ORIGINAL ARTICLE

# EFFECT OF AGING AND OBESITY RELATED TESTOSTERONE DECLINE ON SERUM ADIPONECTIN LEVELS OF HEALTHY MALES

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**Background:** Men experience testosterone decline with both aging obesity which leads to enhanced adiponectin levels. **Methods:** It was a cross-sectional study that consisted of 80 healthy males who were equally divided into younger (20–40 years) and elder (41–60 years) categories, each was further divided equally into non-obese and obese groups. Serum testosterone and adiponectin levels were analyzed via Enzyme Linked Immunosorbent Assay (ELISA). **Results:** Testosterone levels of younger non-obese/obese males were significantly higher as compared to elder non-obese/obese males ($p$=0.00 and $p$=0.00) while testosterone levels of younger non obese participants were significantly higher than their obese counterparts ($p$=0.003). Adiponectin levels, however, of younger non obese participants were significantly lower than their elder non-obese and younger obese counterparts ($p$=0.001 and $p$=0.008 respectively). Moreover, elder non-obese and obese participants showed significant negative correlation between testosterone and adiponectin levels [($p$=0.00) and ($p$=0.01)]. Also, younger and elder (regardless of obesity) and non-obese/obese participants (regardless of age) showed a significant negative correlation between serum testosterone and serum adiponectin levels [($p$=0.00), ($p$=0.00), ($p$=0.00) and ($p$=0.00) respectively]. **Conclusion:** Testosterone levels decline with both aging and obesity, in otherwise healthy males, which makes adiponectin levels to rise. This in turn, though intricate physiological pathways, further deranges testosterone levels and thus puts aging and obese men at an increased risk of endo-metabolic disorders.

**Keywords:** Aging, Obesity, Testosterone, Adiponectin, Waist Hip Ratio (WHR), Waist Circumference (WC), Body Mass Index (BMI)

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## INTRODUCTION

Primary male androgen, testosterone, exists in plasma having a daytime level of 300 ng/dL to 1,000 ng/dL.[1] It increases insulin receptor sensitivity (improves glucose metabolism), enhances activity of hormone-sensitive lipase (promotes lipolysis and inhibits the process of reverse cholesterol transport[2], which reduces the adipocyte size and hence overall fat mass), activates androgen receptor (AR) within various vascular beds resulting in the generation of nitric oxide, NO, which produces an overall vasodilatory effect[3] and affects levels of inflammatory cytokines such as tumour necrosis factor alpha (TNFα), interleukin-1β (IL-1β) and IL-12. All these modulations prevent the development of proliferative (atherosclerotic) and/or inflammatory (metabolic syndrome/s) states in men.[4]

Adiponectin, an adipocytokine with a molecular weight of 30 kDa, has a plasma concentration of 5–30 μg/mL.[5] It has two serpentine membrane receptors, AdipoR1 and AdipoR2, through which (via a pleckstrin adaptor protein) it affects energy metabolism by reducing the process of gluconeogenesis[6] and by modulating insulin receptor sensitivity[7]. Moreover, it suppresses the formation of foam cells by inhibiting the expression of macrophage scavenger receptor A and by reducing the uptake of low-density lipoprotein by cells which prevents the emergence of proliferative disorders like atherosclerosis.[8]

A negative correlation is said to exist between testosterone and adiponectin levels since testosterone suppresses plasma adiponectin levels by reducing adipocyte size and by modulating the cellular signalling pathways such as peroxisome proliferator activated receptor signalling pathway for instance.[9] Hence aging[10] and obesity[11] are the conditions that are associated with low serum testosterone levels and are likely to present with enhanced adiponectin levels. Due to negative feedback mechanism of the hypothalamo-pituitary gonadal axis, serum testosterone levels are further reduced.[12] This deprives men with (aging and/or obesity induced) hypogonadal status off testosterone's metabolic, anti-proliferative and anti-inflammatory effects and paves way for emergence of systemic disorders.

