www.nephropathol.com DOI: 10.34172/jnp.2020.27 J Nephropathol. 2020;9(3):e27

Journal of Nephropathology

Association of plasma total testosterone level and metabolic syndrome in adult males

Alireza Hejrati[1], Amir Ziaee[2], Mohammad Pourmahmoudian[2], Elham Bayani[3], Mehrnaz Ghavamipour[3], Maryam Saatchi[3*]

[1]Department of Internal Medicine, Rasoul Akram Hospital, Iran University of Medical Science, Tehran, Iran
[2]Pediatric Growth and Development Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Science, Tehran, Iran
[3]General Practitioner, Iran University of Medical Science, Tehran, Iran

ARTICLE INFO

Article type:
Original Article

Article history:
Received: 9 July 2019
Accepted: 13 September 2019
Published online: 18 October 2019

Keywords:
Testosterone
Metabolic syndrome
Cardiovascular disease
Type II diabetes
Renal disease
Interleukin 10

ABSTRACT

Introduction: Low testosterone level has strongly been correlated with body fat accumulation and abdominal obesity in men.

Objectives: This study aimed to evaluate testosterone level in men with and without metabolic syndrome to determine the relationship between testosterone and metabolic syndrome.

Patients and Methods: This case-control study was conducted on 172 cases of metabolic syndrome and 172 participants as a control group in Rasoul Akram hospital, Tehran, Iran. Demographic characteristics, fasting blood sugar (FBS), high-density lipoprotein (HDL), low-density lipoprotein (LDL), cholesterol, triglyceride (TG), and testosterone levels were recorded. SPSS version 21.0 and SAS version 9.1 were used for statistical analysis. Level of significance was considered 0.05.

Results: The mean age of the two groups were 45.1 ± 9.3 years and 41.5 ± 11.2 years, respectively. There was a significant difference in serum testosterone levels between both groups and low testosterone levels were associated with metabolic syndrome ($P<0.001$). Serum testosterone levels showed a significant negative correlation with age in the metabolic syndrome group ($r=-0.16$, $P=0.02$). The relationship between metabolic syndrome and total plasma testosterone level using logistic regression model showed that, by increasing the total plasma testosterone level, the odds ratio for metabolic syndrome was 0.076 (95% CI: 0.027-0.216; $P<0.001$).

Conclusion: According to the results, low level of testosterone was related to the presence of metabolic syndrome in adult males. Future studies can investigate diagnostic value of testosterone level in this syndrome.

Implication for health policy/practice/research/medical education:
In a case-control study on 172 cases of metabolic syndrome, we found a significant difference in serum testosterone levels between both groups. Serum testosterone levels showed a significant negative correlation with age in the metabolic syndrome group too.

Please cite this paper as: Hejrati A, Ziaee A, Pourmahmoudian M, Bayani E, Ghavamipour M, Saatchi M. Association of plasma total testosterone level and metabolic syndrome in adult males. J Nephropathol. 2020;9(3):e27. DOI: 10.34172/jnp.2020.27.

Original Article

Introduction

Metabolic syndrome is one of the main threats to public health in the 21st century according to its association with type 2 diabetes mellitus and cardiovascular diseases (1). It is characterized with insulin resistance, abdominal obesity, hypertension, renal disease, hyperglycemia, and dyslipidemia profile (2). These factors lead to the high prevalence of cardiovascular diseases and diabetes (3). The prevalence of metabolic syndrome is growing worldwide especially in children and young adults (4,5).

Since metabolic syndrome has several components such as metabolic, cardiovascular and anthropometric factors, it is complicated to understand the etiology of this syndrome. The risk factors of metabolic syndrome affecting testosterone level can be demonstrated easily because of their correlation with waist circumference; such as overweight-obesity, lifestyle, surgery, aging, diabetes mellitus, cardiovascular diseases, and lipodystrophy (6,7).

*Corresponding author: Maryam Saatchi,
Email: m.saatchi92@gmail.com

Low testosterone level has strongly correlated with body fat accumulation and abdominal obesity in men (8). Testosterone is a sex hormone in males which is produced by testicular Leydig cells (9). It increases lipolysis and decreases visceral fat, while lack of testosterone leads to insulin resistance due to increased fatty acids (10). Endogenous androgens decreased with increasing age in men and it is associated with cardiovascular diseases, diabetes and hypertension. However, there is not sufficient evidence to show the relationship between low testosterone levels and male obesity (11,12).

Objectives

This case-control study was performed to investigate the relationship of testosterone levels with metabolic syndrome in Iranian men. It is promising to provide ground work for further studies to use testosterone levels and testosterone analogs to predict or treat this syndrome.

