.05 ± 0.9 kg / m^2 in the adult group (P = < 0.0001). Obesity parameters was significantly higher in the OWOB groups compared to the normal BMI groups (Table 1).

Among the adolescents, majority of the patients were in Tanner staging 3 and 4 in OVOB group [Tanner 2 - 27 (26.5 %), Tanner 3 – 32 (31.4 %), Tanner 4 – 31 (30.4 %), Tanner 5 – 12 (11.8 %)] and majority of adolescents with normal BMI were in Tanner 3 & 4 [Tanner 2 - 6 (12.5 %), Tanner 3 – 13 (27.1 %), Tanner 4 – 17 (35.4 %), Tanner 5 – 12 (25 %)]. There was a significantly lower testicular volume and SPL in the OWOB adolescents, but no difference was seen among OWOB adults. Among metabolic parameters (summarized in Table 3), FPG was significantly higher in the overweight and obese adolescents compared to controls [93.12 ± 11.1 mg / dl (range 75 - 125) v / s 87.5 ± 7.8 mg / dl (range 72 - 98), P = < 0.0001] and was also significantly higher in the overweight and obese adults compared to cases [96.36 ± 14.08 mg / dl (range 76 - 124) v / s 89.8 ± 6.7 mg / dl (range 79 - 100), P = < 0.0001]. OGTT was also significantly higher in the OWOB groups compared to the normal BMI groups. Lipid profile, AST and ALT were also significantly different in the OWOB groups compared to the normal BMI groups. hs-CRP was also significantly higher in the both the OWOB groups [adolescents 3.9 ± 2.6 mg / L (range 0.9 - 9.5) v / s 2.4 ± 0.7 (range 0.8 - 3.7), P = < 0.0001 & adults 5.2 ± 5.05 mg / L (range 0.9 - 20) v / s 3.2 ± 1.2 (range 1.4 - 6.8), P = < 0.0001]. Hormonal parameters are summarised in Table 3. FSH [4.10 ± 1.27 mIU / ml (1.8 - 6.5) v / s 4.8 ± 1.7 mIU / ml (1.9 - 8.1) (P < 0.0001)] and LH [3.5 ± 1.56 mIU / ml (0.8 - 6.4 v / s 4.2 ± 1.2 mIU / ml (1.6 - 6.0 (P = < 0.0001)] were significantly lower in the OWOB adult groups and LH was lower in OWOB adolescent groups [1.7 ± 0.9 mIU / ml (0.4 - 3.6) v / s 2.05 ± 1.2 mIU / ml (0.5 - 4.9) (P = 0.001)].

There was significant difference in total testosterone [adolescents - 216.6 ± 82.2 ng / dl (94 - 506) v / s 259.0 ± 111.1 ng / dl (98 - 497)], P < 0.0001, adults - 392.3 ± 131.4 ng / dl (180 - 703) v / s 500.24 ± 137.8 ng / dl (290 - 725), P = < 0.0001], SHBG [adolescents 25.4 ± 8.7 nmol / L (15 - 45) v / s 29.37 ± 9.34 nmol / L (15 - 51)], P = < 0.0001, adults - 32.11 ± 14.4 nmol / L (12 - 60) v / s 44.95 ± 13.7 nmol / L (22 - 66), P = < 0.0001 and calculated free testosterone [adolescents 48.6 ± 17.7 pg / ml (22.9 - 87) v / s 53.59 ± 22.45 pg / ml (16.8 - 99)], P = 0.010, [adults - 78.9 ± 22.04 pg / ml (38 - 147) v / s 87.3 ± 14.7 pg / ml (65 - 123) P = < 0.0001]. TSH was significantly higher in the overweight and obese groups but no difference was seen with free T4. Fasting insulin and HOMA-IR, HOMA2-IR were significantly higher in OWOB groups while serum adiponectin was significantly lower. TT showed significant negative correlation with obesity parameters except waist hip ratio in OWOB adolescents and adults (Table 4). SHBG and CFT showed no correlation in adolescents but showed significant

negative correlation with obesity parameters except waist hip ratio in OWOB adults (Table 4). TT and CFT showed significant correlation with HOMA-IR and HOMA2-IR in OWOB adolescent and adults, however, SHBG showed correlation only in OWOB adults (Table 5). There was significant correlation between TT, SHBG, cFT and hs-CRP in OWOB adults but not adolescents. Adiponectin positively correlated with TT, SHBG, cFT in OWOB adolescents and adults (Table 5).