Though the relationship of testosterone and adiponectin has been studied in men harbouring metabolic and/or proliferative disorders, its relationship in otherwise healthy men is not well studied. This was the first study of its kind in South Punjab, to the best of our knowledge, which was

conducted at various teaching hospitals of Multan that observed the effect of aging and obesity induced testosterone decline on serum adiponectin concentration in men without any other systemic ailment. The study hypothesized that aging and obesity shall independently affect testosterone and adiponectin levels in men.

## MATERIAL AND METHODS

It was a cross sectional (comparative correlational) study whose sample size (n=20 for each group) was calculated with a power (1-β) of 90% and a significance (α) level of 5% by utilizing the formula $\mathbf{n=\sigma^2(Z_{1-\alpha/2}+Z_{1-\beta})^2/(\mu_0-\mu_1)^2}$ derived from WHO (Geneva) extended software 'sample size determination in health studies: a Practical Manual' version 2.0. Total study population, after gaining written and informed consent of theirs, consisted of 80 healthy participants divided equally into younger (20–40 years) and elder (41–60 years) groups each of which was equally segregated into non obese and obese categories. Since serum testosterone levels decline in men from fourth decade of life onwards, hence 40th year of life was considered as a cut-off beyond which study participants were considered elder.[13] Group A and Group B of our study, thus, consisted of 20 non-obese younger and 20 non obese elder participants respectively while Group C and Group D consisted of 20 obese younger and 20 obese elder participants respectively.

Genetically obese men and those with morbid obesity (BMI of ≥30, WHO 2000 guidelines) along with those on testosterone treatment were excluded from this study. Participants were screened, twice in the week preceding sample collection, for derangements within their fasting blood glucose levels and blood pressure. Participants who had a fasting blood glucose level of ≥126 mg/dL (WHO 2008 guidelines for hyperglycaemia), those with a systolic blood pressure ≥140 and/or diastolic blood pressure of ≥90 (WHO 2013 guidelines for hypertension) on one and/or both of screening occasions were also excluded from study.

As per WHO (2000 and 2008) guidelines South Asian males with a BMI of ≥25 and/or a WHR of >0.9 are termed as obese, hence we used these cut-off values below or beyond which the participants were termed as non-obese or obese respectively. To measure weight (Kg) portable weighing machine (Camry-Model-BR9709, Camry Electronic Ltd., Zhaoqing), to measure height (m) portable height/ length measuring board (Model-RE-160 Made in China) was used and to measure Waist Circumference (WC)/Hip Circumference (HC) standard WHO (2008) procedures were followed. BMI and WHR were later derived, through standard formulas, using the aforementioned indices. Three millilitre of venous blood of participants was drawn in early hours of morning with an overnight fast of 10 hours. Collected blood samples were immediately centrifuged at 3,000 rpm for 3 minutes after which the serum samples were immediately stored at -20 °C for a later analysis.

Serum testosterone levels were measured by using ASTRA BIOTECH Testosterone ELISA Kit Ref: 21-02A (Germany) which was based on competitive solid phase enzyme linked radioimmunosorbent assay (ELISA) technique. It had an assay range of 0.2–50 nmol/L (6–1154 ng/dL), an assay sensitivity of 0.2 nmol/L (6 ng/dL), an assay specificity of 100% for human serum testosterone, an intra-assay precision of 3.77% and an inter-assay precision of 7.39%.

Serum adiponectin levels were analyzed using the technique of ELISA through AviBion Human adiponectin (Acrp30) ELISA Kit, Ref: ADIP025 (Finland). It had a range of 1.56–100 ng/mL, had a sensitivity of <3 ng/mL, a specificity of 100% for human serum adiponectin, an Intra-assay precision of ≤10% and an inter-assay precision ≤12%. The tests were run on Reid Well Plate Reader.

