INTER-RELATIONSHIP OF SERUM TESTOSTERONE AND ADIPONECTIN LEVELS, AND ANTHROPOMETRIC PARAMETERS OF OBESITY IN HEALTHY YOUNG MALES OF SOUTH PUNJAB

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Background: Testosterone not only has its own metabolic functions but it also controls production of adipocytokines (like adiponectin) which govern metabolic and immune status of men. Serum testosterone levels are specifically reduced with expansion of circumferential fat mass in men which not only deprives them of its beneficial functions but also reduces the metabolic and immune support extended by adipocytokines it governs. This, in turn paves way for development of metabolic disorders in obese men. Methods: It was a cross-sectional comparative study on 40 male subjects, aged 20–40 years, equally from non-obese and obese categories. Serum testosterone and adiponectin levels of these subjects were measured through ELISA. Results: Serum Testosterone levels of obese males were significantly lower as compared to their non obese counterparts (p=0.003) while serum adiponectin levels of obese subjects were significantly higher as compared to their non obese counterparts (p=0.005). Moreover, serum testosterone and adiponectin levels had a negative relationship with each other (p=0.001). Also, serum testosterone levels had an inverse correlation with waist circumference (WC) (p=0.002) and waist hip ratio (WHR) (p=0.004) of subjects while serum adiponectin levels had a direct correlation with WC (p=0.033) and WHR (p=0.002) of subjects. Conclusion: Circumferentially obese men have lower testosterone and higher adiponectin levels. Serum testosterone levels have an inverse correlation with WC and WHR while serum adiponectin levels are directly related to these. Keywords: Obesity, testosterone, adiponectin, Waist Hip Ratio, WHR, Waist Circumference, WC, Body Mass Index, BMI

INTRODUCTION

Testosterone is the prime androgen in men and its daytime levels range from 300 ng/dl to 1000 ng/dl.1 It increases insulin receptor sensitivity and hence, a reduced serum testosterone level is likely to result in the development of insulin resistance.2 Testosterone by enhancing the activity of hormone sensitive lipase promotes lipolysis (reducing adipocyte size) and reduces triglyceride (TG) uptake by the adipose tissue through the process of reverse cholesterol transport. Reduced testosterone level can thus result in the development of dyslipidemia and atherosclerosis.3 Testosterone, through aromatase receptor (AR_m) and androgen receptor (AR) activation in vascular smooth muscle, results in generation of nitric oxide (NO) which produces an overall vasodilatory effect and a reduced testosterone level, hence, is most likely to promote a vasoconstrictive state.

Adiponectin, a 30 kDa protein, exists in the plasma at a range of 5–30 μg/ml.4 It has got two serpentine membrane receptors AdipoR1 (which regulates adiposity) and AdipoR2 (which regulates glucose tolerance) through which it plays an important role in regulating systemic energy metabolism and insulin receptor sensitivity.6 Deranged levels of adiponectin have been found to be involved in the pathophysiology of atherosclerosis, insulin resistance, type 2 diabetes mellitus, metabolic syndrome and coronary artery disease.7

Obesity has turned out to be the de-facto epidemic of 21st century. National health survey of Pakistan, conducted in 1990–94, had projected that 25% of population was obese (in terms of BMI) back then. However recent projections, depicting its prevalence in terms of waist circumference (WC) and waist hip ratio (WHR), are putting it at around 57% which indicates that circumferential obesity is the predominant form of obesity afflicting our society.8

Development of circumferential obesity and the resultant changes in BMI and WHR lead to several endocrine abnormalities, including a decline of serum testosterone levels, which help in the emergence of insulin resistance followed by a compensatory hyperinsulinemia. This in turn results in dysregulated levels of (Luteinizing Hormone) LH, sex hormone binding globulin (SHBG) and a deranged LH/FSH ratio, which further reduces testosterone levels and hence puts an obese male’s body in a vicious cycle of non-ending endocrine abnormalities.
The relationship between serum testosterone and adiponectin in humans is currently under study and it is being suggested that their levels are inversely related to each other. This proposition is not only supported by studies, based on animal models (where castration in male mice lead to enhanced adiponectin) but also by the results of those conducted on human models (which state that testosterone replacement therapy, in hypogonadal men, results in decreased adiponectin levels). It is being said that low testosterone level is likely to reduce inhibitory effect (of testosterone) on adiponectin secretion, from adipocytes, and hence causes its levels to rise. Moreover, since adiponectin secretion is also affected by the adipocyte size and since testosterone has profound effect on size of adipocytes, a deranged testosterone level is likely to alter adipocyte size and hence adiponectin levels too.

