ORIGINAL RESEARCH PAPER
Volume-9 | Issue-2 | February-2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

TO STUDY THE CORRELATION OF ENDOGENOUS SEX STEROID HORMONES LEVELS WITH METABOLIC SYNDROME IN POST MENOPAUSAL FEMALES

General Medicine

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ABSTRACT

Objective: to study the correlation of endogenous sex steroid hormones levels with metabolic syndrome in postmenopausal females
Study methodology: In this case control cross sectional study 100 postmenopausal women were enrolled (50 cases and 50 control with and without metabolic syndrome respectively). Detailed history and medical examination were done. Serum evaluation for lipid profile, fasting blood sugar, SHBG, estradiol and testosterone was done. Metabolic syndrome was defined according to definition of NCEP-ATP III with ethnic specificity for Asian Indian. **Results:** Hormone profile had significantly higher value of serum testosterone both total (p= 0.027) and free (p= 0.00066) in cases than controls but no significant difference in levels of estradiol (p= 0.983). Also, serum SHBG levels (p= <0.001) were significantly low in cases. Negative correlation of SHBG with systolic BP (p= 0.032, r= -.303) and testosterone with diastolic BP (p= 0.021, r= -.326) in cases and positive correlation of SHBG with fasting blood sugar in controls with statistical significance (p= 0.021, r= .326). **Conclusion:** Testosterone and SHBG were significantly associated with the emergence of metabolic syndrome in postmenopausal females. No relation was found between estradiol and emergence of metabolic syndrome.

KEYWORDS

Endogenous Sex Steroid Hormone, Metabolic Syndrome, Postmenopausal Women

INTRODUCTION

The metabolic syndrome is a combination of disorders that cause increase risk of cardiovascular disease and therefore increased mortality. [1, 2, 3, 4] It is a cause of major public health and clinical challenge worldwide in the era of urbanization, high energy intake, increasing obesity, and sedentary lifestyle. Recently in joint statement by a number of health organizations, the metabolic syndrome was redefined as presence of more than equal to 3 out of 5 factors (or on treatment for the same) namely increased waist circumference, raised serum triglycerides, increased fasting plasma glucose, hypertension, low serum HDL.

After first decade of life many chronic diseases emerge affecting both quality and quantity of life. The sex steroid hormones depletion is an important consequence of normal aging and gonadal failure, causing increased risk to disease in hormone responsive tissues including brain, bone and CVS.[5]

Endogenous estrogen appears to be cardioprotective and postmenopausal estrogen deficiency indicates a close association of adverse changes in metabolic risk factors. The emergence of these risk factors may be a direct result of ovarian failure or alternatively an indirect result of metabolic consequences of central obesity with estrogen deficiency.[6]

Similarly, as testosterone hormone dominates in hormonal milieu during menopausal transition, the prevalence of metabolic syndrome increase as the testosterone rise is associated with insulin resistance, low HDL, raised blood glucose and triglycerides levels. [7, 8, 9]

SHBG is a glycoprotein involved in transport of sex steroids, several reports have demonstrated significant association between SHBG levels and variables of metabolic syndrome. However, whether SHBG is a causal agent of metabolic syndrome or only the representative marker for primary endocrine abnormality, leading to these metabolic abnormalities remains unclear until now.[10]

The present is being conducted for a better understanding of correlation between these endogenous sex steroid hormone levels (estradiol, testosterone, SHBG) in postmenopausal women with metabolic syndrome.

MATERIAL AND METHODS

This case control cross sectional observational study was carried out in PGIMER and Dr RML hospital from November 2015 to March 2017 on 100 post-menopausal women aged between 45-75 years, with and without metabolic syndrome as 50 cases and 50 control respectively. Cases were with more than two components of metabolic syndrome (or on treatment for the same), and controls were less than three components of metabolic syndrome (consensus statement for diagnosis of metabolic syndrome).[11] The subjects were enrolled in the study after written informed consent, and study was approved by Institutional Ethical Committee. The subjects with cardiac disease, thyroid disease, deranged LFT and KFT, anemia, surgical menopause, history of carcinoma breast/ ovary/ uterus were excluded from the study. The detailed history and medical examination were done for subjects fulfilling the study criteria.