Parameters	Overweight and Obese Adolescents (N = 102)	Healthy Adolescents (N = 48)	P-Value	Overweight and Obese Adults (N = 118)	Healthy Adults (N = 55)	P-Value
Age (years)	14.3 ± 1.77	14.7 ± 1.59	0.319	37.2 ± 11.19	35.8 ± 11.8	0.852
Height (meters)	1.57 ± 0.10	1.55 ± 0.07	0.24	1.66 ± 0.05	1.67 ± 0.06	0.615
Weight (kg)	69.8 ± 20.12	52.1 ± 7.18	< 0.0001	81.2 ± 19.2	62.14 ± 5.6	< 0.0001
BMI (Kg / m^2)	28.5 ± 5.5	20.42 ± 1.32	< 0.0001	29.15 ± 6.55	22.05 ± 0.9	< 0.0001
Waist circumference (cm)	89.9 ± 10.44	73.8 ± 4.89	< 0.0001	100.21 ± 10.31	77.38 ± 3.54	< 0.0001
Hip circumference (cm)	91.5 ± 12.64	74.7 ± 5.06	< 0.0001	99.2 ± 9.93	78.7 ± 3.17	< 0.0001
Neck circumference (cm)	32.8 ± 4.73	24.6 ± 1.89	< 0.0001	35.7 ± 5.15	27.2 ± 1.84	< 0.0001
Wrist circumference (cm)	16.49 ± 2.27	14.14 ± 1.36	< 0.0001	17.44 ± 2.16	15.15 ± 1.31	< 0.0001
Waist-hip ratio	1.02 ± 0.06	0.88 ± 0.02	< 0.0001	1.01 ± 0.02	0.86 ± 0.02	< 0.0001
Testicular volume (ml)	13.40 ± 5.02	15.8 ± 4.98	< 0.0001	22.54 ± 3.18	21.9 ± 3.4	0.72
Stretched penile length (cm)	9.65 ± 1.50	10.38 ± 1.11	< 0.0001	10.91 ± 0.78	10.99 ± 0.85	0.45

Table 1. Baseline Characteristics of Overweight and Obese Patients Compared to Controls

Parameters	Overweight and Obese Adolescents N = 102	Healthy Adolescents N = 48	P-Value	Overweight and Obese Adults N = 118	Healthy Adults N = 55	P-Value
FPG (mg / dl)	93.12 ± 11.1 (75 - 125)	87.5 ± 7.8 (72 - 98)	< 0.0001	96.36 ± 14.08 (76 - 124)	89.8 ± 6.7 (79 - 100)	< 0.0001
OGTT (2 hr.) (mg / dl)	128.09 ± 26.1 (88 - 189)	111.3 ± 12.2 (96 - 135)	< 0.0001	134.45 ± 31.9 (89 - 198)	112.1 ± 14.07 (92 - 142)	< 0.0001
Total cholesterol (mg / dl)	166.2 ± 28.2 (92 - 210)	149.4 ± 15.9 (86 - 181)	< 0.0001	180.4 ± 42.1 (135 - 288)	142.8 ± 27.4 (98 - 200)	< 0.0001
Triglyceride (mg / dl)	180.6 ± 63.6 (89 - 315)	152.4 ± 14.6 (68 - 176)	< 0.0001	200.3 ± 67.8 (106 - 376)	143.6 ± 41.6 (67 - 254)	< 0.0001
LDL (mg / dl)	74.5 ± 28.5 (16.2 - 113)	60.8 ± 23.3 (21 - 108)	< 0.0001	88.7 ± 35.7 (41 - 181.5)	56.7 ± 20.6 (28.6 - 109)	< 0.0001
HDL (mg / dl)	55.5 ± 12.49 (36.8 - 83)	58.4 ± 13.3 (39 - 84)	0.025	51.5 ± 9.9 (35 - 68)	57.4 ± 14.7 (32 - 84)	< 0.0001
ALT (IU / L)	33.3 ± 15.1 (12 - 112)	29.2 ± 10.4 (16 - 48)	0.007	58.08 ± 48.4 (15 - 256)	28.58 ± 11.6 (14 - 50)	< 0.0001
AST (IU / L)	34.3 ± 18.4 (6 - 68)	28.6 ± 12.4 (12 - 54)	0.002	50.57 ± 48.4 (14 - 223)	28.85 ± 10.36 (14 - 62)	< 0.0001
Hs-CRP (mg / L)	3.9 ± 2.6 (0.9 - 9.5)	2.4 ± 0.7 (0.8 - 3.7)	< 0.0001	5.2 ± 5.05 (0.9 - 20)	3.2 ± 1.2 (1.4 - 6.8)	< 0.0001