Hence we can say, from facts scripted above, that serum testosterone levels correlate inversely to serum adiponectin levels and to anthropometric parameters of circumferential obesity in men. Since obesity related endocrine and metabolic plus infertility (due to altered testosterone levels) are important clinical presentations in Pakistan, this study shall pave way to understand novel mechanisms involved behind emergence of these disorders and their complications and hence shall help clinicians deal with them in astute ways.

PATIENTS AND METHODS

It was a cross-sectional comparative study, based on convenience sampling, conducted on age and ethnicity matched adult male population of south Punjab with the objective to note the effects of obesity on endocrine environment of young men of south Punjab and look for the possible evolving mechanisms that could be the cause of several metabolic and inflammatory disorders in obese men. The sample size for each group was calculated with a power of 90% and an alpha level of 5% through WHO (Geneva) extended software, ‘sample size determination in health studies: a Practical Manual’ version 2.0. Study population, consisting of 40 healthy male subjects, 20 non-obese (Group A) and 20 obese (Group B) between 20 and 40 years of age.

Testosterone levels show an age related decline from the fourth decade of life onwards. It was a study to determine the effect of circumferential obesity on serum testosterone and adiponectin levels. To prevent the effect of age related testosterone decline on study parameters, only those who were below 40 years of age (fulfilling the criteria of obese and non-obese subjects) were included in the study. As per WHO (2000 and 2008) standards, a BMI of ≥25 and a WHR of ≥0.9 was taken as a cut-off value (for South Asians) to differentiate between non-obese and obese subjects.

Genetically obese males, males with morbid obesity (BMI of ≥30 as per WHO, 2000), and/or taking exogenous testosterone were excluded from this study. All the subjects were screened, twice in the week preceding study, for deranged fasting blood glucose levels. Subjects who had a fasting blood glucose level ≥126 mg/dl (WHO 2008), on first and/or second screening occasion, were excluded from study. Moreover, as per WHO 2013 guidelines for hypertension, subjects with a systolic blood pressure ≥140 and/or diastolic blood pressure of ≥90 on one and/or both of the screening occasions were also excluded from study.

BMI and WHR of subjects were measured according to WHO guidelines 2000 and 2008 respectively. For collection of blood sample, selected subjects were instructed to hold an overnight fast of 10 hours before the day of sampling. Serum samples of subjects, derived after centrifugation of 3 ml of venous blood (drawn between 8 AM and 10 AM), were immediately stored at -20 °C for a later analysis.

Serum testosterone levels were measured by enzyme linked radioimmunosorbent assay (ELISA) through utilization of ASTRA BIOTECH Testosterone ELISA Kit Ref: 21–02A (Germany). This had an Assay Range of 0.2–50 ηmol/L (6–1154 ng/dl), an Assay Sensitivity of 0.2 ηmol/L (6 ng/dl), an Assay specificity of 100% for human serum testosterone, an Intra-assay precision of 3.77% and Inter-assay precision of 7.39%. However, to measure serum adiponectin levels (Through Elisa) AviBion Human adiponectin (Acrp30) ELISA Kit, Ref: ADIP025 (Finland Make) was used which had an Assay Range of 1.56–100 ng/ml, an Assay Sensitivity of <3 ng/ml, an Assay Specificity of 100% for human adiponectin, an Intra-assay precision of ≤10% and an Inter-assay precision ≤12%. The tests were run on QMlab Plate Reader (Reid Well Plate).