Patients and Methods

Study design

This case-control study was conducted on patients of internal medicine clinic in Rasoul Akram hospital, Tehran, Iran. Participants were categorized into two groups. First group consisted of 172 patients with metabolic syndrome and the second group consisted of 172 patients who referred to the clinic for other complaints irrelevant to metabolic syndrome and did not have metabolic syndrome. Using ATP III (adenosine triphosphate) criteria patients with metabolic syndrome were diagnosed. The ATP III declared presentation of metabolic syndrome if three or more of these five criteria are met;

1. Waist circumference over 102 centimeters in men or 88 centimeters in women,
2. Systolic blood pressure over 130 mm Hg and diastolic blood pressure over 85 mm Hg,
3. Fasting triglyceride (TG) level over 150 mg/dL,
4. Fasting high-density lipoprotein (HDL-C) level less than 40 mg/dL in men or 50 mg/dL in women,
5. Fasting blood sugar (FBS) levels over 100 mg/dL or diagnosed type 2 diabetes.

Patients with micro and macro-vascular complications from diabetes or any other complication were not included in this study. The control group and the metabolic syndrome group were chosen to be similar in demographic features as much as possible.

The collected data were entered into a pre-designed checklist consisting of; demographic features (age, weight, height, Body mass index [BMI]), FBS, HDL, LDL, total testosterone, cholesterol, and TG. Blood samples (10 ml) were collected in mornings from participants with at least 10-hour fasting. All samples were tagged and labeled to minimize misunderstandings. Serum levels of cholesterol, TG, and FBS were measured by photometry, HDL and LDL levels were assessed using enzymatic direct tests, and total testosterone with chemiluminescence (ECL) method.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients. The study was approved by the ethical committee of Iran University of Medical Sciences (ethical code; IR.IUMS.FMD.REC.1396.8911215299). This work supported by deputy research and technology of Iran University of Medical Sciences in Iran (Research code: 2938).

Statistical analysis

Statistical analysis was done using Statistical Package for Social Sciences, version 21.0 (IBM SPSS Statistics Inc., Chicago, IL, USA) and Statistical Analysis Software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Mean ± standard deviation (SD) was reported to describe quantitative variables; and categorical data were described using counts and percentages. *T* test was used to compare quantitative variables with normal distribution and quantitative variables without normal distribution were analyzed by Mann-Whitney test. To compare the qualitative variables, Chi square test and Fisher's exact test was used. Correlations between quantitative variables were tested using Spearman's rank correlation and Pearson's correlation coefficient. Additionally, to investigate confounding factors, multivariate logistic regression analysis was implemented and results were expressed by odds ratio (95 percent confidence interval). Level of significance was considered 0.05.

Results

The mean age for the metabolic syndrome group was 45.1 ± 9.3 years and for the control group 41.5±11.2 years. The participants were categorized into three age groups (20-39, 40-59, and over 60 years) demonstrated in Table 1. The means and ranges for quantitative variables are described in Table 2. In participants with metabolic syndrome a significant negative correlation between age and testosterone level was observed (r=-0.16, $P=0.02$; Figure 1), but this correlation was not recorded in the control

Table 1. Quantitative variables

Age group (y)	Patients with metabolic syndrome		Patients without metabolic syndrome	
	No.	%	No.	%
20-39	30	17.4	63	36.2
40-59	135	78.5	101	0.58
Over 60	7	4.1	7	4.1

Table 2. Participants age groups

Variable	Patients with metabolic syndrome			Patients without metabolic syndrome		
	Mean	SD	Range	Mean	SD	Range
Age (y)	45.1	9.3	20-84	41.5	11.2	20-84
Waist circumference (cm)	96.6	11.3	72-189	90.4	9.1	72-130
Systolic BP (mm Hg)	12.8	17.1	80-165	115.1	16	85-200
Diastolic BP (mm Hg)	77.6	12	50-115	72	10.7	50-100
FBS (mg/dL)	119.5	43.6	83.5-444	90	5.6	73.5-108
Cholesterol (mg/dL)	194.1	38.3	104-296	175.6	32.5	106-257
LDL-C (mg/dL)	114.6	24.7	59-182	103.3	24.1	54-169.1
HDL-C (mg/dL)	37	8	15.3-60.5	39.7	7.3	25-71
TG (mg/dL)	194.9	101.2	41-688	145.7	76.8	52-496
BMI (kg/m^2)	26.3	3.4	16.4-34.9	24.8	3.2	17.5-32.5
Testosterone serum level (ng/mL)	4.7	1	2.5-7.6	7.2	1.3	4.2-9.5