Table 2. Baseline Metabolic Profile (with Range) of Overweight and Obese Patients Compared to Controls

Parameters	Overweight and Obese Adolescents (N = 102)	Healthy Adolescents (N = 48)	P Value	Overweight and Obese Adults (N = 118)	Healthy Adults (N = 54)	P Value
TSH (mIU / L)	3.1 ± 1.2 (0.9 - 6.7)	2.4 ± 1.2 (4.5 - 0.89)	0.009	3.4 ± 1.3 (0.8 - 6.5)	2.5 ± 1.1 (0.8 - 4.1)	< 0.0001
Free T4 (ng / dl)	1.03 ± 0.2 (0.6 - 1.9)	1.1 ± 0.2 (0.8 - 1.5)	0.204	1.1 ± 0.3 (0.8 - 1.8)	1.01 ± 0.2 (0.6 - 1.6)	0.057
FSH (mIU / ml)	2.8 ± 1.6 (0.6 - 6.3)	2.39 ± 1.2 (0.7 - 4.8)	0.25	4.10 ± 1.27 (1.8 - 6.5)	4.8 ± 1.7 (1.9 - 8.1)	< 0.0001
LH (mIU / ml)	1.7 ± 0.9 (0.4 - 3.6)	2.05 ± 1.2 (0.5 - 4.9)	0.001	3.5 ± 1.56 (0.8 - 6.4)	4.2 ± 1.2 (1.6 - 6.0)	< 0.0001
Total testosterone (ng / dl)	216.6 ± 82.2 (94 - 506)	259.0 ± 111.1 (98 - 497)	< 0.0001	392.3 ± 131.4 (180 - 703)	500.24 ± 137.8 (290 - 725)	< 0.0001
Sex hormone binding globulin (nmol / l)	25.4 ± 8.7 (15 - 45)	29.37 ± 9.34 (15 - 51)	< 0.0001	32.11 ± 14.4 (12 - 60)	44.95 ± 13.7 (22 - 66)	< 0.0001
Calculated free testosterone (pg / ml)	48.6 ± 17.7 (22.9 - 87)	53.59 ± 22.45 (16.8 - 99)	0.010	78.9 ± 22.04 (38 - 147)	87.3 ± 14.7 (65 - 123)	< 0.0001
Fasting insulin (uIU / mL)	12.2 ± 8.2 (4.9 - 32.1)	7.8 ± 3.8 (2.8 - 15)	< 0.0001	13.2 ± 9.34 (4.1 - 44)	8.34 ± 2.46 (4.5 - 12.8)	< 0.0001
Serum adiponectin (µg / ml)	5.2 ± 3.0 (1.6 - 11.5)	6.6 ± 3.4 (2.8 - 14)	< 0.0001	6.05 ± 3.6 (1.9 - 13.1)	6.79 ± 2.63 (3.4 - 13)	0.027
HOMA-IR	2.95 ± 2.25 (1.01 - 7.84)	1.69 ± 0.85 (0.6 - 3.2)	0.009	3.38 ± 2.89 (0.8 - 13.03)	1.8 ± 0.49 (1.0 - 2.83)	< 0.0001
HOMA2-IR	1.7 ± 1.09 (0.6 - 4.1)	1.0 ± 0.48 (0.4 - 1.9)	< 0.0001	1.7 ± 1.23 (0.5 - 5.7)	1.1 ± 0.30 (0.6 - 1.6)	< 0.0001