The data was entered on SPSS-22 and was analyzed first for normality distribution trough application of Shapiro-Wilk’s and Kolmogorov Smirnov’s tests. Mean±SD of the normally distributed variables while Median (IQR) of the non-normally distributed variables (anthropometric and biochemical) were calculated. Mann-Whitney U-test was applied to compare [Median (IQR)] of serum testosterone levels (between groups A and B) while t-test was applied to compare serum adiponectin levels (Mean±SD) of the subjects. Spearman’s rho correlation was applied to determine a correlation between various quantitative variables, and p≤0.05 was considered as statistically significant.

RESULTS

Overall group characteristics, of both the study groups, have been presented in Table-1. Serum testosterone levels of non-obese subjects of group A were compared
to their obese counterparts in group B by application of Mann-Whitney U-test and the difference was statistically significant ($p=0.003$). Similarly, serum adiponectin levels of non-obese subjects of group A were compared to their obese counterparts in group B, by application of independent sample t-test, and the difference was statistically significant yet again ($p=0.005$) (Table-2).

To establish an inter-relationship between anthropometric parameters of obesity and serum testosterone and/or serum adiponectin levels Spearman’s rho correlation was applied. It was found that serum testosterone levels of the subjects of groups A and B combined together, regardless of their obesity status ($n=40$), depicted an inverse correlation with WC ($r=-0.472, p=0.002$) and with WHR ($r=-0.451, p=0.004$) but not with BMI ($r=-0.308, p=0.058$). Similarly, it was also found that serum adiponectin levels of the subjects of groups A and B, combined together regardless of their obesity status ($n=40$), depicted a direct correlation with WC ($r=0.337, p=0.033$) and with WHR ($r=0.474, p=0.002$) but not with BMI ($r=0.286, p=0.074$). It was also found that serum testosterone levels of the subjects of groups A and B combined together, had an inverse correlation with serum adiponectin levels ($r=-0.517, p=0.001$) (Table-3, Figure-1).

Table-1: Anthropometric and biochemical variables of the subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n=20)</th>
<th>Group B (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Year) [Median (IQR)]</td>
<td>25.0 (22.0–25.5)</td>
<td>28.5 (25.0–31.0)</td>
</tr>
<tr>
<td>Height (m) [Median (IQR)]</td>
<td>1.74 (1.55–1.74)</td>
<td>1.70 (1.68–1.74)</td>
</tr>
<tr>
<td>Weight (Kg) [Mean±SD]</td>
<td>66.08±7.56</td>
<td>79.91±7.47</td>
</tr>
<tr>
<td>Body Mass Index [Mean±SD]</td>
<td>23.24±1.87</td>
<td>27.07±1.65</td>
</tr>
<tr>
<td>Waist Circumference (Cm) [Median (IQR)]</td>
<td>81.28 (76.20–83.82)</td>
<td>91.44 (86.36–93.98)</td>
</tr>
<tr>
<td>Hip Circumference (Cm) [Median (IQR)]</td>
<td>97.79 (91.44–101.60)</td>
<td>99.06 (93.98–101.60)</td>
</tr>
<tr>
<td>Waist Hip Ratio [Median (IQR)]</td>
<td>0.83 (0.81–0.85)</td>
<td>0.92 (0.92–0.92)</td>
</tr>
<tr>
<td>Testosterone (µg/ml) [Median (IQR)]</td>
<td>680 (575.0–778.5)</td>
<td>412.5 (338.0–542.5)</td>
</tr>
<tr>
<td>Adiponectin (µg/ml) [Mean±SD]</td>
<td>21.1±12.6</td>
<td>32.9±12.6</td>
</tr>
</tbody>
</table>

Table-2: Comparison of serum testosterone (through Mann Whitney U-test) and serum adiponectin levels (through Independent Sample t-test) between subjects of groups A and B

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n=20)</th>
<th>Group B (n=20)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (µg/ml) [Median (IQR)]</td>
<td>680 (575.0–778.5)</td>
<td>412.5 (338.0–542.5)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Adiponectin (µg/ml) [Mean±SD]</td>
<td>21.1±12.6</td>
<td>32.9±12.6</td>
<td>0.005*</td>
</tr>
</tbody>
</table>