As per consensus statement metabolic syndrome for Asian Indian is defined by more than or equal to 3 out of 5 factors should be present, which includes:[11]

TABLE 1

Abdominal obesity (cm)	Males ≥90, females ≥80
Fasting blood glucose (mg/dL)	≥100
Hypertension (mmHg)	≥130 systolic or ≥85 diastolic
High triglycerides (Tg) (mg/dL)	≥150
Low HDL (mg/dL)	Males <40, females <50

It is similar to modified NCEP/ATP III definition with ethnic specific definition of waist circumference.

On examination height (Ht), weight (Wt), waist circumference (WC), waist hip ratio (WHR), BMI, blood pressure (BP) were measured by standard technique. For lab investigations venous blood samples were

drawn after overnight 12 hours of fasting and samples were sent for CBC, TFT, KFT, LFT, lipid profile (serum cholesterol, HDL-C, LDL, VLDL, triglycerides), blood glucose levels (fasting and post prandial), serum insulin level (by insulin ELISA kit), endogenous sex steroids hormone levels.

Lipid profile was measured by enzymatic method using reagent kit and fully automated calorimetric method. Blood glucose was determined by enzymatic method by using reagent kit (RANDOX, GLUPAP), post prandial samples were taken 2 hours after meal. HOMA-IR was calculated using formula [FBS (mg/dl) x fasting insulin (uIU/ml)]/ 405.

Estradiol and testosterone assay were done using chemiluminescence based method and samples were processed on Vitioseci analyzer. Free testosterone levels were calculated using serum total testosterone, serum albumin, SHBG levels. SHBG levels were obtained by using direct immune enzymatic calorimetric method in automatic dispenser reading the microplates at 450nm, 620-630nm.

Accordingly, the subjects were included and excluded in the study and the included subjects were divided as cases and controls as per definition for metabolic syndrome.

STATISTICALANALYSIS

Independent sample t-test was used to compare mean values between the two groups and Pearson chi-square test was used for categorical variable for determination of correlation. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

As seen in table 2 the mean age and duration of menopause in both the groups were comparable. Hormone profile had significantly higher value of serum testosterone (total and free) in cases than controls but no significant difference in levels of estradiol in both the groups. Also, serum SHBG levels were significantly low in cases and controls.

On calculation with Pearson correlation (r), results showed negative correlation of SHBG with systolic BP (SBP) and testosterone with diastolic BP (DBP) in cases and positive correlation of SHBG with fasting blood sugar in controls with statistical significance.

TABLE 2: -MEAN VALUES AND STANDARD DEVIATION OF THE MAIN ANTHROPOMETRIC, CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF THE SUBJECTS

PARAMETERS	CASES (MEAN ± S.D.) (n = 50) (Group A)	CONTROLS (MEAN ± SD) (n= 50) (Group B)	p-value
Age (Years)	59.34 ± 5.59	58.34 ± 5.81	0.382
Duration of Menopause (Years)	12.56 ± 5.95	10.92 ± 5.70	0.162
Total Testosterone (ng/dL)	0.05 ± 0.02	0.04 ± 0.02	0.027
Estradiol (pg/ml)	463.32 ± 189.31	462.37 ± 241.96	0.983
SHBG (nmol/L)	29.48 ± 15.78	44.11 ± 22.62	<0.001
Free (Calculated) Testosterone (ng/dL)	0.001 ± 0.0005	0.0007 ± 0.0004	0.00066
T/E Ratio	0.000026 ± 0.000019	0.000021 ± 0.000024	0.203