Table 3. Baseline Hormonal Profile (with Range) of Overweight and Obese Patients Compared to Controls

Overweight and Obese Adolescents						
Parameter	**Body Mass Index**	**Waist Circumference**	**Hip Circumference**	**Waist-Hip Ratio**	**Neck Circumference**	**Wrist Circumference**
TT	r = - 0.287 (P = 0.003)	r = - 0.298 (P = 0.002)	r = - 0.333 (P = 0.001)	r = 0.157 (P = 0.115)	r = - 0.192 (P = 0.033)	r = - 0.212 (P = 0.045)
SHBG	r = - 0.027 (P = 0.786)	r = - 0.058 (P = 0.564)	r = 0.002 (P = 0.985)	r = - 0.099 (P = 0.320)	r = - 0.025 (P = 0.801)	r = - 0.035.(P = 0.725)
CFT	r = 0.118 (P = 0.058)	r = 0.092 (P = 0.066)	r = 0.042 (P = 0.723)	r = - 0.075 (P = 0.451)	r = 0.049 (P = 0.816)	r = 0.127 (P = 0.622)
Overweight and Obese Adults						
Parameter	**Body Mass Index**	**Waist Circumference**	**Hip Circumference**	**Waist-Hip Ratio**	**Neck Circumference**	**Wrist Circumference**
TT	r = - 0.435 (P = < 0.0001)	r = - 0.272 (P = < 0.0001)	r = - 0.235 (P = 0.01)	r = 0.123 (P = 0.183)	r = - 0.394 (P = < 0.0001)	r = - 0.309 (P = 0.001)
SHBG	r = - 0.519 (P = < 0.0001)	r = - 0.306 (P = 0.001)	r =- 0.266 (P = 0.003)	r = - 0.046 (P = 0.619)	r = - 0.407 (P = < 0.0001)	r = - 0.400 (P = < 0.0001)
CFT	r = - 0.369 (P = < 0.0001)	r = - 0.261 (P = 0.004)	r = - 0.232 (P = 0.011)	r = 0.140 (P = 0.128)	r = - 0.364 (P = < 0.0001)	r = - 0.245 (P = 0.007)

Table 4. Correlation of Total Testosterone (TT), Sex Hormone Binding Globulin (SHBG), Calculated Free Testosterone (CFT) with the Anthropometric Parameters of Obesity in Overweight and Obese Individuals

TT = Total Testosterone, SHBG = Sex Hormone Binding Globulin, CFT = Calculated Free Testosterone

Overweight and Obese Adolescents				
Parameter	**HOMA-IR**	**HOMA2-IR**	**hs-CRP**	**Adiponectin**
TT	r = 0.393 (P = < 0.0001)	r = 0.453 (P = < 0.0001)	r = 0.153 (P = 0.125)	r = 0.398 (P = < 0.0001)
SHBG	r = - 0.028 (P = 0.783)	r = - 0.097 (P = 0.334)	r = 0.002 (P = 0.983)	r = 0.227 (P = 0.005)
CFT	r = 0.496 (P = < 0.0001)	r = 0.535 (P = < 0.0001)	r = 0.150 (P = 0.132)	r = 0.368 (P = < 0.0001)
Overweight and Obese Adults				
Parameter	**HOMA-IR**	**HOMA2-IR**	**hs-CRP**	**Adiponectin**
TT	r = - 0.479 (P = < 0.0001)	r = - 0.483 (P = < 0.0001)	r = - 0.404 (P = < 0.0001)	r = 0.224 (P = 0.015)
SHBG	r = - 0.501 (P = < 0.0001)	r = - 0.495 (P = 0.001)	r = - 0.437 (P = 0.003)	r = 0.324 (P = 0.001)
CFT	r = - 0.399 (P = < 0.0001)	r = - 0.399 (P = < 0.0001)	r = - 0.353 (P = < 0.0001)	r = 0.200 (P = 0.03)