FBS, Fasting blood sugar; BMI, body mass index; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BP, blood pressure.

group ($P=0.211$). Serum testosterone levels did not show any significant correlation with waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), FBS, cholesterol, LDL-C, HDL-C, TG, and BMI in any either of the groups. As demonstrated in Table 2, mean testosterone serum levels for metabolic syndrome group and control group are 4.7 ± 1 ng/mL and 7.2 ± 1.3 ng/ml respectively, which was significantly different ($P<0.001$). The relationship between metabolic syndrome and total plasma testosterone level using logistic regression model showed that, by increasing the total plasma testosterone level, the odds ratio for metabolic syndrome was 0.076 (95% CI: 0.027-0.216) ($P<0.001$). The results also showed that by increasing one unit of FBS, the odds ratio for metabolic syndrome was 1.425 (95% CI: 1.267-1.604) ($P<0.001$). Other variables such as age, waist, SBP, DBP, serum cholesterol, FBS, LDL-C, HDL-C, BMI and TG had no significant correlation with metabolic syndrome ($P>0.05$). Table 3 shows the results of the logistic regression model for the association between metabolic syndrome with variables of age, waist, SBP, DBP, symptom-limited treadmill test (SLTT), serum cholesterol, LDL-C, HDL-C, TG and also BMI.

Discussion

Metabolic syndrome is recognized as an important risk that predisposes patients to cardiovascular disease and type II diabetes and also renal disease (13). According to WHO's statistical data, cardiovascular disease is the major reason of mortality and morbidity in the world (14). The prevalence of death caused by cardiovascular in men is higher than women (15). Recent studies suggest that low testosterone levels have correlation with cardiovascular damage, as testosterone has a key role in decreasing serum levels of pro-inflammatory factors such as interleukin 1 and tumor necrosis factors. Furthermore, testosterone

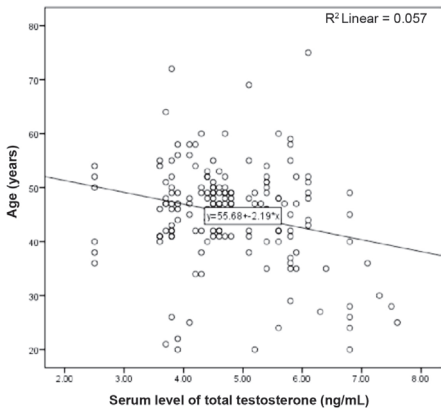

Figure 1. Correlation between serum testosterone level and age in metabolic syndrome group.

Table 3. Logistic regression model for metabolic syndrome with age, waist, SBP, DBP, SLTT, CHOL, LDL-C, HDL-C, BMI and TG

Variable	OR	95% CI		P value
		Lower	Upper	
Age	0.95	0.884	1.033	0.255
Waist	1.056	0.924	1.207	0.425
SBP	0.959	0.897	1.024	0.211
DBP	1.021	0.940	1.110	0.616
FBS	1.425	1.267	1.604	<0.001
CHOL	1.021	0.971	1.073	0.414
LDL-C	0.989	0.929	1.053	0.730
HDL-C	1.078	0.974	1.194	0.148
BMI	0.937	0.660	1.328	0.713
SLTT	0.076	0.027	0.216	<0.001
TG	1.008	0.997	1.019	0.143

FBS, Fasting blood sugar; BMI, body mass index; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SLTT, symptom-limited treadmill test; SBP, systolic blood pressure; DBP, diastolic blood pressure.

increases anti-inflammatory cytokine interleukin 10. It has been proved that testosterone improves insulin sensitivity and reduces BMI and visceral fat (16). In the past decades, several studies have shown that low- testosterone serum levels in men correlate strongly with obesity (17). In this study we reported a significant association between low levels of testosterone and metabolic syndrome in adult males. Additionally, we recorded that, testosterone levels and age in patients with metabolic syndrome have negative correlation. A similar investigation was conducted by Kaplan et al, which showed that old men with metabolic syndrome show a significant reduction in testosterone serum levels (18) which was consistent with our results.