TABLE 3: -CORRELATION OF ESTRADIOL, TESTOSTERONE AND SHBG WITH THE COMPONENTS OF METABOLIC SYNDROME IN CASES

		Estradiol	Testosterone	SHBG
WC	r	0.142	-0.117	-0.035
	p	0.326	0.418	0.812
SBP	r	-0.125	-0.057	-.303*
	p	0.387	0.695	0.032
DBP	r	-0.168	-.326*	-0.128
	p	0.243	0.021	0.376
FBS	r	0.156	0.077	-0.012
	p	0.278	0.595	0.935
Tg	r	-0.066	0.176	0.088
	p	0.65	0.221	0.544
HDL	r	-0.17	0.014	0.097
	p	0.239	0.921	0.503

p= p value, r= Pearson correlation

TABLE 4: - CORRELATION OF ESTRADIOL, TESTOSTERONE AND SHBG WITH THE COMPONENTS OF METABOLIC SYNDROME IN CONTROLS

		ESTRADIOL	TESTOSTERONE	SHBG
Waist circumference (cm)	r	-0.17	-0.011	0.162
	p	0.239	0.939	0.26
SBP	r	-0.069	0.195	-0.034
	p	0.632	0.175	0.812
DBP	r	-0.001	0.238	-0.034
	p	0.994	0.096	0.813
FBS	r	0.121	-0.11	.326*
	p	0.401	0.447	0.021
Tg	r	0.103	0.25	0.137
	p	0.477	0.079	0.342
HDL	r	-0.039	0.085	-0.02
	p	0.787	0.558	0.892

p= p value, r= Pearson correlation

FIGURE 1: - Scatter diagram of correlation between testosterone and BP

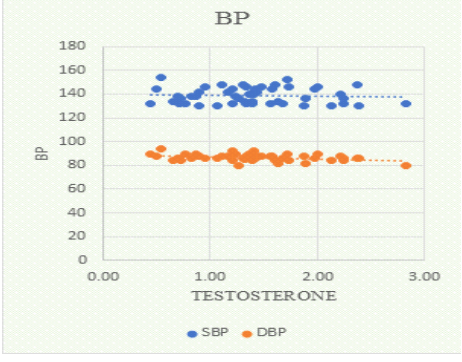
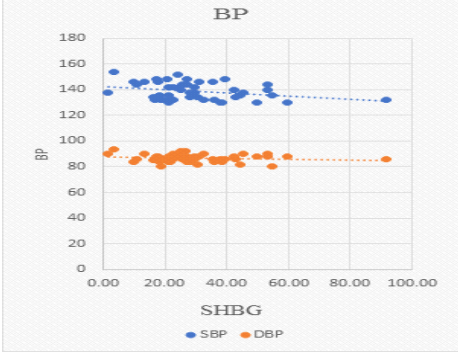


FIGURE 2: -Scatter diagram of correlation between SHBG and BP



DISCUSSION

In our study, most of the cases were between age group of 51-65 years implying that metabolic syndrome was more common in this age group of postmenopausal women. The results were similar to a study in western India [12] relating menopause and metabolic syndrome showed statistically significant relationship (p-value <0.0001) between increase in age and prevalence of metabolic syndrome with

results showing 4.7 times increase in risk of metabolic syndrome among women aged 56-65 years (OR: 4.747, CI: 1.914-11.774) compared to those less than 40 years.

Waist circumference in both the groups was raised with significantly higher value in cases than in controls, indicating that central obesity after menopause can be one of the factors adding to the emergence of metabolic syndrome in postmenopausal females. Mean triglyceride levels in both the groups was within normal range but HDL-C levels were low in both the groups with significantly lower in cases than in controls, indicating that postmenopausal status is more related to fall in HDL-C levels than the rise in triglycerides levels in relation to metabolic syndrome.

Studies looking at the relation between menopause and metabolic syndrome conducted over recent years have mostly focused on the analysis of endogenous sex hormone balance parameters as: 17b-oestradiol, free oestradiol, oestrone and androgenic indicators: total testosterone, free testosterone, sex hormone binding globulin (SHBG) or dihydroepiandrosterone sulfate (DHEA-S). In most cases, the results of the research indicate a greater importance of androgenic markers (especially testosterone and SHBG) in the assessment of metabolic syndrome and cardio-metabolic risk factors occurrence in perimenopausal and postmenopausal women. [10, 13]