Table-3: Correlations of serum testosterone and serum adiponectin levels with anthropometric parameters of obesity using Spearman’s correlation

<table>
<thead>
<tr>
<th>Parameter (n=40)</th>
<th>WC</th>
<th>WHR</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>-0.472*</td>
<td>0.002*</td>
<td>-0.451</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>0.337*</td>
<td>0.033*</td>
<td>0.474</td>
</tr>
</tbody>
</table>

DISCUSSION

Testosterone levels of the non-obese subjects of group A were found to be higher than their obese counterparts in group B, suggesting that testosterone levels decline in circumferentially obese men. This finding is in line with the results being projected in contemporary literature which suggest that circumferential obesity (through aromatization of testosterone to estradiol) lowers testosterone levels in men as it negatively regulates them.13,14

Testosterone levels were correlated with WC of subjects and it was found that testosterone had a stronger inverse relationship with WC than any other anthropometric parameter of obesity. This finding, of our study, is in accordance with the findings of those studies which suggest that WC is a better indicator for the prediction of testosterone decline (in obese men) as compared to other anthropometric parameters of obesity since these two are negatively related to each other in a stronger fashion.15

The subjects of groups A and B, regardless of their obesity status, showed an inverse correlation between serum testosterone levels and WHR ($p=0.004$) too. It has been suggested that deranged WHR related insulin resistance leads to a compensatory hyperinsulinemia which in turn suppresses the secretion of LH and hence testosterone. Moreover, insulin levels have been proposed to affect the negative feedback control over hypothalamo-pituitary-adrenal axis too. Therefore deranged insulin sensitivity, associated with changes of WHR, is likely to disrupt gonadotropic axis
which in turn results in decreased testosterone levels through disruption of one or more of the control mechanisms involved in its synthesis.16,

It was found that testosterone levels did not have a significant correlation with BMI. Although a negative correlation of testosterone with BMI has been reported17, it is however suggested that only an extreme change in BMI (especially if it crosses the limit of 40), will result in significant decline in testosterone levels. This decline may be attributed to raised leptin levels which suppress testosterone secretion.14 This proposition is supported by an earlier work where it was suggested that testosterone levels had an inverse relation with BMI in men if their BMI was ≥35, since above this cutoff dysregulated levels of LH and SHBG (associated with deranged BMI) start to negatively influence testosterone levels.18

Non-obese subjects of groups A had lower adiponectin level as compared to their obese counterparts in group B. These findings are in accordance with those, being projected in contemporary literature, which propose that testosterone has an inverse relationship with adiponectin since it regulates adiponectin levels by keeping a check on adipocyte size and by suppressing adiponectin gene expression within adipocytes.19 Thus non-obese subjects, who are likely to have higher testosterone levels, are most likely to have low adiponectin concentrations and vice versa.20,21

Results of some of the other contemporary studies however, are in contrast with our results. It has been shown elsewhere, that adiponectin levels decline with obesity.22 However, this inverse relationship of adiponectin with obesity (wherever projected) has been reported without taking testosterone concentrations into consideration. Moreover, these contradictory results have been projected for non-healthy subjects (either in the background of established insulin resistance and/or glucose intolerance23 or else in presence of inflammatory and vascular pathologies) where derangements related to multiple inflammatory cytokines co-exist with obesity24 and not for healthy individuals.

CONCLUSION

Testosterone levels decline while adiponectin levels rise significantly in circumferentially obese men. Waist Circumference and Waist Hip Ratio are better parameters as compared to Body Mass Index, to predict the risk of obesity associated endocrine abnormalities in men of South Asian origin. Serum testosterone levels have an inverse correlation with WC and with WHR while WC and WHR are directly related to serum adiponectin levels. Serum testosterone levels have an inverse correlation with serum adiponectin levels. Serum testosterone and/or serum adiponectin levels have no correlation with BMI.

REFERENCES


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