Moreover, a cross-sectional study in 2016 demonstrated that the prevalence of metabolic syndrome and its components increase with age especially with high BMI and lack of physical activity and obesity. This study had a large population about 20 000 participants, since it consisted of men and women which makes its result more reliable (19). A study conducted by Mahdy et al in Egyptian population investigated the levels of testosterone and sex hormones in men with metabolic syndrome. Their study showed that low testosterone levels have conversely correlation with weight, BMI, cholesterol, LDL-C, TG and insulin as our findings. They also find a positive correlation between low-testosterone levels and HDL-C. In our study, we could not find a significant association between HDL-C and serum testosterone levels. Mahdy et al studied only 40 men with metabolic syndrome and 40 men as a control group, so their results need further investigation according to sample size (20).

A meta-analysis in 2011 by Brand et al revealed the correlation of sex-dependent testosterone levels and metabolic syndrome. This study also investigated this relationship in women. Testosterone levels in women with metabolic syndrome were higher, though they were lower in men with metabolic syndrome. Brand et al observed variability in results because of differences in age, BMI, metabolic syndrome criteria and study design. They also demonstrated the higher sex hormone binding globulin (SHBG) levels are associated with decreased metabolic syndrome risk in both genders (21). Siddiqui et al supported an association between SHGB levels and metabolic syndrome. In their cross-sectional study, among Saudi men population, SHBG levels have correlation with age, BMI, TG, HDL-C, and testosterone levels (22). Accordingly, Cunningham stated that low-testosterone and SHBG serum levels are due to increased insulin and inflammatory cytokines. Since low-testosterone levels are associated with cardiovascular disease in men; the relationship is not clear and seems to be independent from metabolic syndrome (3). We, therefore, suggested conducting future studies to investigate serum SHBG levels in metabolic syndrome without the effect of testosterone levels.

Haring et al in prospective cohort study suggested low-testosterone levels as a prognostic factor for incident of metabolic syndrome especially in young and middle-aged men. However, they cannot demonstrate the relationship between low-testosterone levels and metabolic syndrome. Similar to before studies, they cannot affirm whether low-testosterone causes it or is an early mechanism leading to metabolic syndrome (23). Recent studies show testosterone replacement therapy reduces insulin resistance in men with diabetes and metabolic syndrome. Testosterone replacement therapy also has significant effect on reduction of body fat mass, weight loss and decreases waist circumference in men with metabolic syndrome (24). However, it is suggested conducting further investigations to understand the relationship between serum testosterone levels and metabolic syndrome in a larger group and longitudinal studies. Moreover, it requires more exploration to recognize specific tissue actions of testosterone because testosterone replacement therapy has considerable effects on insulin and fat mass.

Conclusion

According to the results, low-level of testosterone was related to the presence of metabolic syndrome in adult males. Future studies can investigate diagnostic value of testosterone level or therapeutic effects of testosterone analogs to treat this syndrome.

Limitations of the study

It had some limitations including lack of follow-up of patients, which would demonstrate long-term metabolic outcomes. However, it was beyond the objective of the present study due to the case-control nature of the study.

Acknowledgments

We would like to thank Iran University of Medical Science and the presidency of the Islamic Republic of Iran due to the financial support of this study.

Authors' contribution

AH, AZ and MS contributed to study design, preparation of manuscript and final revision. MP and AH participated in data gathering. MS and MP conducted data analysis and interpretation. All authors read and approved the paper.

Conflicts of interest

All authors declare no potential conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This work supported by deputy research and technology of Iran University of Medical Sciences in Iran (Research code: 2938).