Table 5. Correlation of Total Testosterone (TT), Sex Hormone Binding Globulin (SHBG), and Calculated Free Testosterone (CFT) with the Surrogate Markers of Insulin Resistance and Inflammatory Markers in Overweight and Obese Individuals

TT = Total Testosterone, SHBG = Sex Hormone Binding Globulin, CFT = Calculated Free Testosterone

DISCUSSION

Cohen[11] proposed the hypogonadal-obesity cycle which suggested bidirectional relationship between testosterone and obesity. The causes of low testosterone in obesity are multifactorial which includes low SHBG, increased aromatase leading to elevation of estradiol, insulin resistance and elevation of inflammatory cytokines and leptin resistance finally leading to suppression of GnRH neurons which causes hypogonadotropic hypogonadism[12]

In our study, total testosterone, SHBG and cFT was significantly lower in the OWOB groups. Reinehr et al.[13] studied androgen levels in 273 obese children (aged 5 - 14 years) before and after weight loss. They did not find a significant difference in testosterone levels among the pubertal boys. This is different from our study probably due to the higher mean age among our adolescent group and the smaller sample size. However, a smaller study which looked at gonadal dysfunction and insulin resistance did find that obese pubertal boys had a lower testosterone compared to normal controls.[14] In a cross sectional study of 25 obese and 25 lean pubertal and post pubertal males the SHBG levels were found to be 37.6 ± 17.2 pmol / L & 21.4 ± 11.6 pmol / L respectively, P = 0.001.[15] The same study also found low free testosterone however, there was no significant difference in FSH and LH among the young obese males compared to the non-obese.[15]

Massachusetts Male Ageing study[16] was a prospective population-based cohort study which found the total testosterone and SHBG progressively declined with overweight and obesity but there was no change in free testosterone. The low SHBG was attributed to increased insulin resistance which decreases the hepatic production of SHBG.[17] Dhindsa et al.[18] studied free testosterone levels (assessed by equilibrium dialysis) in 1849 obese non-diabetic and diabetic adult males. Free testosterone in lean, overweight, and obese nondiabetic males were 62.0 ± 19.4 pg / ml, 60.9 ± 19.3 pg / ml, and 55.5 ± 19.7 pg / ml respectively (P < 0.001).[18] In our study that used a calculated free testosterone, we found that OWOB adults and normal BMI participants had a level of 78.9 ± 22.04 pg / ml (38 - 147) and 87.3 ± 14.7 pg / ml (65 - 123) respectively. cFT were also higher compared to the above study, perhaps due to the difference in lab techniques and the lower mean age in our study (37.2 ± 11.19 years v / s 60.9 ± 10.2 years).

With respect to obesity parameters, our study found that TT, SHBG and cFT had a significant negative correlation with BMI, waist, hip, neck and wrist circumference but not with the waist hip ratio in OWOB adults. A study on 120 Yemeni males on impact of metabolic syndrome factors on testosterone and SHBG, Mohammed et al.[19] found that TT negatively correlated with BMI, waist circumference and insulin, HOMA-IR, and HOMA-β. SHBG levels were negatively correlated with BMI, waist circumference, insulin and HOMA-IR. cFT negatively correlated with BMI, waist circumference.[19]

Neck circumference as a marker of upper body fat distribution has been used as a community screening tool for the obesity.[20,21] Our study found that neck circumference was significantly higher in OWOB individuals, compared to the non-obese individual. A study among 92 adults in Turkey, Akin et al.[22] found that erectile dysfunction was more common in patients with higher neck circumference. A study on adolescents from South India studied 2D:4D ratio, neck circumference and found no statistical significant correlation of the above parameters in overweight and obese individuals.[23] While our study found that neck circumference had a significant negative correlation with TT, SHBG and cFT in OWOB adults and only with TT in OWOB adolescents.