In the present study, the mean of total and free testosterone levels was high in subjects with metabolic syndrome as compared to subjects without metabolic syndrome. Torrens et al reported a relative androgen excess during the menopausal transition and both baseline total T/E ratio and its rate of change were associated with increase incident metabolic syndrome independent of ethnicity.[14] Accumulating evidence suggested that a high level of endogenous testosterone was associated with unfavourable lipid profile, events of cardiovascular disease and insulin resistance in females. Total testosterone and free testosterone showed positive correlations with total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) and negative correlations with high-density lipoprotein (HDL)-C. [15, 16] A high level of free testosterone is associated with increase in events of cardiovascular disease [17, 18] and insulin resistance. [19, 20] Recently, a high testosterone level has been shown to be associated with subclinical atherosclerosis in healthy menopausal women.[21]

All these findings were in corroboration with the present study, as the testosterone levels were significantly high in postmenopausal females with metabolic syndrome as compared to that in controls. In the present study, total testosterone had significant positive correlation with serum triglyceride levels and negative correlation with SHBG and WHR in all subjects; with significant negative correlation with DBP in cases, but free testosterone was not found to have any significant correlation with any of the variables of metabolic syndrome, yet was significantly high in cases than in controls.

In our study, the mean SHBG levels were significantly low in cases than in controls still being within reference range in both the groups. SHBG had negative correlation with testosterone, and strongly with SBP, DBP and no positive correlation with any of the variables studied in the study, indicating that low levels of SHBG is associated with increase in BP (both SBP and DBP). Approximately 60-65% of testosterone is carried in peripheral blood bound to SHBG, about 35-40% bound to albumin and in small amount bound to CBG (corticosteroid binding globulin). Since the binding to albumin and CBG is relatively weak, SHBG essentially has a function as a circulating SHBG with age is still controversial. SHBG has been seen to decrease steadily with age.[22] In women, a high SHBG level was also associated with favorable lipid profiles, decrease in the occurrence of cardiovascular disease and metabolic syndrome. SHBG was shown to be negatively correlated with total cholesterol, LDL-C and TG and to be positively correlated with HDL-C. Low SHBG level was associated with the occurrence of cardiovascular disease. [17, 18] SHBG level was negatively associated with hyperinsulinemia [24] and risk of metabolic syndrome. [25, 26] In study by Toshiyuki Yasui et al also showed that SHBG level was negatively correlated with Homeostasis Model Assessment (HOMA) index in both men and women.[27] In addition, SHBG level was negatively correlated with Tg level in women but not in men. Therefore, SHBG may have biological functions beyond simply regulation of the level of free sex steroid hormones and may play important roles in lipid metabolism and insulin sensitivity. In our study, SHBG was found to have negative correlation with testosterone, SBP and DBP, and vice-versa, explaining to have raised BP in subjects with lower SHBG levels.

In study by Ziaei S et al., they found significant correlation between testosterone and SHBG with some risk determinants of metabolic syndrome (p-value<0.05) as positive correlation of testosterone with BP (r = 0.29), FBS (r = 0.28), Tg (r = 0.31), and negative correlation of SHBG with Tg (r = -0.199) significantly.

Mean estradiol levels in our study in both the groups were comparable with statistically insignificant p-value (0.983). also, it was found to have no correlation with any of the components of metabolic syndrome. The results in many studies examining association between E2 concentration and the parameters of metabolic syndrome are divergent. Although some studies have shown a positive correlation between estradiol and insulin resistance or type 2 diabetes in postmenopausal women, even after controlling for BMI, [28, 29] other studies have shown no such relationship. [30] In the present study also, we could not find any significant correlation of estradiol with metabolic syndrome or any of its components. Although studies of low-dose exogenous E2 in the form of hormone replacement therapy have been associated with a lower risk of diabetes in postmenopausal women, other studies have found exogenous oral E2 administration at higher doses to be associated with greater insulin resistance. [29] Endogenous E2 is also associated with the development of adiposity. [31, 32] although endogenous E2, itself, results from aromatization of androgens in adipocytes; thus, the relationship between E2 and adiposity is likely to be bidirectional.

Although the research was carefully prepared and has reached its aim, there were some unavoidable limitations.

First, due to time limitation, the research was conducted on a small sample size. More studies need to be done on larger population to unveil the hidden epidemic and its characteristics in order to prevent and manage further occurrences.

Second, the causal relationship between the endogenous sex steroid hormones and the metabolic syndrome in post-menopausal women could not be conclusively established because of the cross-sectional study.