References

1. Salam R, Kshetrimayum AS, Keisam R. Testosterone and metabolic syndrome: The link. Indian J Endocrinol Metab. 2012;16:12-9. doi: 10.4103/2230-8210.94248.
2. Muraleedharan V, Jones TH. Testosterone and the metabolic syndrome. Ther Adv Endocrinol Metab. 2010;1:207-23. doi: 10.1177/2042018810390258.
3. Cunningham GR. Testosterone and metabolic syndrome. Asian J Androl. 2015;17:192-6. doi: 10.4103/1008-682X.148068.
4. Blaya R, Blaya P, Rhoden L, Rhoden EL. Low testosterone levels and metabolic syndrome in aging male. Curr Pharm Des. 2017;23:4470-4. doi: 10.2174/1381612823666170503150955.
5. Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018;20:12. doi: 10.1007/s11906-018-0812-z.
6. Ahmed IZ, Mahdy MM, El Oraby H, Abdelazeem EM. Association of sex hormones with metabolic syndrome among Egyptian males. Diabetes Metab Syndr. 2017;11:1059-64. doi: 10.1016/j.dsx.2017.07.042.
7. Kamenov Z, Assyov Y, Angelova P, Gateva A, Tsakova A. Irisin and testosterone in men with metabolic syndrome. Horm Metab Res. 2017;49:755-9. doi: 10.1055/s-0043-115227.
8. Akishita M, Fukai S, Hashimoto M, Kameyama Y, Nomura K, Nakamura T, et al. Association of low testosterone with metabolic syndrome and its components in middle-aged Japanese men. Hypertens Res. 2010;33:587-91. doi: 10.1038/hr.2010.43.
9. Harada N. Role of androgens in energy metabolism affecting on body composition, metabolic syndrome, type 2 diabetes, cardiovascular disease, and longevity: lessons from a meta-analysis and rodent studies. Biosci Biotechnol Biochem. 2018;82:1667-82. doi: 10.1080/09168451.2018.1490172.
10. Chubb SA, Hyde Z, Almeida OP, Flicker L, Norman PE, Jamrozik K, et al. Lower sex hormone-binding globulin is more strongly associated with metabolic syndrome than lower total testosterone in older men: The Health in Men Study. Eur J Endocrinol. 2008;158:785-92. doi: 10.1530/EJE-07-0893.
11. Bekaert M, Van Nieuwenhove Y, Calders P, Cuvelier CA, Batens AH, Kaufman JM, et al. Determinants of testosterone levels in human male obesity.Endocrine. 2015;50:202-11. doi: 10.1007/s12020-015-0563-4.
12. Jean-Luc Gradidge P, Norris SA, Jaff NG, Crowther NJ. Metabolic and body composition risk factors associated with metabolic syndrome in a cohort of women with a high prevalence of cardiometabolic disease. PLoS One. 2016;11:e0162247. doi: 10.1371/journal.pone.0162247.
13. Rao PM, Kelly DM, Jones TH. Testosterone and insulin resistance in the metabolic syndrome and T2DM in men. Nat Rev Endocrinol. 2013;9:479-93. doi: 10.1038/nrendo.2013.122.
14. World Health Organization. Fact sheet No317, cardiovascular diseases. 2011. http://www.who.int/mediacentre/factsheets/fs317/en/.
15. American Heart Association. Men and cardiovascular diseases. 2012; https://www.heart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_483969.pdf.
16. Jones RD, Nettleship JE, Kapoor D, Jones HT, Channer KS.Testosterone and atherosclerosis in aging men: purported association and clinical implications. Am J Cardiovas Drugs. 2005;5:141-54. doi: 10.2165/00129784-200505030-00001.
17. British Heart Foundation. Coronary heart disease statistics in England 2012. 2011; https://www.bhf.org.uk/informationsupport/publications/statistics/coronary-heart-disease-statistics-2012.
18. Kaplan SA, Meehan AG, Shah A. The age related decrease in testosterone is significantly exacerbated in obese men with the metabolic syndrome. What are the implications for the relatively high incidence of erectile dysfunction observed in these men? J Urol. 2006;176:1524-7. doi: 10.1016/j.juro.2006.06.003.
19. Roos V, Elmstahl S, Ingelsson E, Sundstrom J, Arnlov J, Lind L. Metabolic Syndrome development during aging with special reference to obesity without the metabolic syndrome. Metab Syndr Relat Disord. 2017;15:36-43. doi: 10.1089/met.2016.0082.
20. Mahdy MM, El Oraby H, Zaky E. Association of sex hormones with metabolic syndrome among Egyptian males. Diabetes Metab Syndr. 2017;11:1059-64. doi: 10.1016/j.dsx.2017.07.042.
21. Brand JS, van der Tweel I, Grobbee DE, Emmelot-Vonk MH, van der Schouw YT. Testosterone, sex hormone-binding globulin and the metabolic syndrome: a systematic review and meta-analysis of observational studies. Int J Epidemiol. 2011;40:189-207. doi: 10.1093/ije/dyq158.
22. Siddiqui K, Al-Rubeaan K, Nawaz SS, Aburisheh KH, Alaabdin AMZ, Tolba IA. Serum Sex Hormone Binding Globulin (SHBG) Relation with Different Components of Metabolic Syndrome in Men with Type 2 Diabetes. Horm Metab Res. 2018;50:138-144. doi: 10.1055/s-0043-123348.
23. Haring R, Völzke H, Felix SB, Schipf S, Dörr M, Rosskopf D, et al. Prediction of metabolic syndrome by low serum testosterone levels in men: results from the study of health in Pomerania. Diabetes. 2009;58:2027-31. doi: 10.2337/db09-0031.
24. Kelly DM, Jones TH. Testosterone: a metabolic hormone in health and disease. J Endocrinol. 2013;217:25-45. doi: 10.1530/JOE-12-0455.