Data was entered on SPSS-25 and was analysed for its normality distribution via application of Shapiro-Wilk and Kolmogorov Smirnov tests after which Mean±SD of normally distributed while Median (IQR) of non-normally distributed variables were derived. Mann-Whitney U-test (after finding significant overall differences of serum testosterone levels, between groups, through Kruskall Wallis Test) was applied to compare serum testosterone levels Median (IQR) of various groups. After finding significant overall differences of adiponectin levels, between groups, through ANOVA, post hoc Tukey's test was utilized to draw a comparison of serum adiponectin levels (Mean±SD) between study groups. Spearman's rho correlation was applied to determine a correlation between various quantitative variables, and $p \leq 0.05$ was considered as statistically significant.

## RESULTS

Mean±SD of normally distributed and Median (IQR) of non-normally distributed parameters of study participants (of all four groups) have been represented in Table-1. Serum testosterone levels of younger non-obese and obese participants (Group A and Group C respectively) were significantly higher while their adiponectin levels were significantly lower than their elder non-obese and obese counterparts (Group B and Group D respectively), indicating that serum testosterone levels decline while serum adiponectin levels rise with age (regardless of obesity status) in

otherwise healthy men. These findings have been presented in Table-2.

Serum testosterone levels of younger non-obese participants (Group A) were significantly higher than their obese counterparts (Group C) indicating an obesity associated testosterone decline. Also, Serum adiponectin levels of (younger non-obese) participants of Group A were significantly lower as compared to (younger obese) participants of Group C and (elder non obese) participants of Group B indicating that adiponectin levels rise with both obesity and aging within health males. These findings have been portrayed in Table-2.

Serum testosterone levels showed a negative correlation with serum adiponectin levels in elder non-obese participants of Group B (*rho*= -0.813, *p*=0.00) and within elder obese participants of Group D (*rho*= -0.533, *p*=0.01) too. Also, within younger and elder population (regardless of their obesity status) and within non obese and obese populations (regardless of their age) serum testosterone showed a significant negative correlation with serum testosterone levels. These findings have been presented in Table-3. A significant correlation between serum testosterone and adiponectin levels, for whole of study population has been presented in Figure-1.

**Table-1: Anthropometric/biochemical variables, within study groups [Mean±SD/Median (IQR)]**

| Parameter | Group A (n=20) | Group B (n=20) | Group C (n=20) | Group D (n=20) |
|---|---|---|---|---|
| Age (Year) | 25 (22–25.5) | 45 (42–51.25) | 28.5 (25–31) | 49.5 (4 –50) |
| Height ($m^2$) | 3.06 (2.425–3.06) | 3.15 (3.06–3.24) | 2.89 (2.85–3.06) | 3.06 (2.95–3.24) |
| Weight (Kg) | 66.08±7.56 | 73.35±3.0 | 79.91±7.47 | 84.25±5.25 |
| BMI ($Kg/m^2$) | 23.24±1.87 | 23.5±0.93 | 27.07±1.65 | 27.46±1.4 |
| Waist Circumference (Cm) | 81.28 (76.2–83.82) | 83.82 (83.82–86.99) | 91.44 (86.36–93.98) | 96.52 (93.98–96.52) |
| Hip Circumference (Cm) | 97.79 (91.44–101.6) | 99.06 (96.52–101.6) | 99.06 (93.98–101.6) | 104.14 (101–104.14) |
| WHR | 0.83 (0.81–0.85) | 0.85 (0.84–0.87) | 0.92 (0.92–0.925) | 0.92 (0.92–0.93) |
| Testosterone (ng/dL) | 680 (575–778.5) | 286 (263.5–370) | 412.5 (338–542.5) | 258 (220–287.5) |
| Adiponectin (µg/mL) | 21.1±12.63 | 35±9.34 | 32.85±12.58 | 41.15±10.37 |