CONCLUSION

Triglyceride was found to be positively correlated with testosterone only. All the other components of metabolic syndrome had strong positive correlation with each other except HDL-C, which had negative correlation with all other components. Both Testosterone and SHBG were associated with the emergence of metabolic syndrome in postmenopausal females. We did not find any relation between estradiol and emergence of metabolic syndrome.

Since metabolic syndrome is more prevalent in older age group, it is advisable to screen individuals in age group of 51-65 years. Also, prospective studies are needed to determine whether change in serum endogenous sex steroid hormones and SHBG levels precede the development of metabolic syndrome or is the effect of syndrome. With more studies, it remains to be seen if future recommendations will use changes in these hormones as markers for determining metabolic syndrome and associated risk, the primary target of therapy by modifying them with HRT or other means for management or prevention of syndrome and its components.

REFERENCES

1. Cameron A. The metabolic syndrome: validity and utility of clinical definitions for cardiovascular disease and diabetes risk prediction. Maturitas.2010;65(2):117-21.
2. Ding QF, Hayashi T, Zhang XJ, Funami J, Ge L, Li J, et al. Risks of CHD identified by different criteria of metabolic syndrome and related changes of adipocytokines in elderly postmenopausal women. J Diabetes Complications. 2007;21(5):315-9.
3. Gaspard U. Hyperinsulinemia, a key factor of the metabolic syndrome in postmenopausal women. Matuitas.2009;62(4):362-5.
4. Martinez MA, Puig JG, Mora M, Aragon R, O'Dogherty P, Anton JL, et al. Metabolic syndrome: prevalence, associated factors, and C-reactive protein: the MADRIC (MADrid RIesgo Cardoivascular) Study. Metabolism. 2008;57(9):1232-40.
5. Lobo RA, Davis SR, De Villiers T, Gompel A, Henderson VW, Hodis HN, et al. prevention of disease after menopause. Climacteric. 2014;17(5):540-56.
6. Carr MC. The emergence of the metabolic syndrome with menopause. J Clin Endocrinol Metab. 2003;88(6):2404-11.
7. Haffner SM, Valdez RA. Endogenous sex steroid hormones: impact on lipids, lipoproteins, and insulin. Am J Med. 1995;98(1A):40S-7S.
8. Pugeat M, Moulin P, Cousin P, Fimbel S, Nicolas MH, Crave JC, et al. interrelations between sex hormone-binding globulin (SHBG), plasma lipoproteins and cardiovascular risk. J Steroid Biochem Mol Biol. 1995;53(1-6):567-72.
9. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and

risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2006;295(11):1288-99.
10. Ziaesi S, Mohseni H. Correlation between Hormonal Statuses and Metabolic Syndrome in Postmenopausal Women. J Family Reprod Health. 2013;7(2):63-6.
11. Mishra A, Chowbey P, Makkar BM, Vikram NK, Wasir JS, Chadha D, et al. consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. J Assoc Physicians India. 2009; 57:163-70.
12. Pandey S, Srinivas M, Agashe S, Joshi, Galvankar P, Prakasam CP, et al. menopause and Metabolic syndrome: A study of 498 urban women from wetern india. J Midlife Health. 2010;1(2):63-9.
13. Weinberg ME, Manson JE, Buring JE, Cook NR, Seely EW, Ridker PM, et al. low sex-hormone binding globulin is associated with the metabolic syndrome in postmenopausal women. Metabolism. 2006;55(11):1473-80.
14. Torrens JI, Sutton-Tyrrell K, Zhao X, Matthews K, Brockwell S, Sowers M, et al. relative androgen excess during the menopausal transition predicts incident metabolic syndrome in midlife women: study of Women's Health Across the Nation. Menopause. 2009;16(2):257-64.
15. Shelley JM, Green A, Smith AM, Dudley E, Dennerstein L, Hpper J, et al. Relationship of endogenous sex hormones to lipids and blood pressure in mid-aged women. Ann Epidemiol. 1998;8(!):39-45.
16. Lambrinoudaki I, Christodoulakos G, Rizos D, EconomouE, Argeitis J, Vlachou S, et al. Endogenous sex hormones and risk factors for atherosclerosis in healthy Greek postmenopausal women. Eur J Endocrinol. A2006;154(6):907-16.
17. Rexrode KM, Manson JE, Lee IM, Ridker PM, Sluss PM, Cook NR, et al. Sex hormone levels and risk of cardiovascular events in postmenopausal women. Circulation. 2003;108(14):1688-93.
18. Sutton-Tyrrell K, Wildman RP, Matthews KA, Chae C, Lasley BL, Brockwell to cardiovascular risk factors in multiethnic premenopausal and perimenopausal women enrolled in the Study of Women Across the Nation (SWAN). Circulation. 2005;111(10):1242-9.
19. Kalish GM, Barrett-Cooonor E, LAUGHLIN ga, Gulanski BI, Postmenopausal Estrogen/Progestin Intervention Trial. J Clin Endocrinol Metab. 2003;8(4):1646-52.
20. Lee CC, Kasa-Vubu JZ, Supiano MA, Androgenicity and obesity are independently associated with insulin sensitivity in postmenopausal women. Metabolism. 2004;53(4):507-12.
21. Creasta M, Armeni E, Stamatelopoulos K, Rizos D, Georgiopoulos G, Kazani M, et al. Circulating androgen levels are associated with subclinical atherosclerosis and arterial stiffness in healthy recently menopausal women. Metabolism. 2012;61(2):193-201.
22. Sowers MF, Zheng H, McConnell D, Nan B, Karvonen-Gutierrez CA, Randolph JF Jr. Testosterone, sex-hormone binding globulin and free androgen index among adult women: chronological and ovarian aging. Hum Reprod. 2009;24(9):2276-85.
23. Mudali S, Dobs AS, Ding J, Cauley JA, Szklo M, Golden SH, et al. Endogenous postmenopausal hormones and serum lipids: The atherosclerosis risk in communities' study. J Clin Endocrinol Metab. 2005;90(2):1202-9.
24. Preziosi P, Barrett-Connor E, Papoz L, Roger M, Saint Paul M, Nahoul K, et al. Interrelation between plasma sex hormone-binding globulin and plasma insulin in healthy adult women: the telecome studty. J Clin Endocrinol Metab.1993;76(2):283-7.
25. Hajamor S, Despres JP, Couillard C, Lemieux S, Tremblay A, Prud'homme D, et al. Relationship between sex hormone-binding globulin levels and features of metabolic syndrome. Metabolism. 2003;52(6):724-30.
26. Santoro N, Torrens J, Crawford S, Allsworth JE, Finkelstein JS, Gold EB, et al. Correlates of circulating androgens in mid-life women: the study of women's health across the nation. J Clin Endocrinol Metab. 2005;90(8):4836-45.
27. Yasui T, Tomita J, Miyatani Y, Yamada M, Uemura H, Irahara M, et al. Associations of adiponectin with sex hormone-binding globulin levels in aging male and female populations. Clin Chim Acta. 2007;386(1-2):69-75.
28. Ding EL, Song Y, Manson JE, Rifai N, Buring JE, Liu S. Plasma sex steroid hormones and risk of developing type 2 diabetes in women: a prospective study. Diabetologia. 2007;50(10):2076-84.
29. Godsland IF. Oestrogens and insulin secretion. Diabetologia. 2005;48(11):2213-20.
30. Oh JY, Barrett-Connor E, Wedick NM, Wingard DL, Rancho Bernardo S. Endogenous sex hormones and the development of type 2 diabetes in older men and women: The Rancho Bernardo study. Diabetes Care. 2002;25(1):55-60.
31. Mahabir S, Baer DJ, Johnson LL, Hartman TJ, Dorgan JF, Campbell WS, et al. Usefulness of body mass index as a sufficient adiposity measurement for sex hormone concentration associations in postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2006;15(12):2502-7.
32. McTiernan A, Wu L, Chen C, Chlebowski R, Mossavar-Rahmani Y, Modugno F, et al. Relation of BMI and physical activity to sex hormones in postmenopausal women. Obesity (Silver Spring). 2006;14(9):1662-77.