Wrist circumference is a relatively new predictor of obesity and insulin resistance in both adolescents and adults.[24-27.] There is no published data available regarding the correlation of wrist circumference to the testosterone levels, however, a study from Namibia found a negative correlation between wrist breadth and androgen levels.[28] Our study found a significant negative correlation of wrist circumference with TT, SHBG and cFT in OWOB adults and only with TT in OWOB adolescents.

HOMA-IR and HOMA2-IR was significantly higher in the OWOB groups compared to non-obese. HOMA2-IR is a better predictor of insulin resistance as it takes into account the variation in hepatic and peripheral insulin resistance.[10] In a study in 691 urban adolescent population from Delhi, Singh et al.[29] found that HOMA-IR progressively increased with weight [normal weight 1.70 ± 1.44 (95 % CI 1.46-1.94), overweight 2.67 ± 1.41 (95 % CI 2.40 - 2.94), obese 4.39 ± 2.14 (95 % CI 3.95 - 4.83), P-value < 0.0001].[29] Our study showed a stronger correlation of HOMA2-IR with total testosterone compared to HOMA-IR in both OWOB adolescents and adults. Hyperinsulinaemic euglycemic clamp methods have shown a decline in serum testosterone with lower insulin sensitivity in pubertal and post pubertal males.[14] Similar results were also seen in longitudinal studies in the adult population.[30]

Hs-CRP was significantly higher in overweight and obese groups compared to non-obese groups. Namburi et al.[31] studied hs-CRP levels in obese children and adolescents and found that there was significant difference in levels of hs-CRP in obese patients compared to controls. Recent studies by Lavanya et al.[32] and Premanath et al.[33] in adults also found a significant correlation between BMI and hs-CRP. These results reinforce the finding that low-grade inflammatory state of overweight and obesity is seen from a younger age onwards. We found that hs-CRP had significant correlation with TT, SHBG and cFT with OWOB adults but not in OWOB adolescents. The relationship of metabolic syndrome with testosterone and inflammation was studied in 309 males aged between 30 - 70 years in Galle, Sri Lanka.[34] This study found a significantly higher hs-CRP and lower TT in patients with metabolic syndrome (34). Mogri et al.[15] showed a significant correlation between TT and free testosterone with CRP (r = − 0.32, P = 0.03) in pubertal males however, their study had a lower sample size compared to ours.

With respect to serum adiponectin, Premanath et al.[33] did not find a significant difference between obese males and non-obese males (10.53 ± 6.17 v / s 13.34 ± 7.45 µg / ml, p = not significant). However, Tamang et al.[35] in a cross-sectional study in Nepalese adult population found a

significant inverse correlation of adiponectin with BMI. Punthakee et al.[36] found a strong correlation between BMI Z scores and adiponectin in French Canadian children and adolescent population. However, a cross sectional study on Indian teenagers (12 - 18 years) in Chennai did not find a correlation between adiponectin with measures of insulin sensitivity, overweight, and other cardiometabolic variables.[37] Testosterone exerts an anti-inflammatory effect on adipose tissue and it decreases the amount of proinflammatory adipokines and increases adiponectin.[12] Low testosterone causes hypertrophy of the adipocyte which leads to decreased secretion of adiponectin and increased proinflammatory adipokines.[12] Our study found a significant correlation between TT, SHBG and cFT and serum adiponectin in both OWOB adolescents and adults.

CONCLUSIONS

Testosterone was found to have a significant correlation with parameters of obesity, insulin resistance and inflammation in overweight and obese adolescent and adult males. With the increasing number of obese individuals in India, further such studies may give us further insights into this complex relationship between obesity and the hypothalamic-pituitary-gonadal axis.

Limitations

Since our study is cross sectional in design, it can only show association but cannot prove causality. Another limitation is the sample size beside a referral bias, as our hospital is a tertiary care centre. Also, as adolescents are in different stages of puberty, a subgroup analysis among the adolescent population grouping them into their Tanner stage would have given a clearer picture.

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