**Table-2: Comparison of serum testosterone levels (via Mann-Whitney U test) and serum adiponectin levels (via Post Hoc Tukey's test) between various study groups**

| Variable | Groups in Comparison (n=20 for each group) | | | | *p* |
|---|---|---|---|---|---|
| Testosterone (ng/dL) [Median (IQR)] | Group A | 680 (575.0–778.5) | Group B | 286 (263.5–370.0) | 0.000* |
| | Group C | 412.5 (338.0–542.5) | Group D | 258 (220.0–287.5) | 0.000* |
| | Group A | 680 (575–778.5) | Group C | 412.5 (338–542.5) | 0.003* |
| | Group B | 286 (263.5–370.0) | Group D | 258 (220.0–287.5) | 0.114 |
| Adiponectin µg/mL (Mean±SD) | Group A | 21.1±12.63 | Group B | 35±9.34 | 0.001* |
| | Group C | 32.8±12.58 | Group D | 41.15±10.37 | 0.103 |
| | Group A | 21.1±12.63 | Group C | 32.85±12.58 | 0.008 |
| | Group B | 35±9.34 | Group D | 41.15±10.37 | 0.322 |

**Table-3: Correlation of serum testosterone with serum adiponectin levels, by using Spearman's correlation, in younger, elder, non-obese and obese study participants (n=40)**

| | A+B (Younger) | | C+D (Elder) | | A+C (Non-Obese) | | B+D (Obese) | |
|---|---|---|---|---|---|---|---|---|
| Spearman's Correlation | *rho* | *p* | *rho* | *p* | *rho* | *p* | *rho* | *p* |
| Testosterone and Adiponectin | -0.517 | 0.001* | -0.718 | 0.000* | -0.756 | 0.000* | -0.444 | 0.004* |

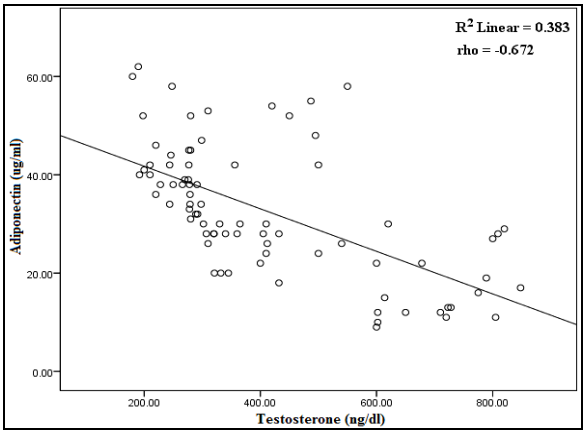


**Figure-1: Scatter plot showing significant negative correlation between serum testosterone and adiponectin (n=80)**

## DISCUSSION

Younger non-obese and obese participants had higher testosterone levels as compared to their elder non obese and obese counterparts indicating an age-related decline in serum testosterone levels. Such findings have been reported elsewhere also where it has been projected that testosterone levels decline at a rate of up to 2% per year, after third decade of life, because of several changes within the hypothalamo-pituitary axis and age associated testicular impairment.[14]

Testosterone levels of younger non-obese participants were found to be higher than their age matched obese counterparts, suggesting that testosterone levels decline with the emergence of obesity (specifically circumferential). This finding is in line with results of certain other studies too which

project that obesity negatively affects testosterone levels in men.[15]

It is suggested that aromatization of testosterone to estradiol is responsible for testosterone decline in obese men.[16] Moreover, Obesity associated enhancement of adipose tissue also leads to development of hyperinsulinemia (due to emergent insulin resistance) which in turn leads to suppression of LH secretion and hence testosterone.[17] Also, obesity in men is associated with low Sex Hormone Binding Globulin (SHBG) levels which are likely to lower testosterone levels too.[18] Thus, we can say that through several intricate physiological interactions, testosterone levels tend to decline in obese men.

Testosterone levels of the non-obese elder participants, though lower, were not significantly different from their age matched obese counterparts. It is suggested that a single time sampling may reveal inconsistent results regarding testosterone levels as compared to those deduced by serial samplings.[19] Since our study was a single time cross sectional study, this could have led to our results being inconsistent with those being projected by literature available on academic front.

Younger non-obese participants had lower adiponectin levels as compared to their elder non-obese counterparts which may be attributed to higher testosterone levels in non-obese younger participants, indicating that higher testosterone levels exist with lower adiponectin levels and vice versa. Younger obese participants had higher adiponectin levels as compared to their age matched non-obese counterparts indicating, yet again, that adiponectin levels rise with obesity (as testosterone levels fall) in otherwise healthy men.

These findings are in accordance with those of contemporary studies which propose that testosterone has an inverse relationship with adiponectin.[20] A recent study revealed that women (who have negligible levels of testosterone) have approximately 50% higher levels of adiponectin as compared to their age and BMI matched male counterparts which indicates that testosterone negatively regulates adiponectin secretion[21], most likely by inhibiting adiponectin expression within adipose tissue.[22] Moreover, certain studies also indicate that lower testosterone and higher estradiol concentrations (due to aromatization of testosterone within obese men) are associated with high adiponectin levels[23] because estradiol inhibits gonadotropic axis[24], lowers testosterone levels and thus reduces suppressive effect of testosterone on adiponectin secretion which leads to adiponectin rise (in states with low testosterone levels).

Results of some of the other contemporary studies however are in contrast with our results. It has been studied, that adiponectin levels decline with obesity.[25] However this inverse relationship of adiponectin with obesity, wherever projected, has been reported without taking testosterone concentrations into consideration.[26] Studies which show a negative relationship between obesity and adiponectin levels do not report it for healthy participants either. They report it either in the background of insulin resistance, glucose intolerance[27] or else in presence of inflammatory and vascular pathologies, where derangements related to inflammatory cytokines co-exist with obesity[28].

It was found that testosterone has a strong negative correlation with adiponectin in elder non obese and obese participants. A negative correlation between testosterone and adiponectin was derived for the younger and elder participants, regardless of their obesity status, too. Moreover, a negative correlation of testosterone with adiponectin existed between non obese and obese participants, regardless of their age also. A similar negative correlation of serum testosterone levels with serum adiponectin levels for whole of study population was derived too. These results support our postulate, yet again, that testosterone levels negatively regulate adiponectin levels and that a high testosterone levels in men is associated with low adiponectin concentration[29] and *vice versa*.

The most likely physiological reasoning behind these finding is to be that hypogonadal states (associated with aging and/or obesity) are accompanied by insulin resistance, high insulin levels, deranged SHBG levels and disturbed LH/FSH ratio which keep on altering hypothalamo-pituitary-gonaldal axis (evident by low Insulin Like Protein-3 levels within testicular tissue) in the long run.[30] These intricate interplays, combined together, minimize secretion of testosterone and reduce its suppressive effects on adiponectin secretion which is evident by adiponectin rise.

An inverse correlation, of testosterone with adiponectin, could not be derived for the younger non obese and obese participants. This, though in contrast with popular belief, is not an unheard finding on scientific fronts. Since inter-relation of testosterone and adiponectin is yet a not very well explored domain of medical science, hence conflicting results are being projected by contemporary researchers who project that testosterone may not have an inverse correlation with adiponectin[31], may show a weak negative correlation[32] or even a positive correlation[33]. All these projections regarding relationship of testosterone with adiponectin however are being made in the background of inflammatory/proliferative/endocrine abnormalities and little data is available for healthy males.

## CONCLUSION

Both aging and obesity result in testosterone fall which makes adiponectin levels to rise and this effect is rather more marked when aging and obesity get combined together.

## LIMITATIONS & RECOMMENDATIONS

This was a cross sectional study, based on a single time observation, with a limited sample size. To support our results further, or elsewise, cohort studies with enhanced sample size are recommended.

Also since our results indicate that aging and obesity induced testosterone decline in men results in adiponectin rise, hence clinicians treating ageing and obese men for systemic disorders shall consider their testosterone levels too and shall consider their normalization also so that beneficial effects of endocrine homeostasis could bring forth better results regarding treatment of systemic disorders.

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**HH:** Concept, Commencement, Field Work, Statistical Analysis and referencing
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**MSN:** Referencing and proofreading


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