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The Metabolic Syndrome and Disturbances in Sex Hormones Levels in both gender

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Abstract
Background: Sex hormones play an important role in lipid metabolism, but also on elements of the metabolic syndrome. Gonadal hormones have been associated with an increased cardiovascular risk and with severity of atherosclerosis in diabetes mellitus patients and healthy men. Furthermore, low levels of serum testosterone and high levels of estradiol have been associated with obesity, dyslipidemia, and insulin resistance .This study aimed to study the disturbances in sex hormone in both gender and evaluated the correlation between sex hormone with phsio-biochemical parameters in both group.
Methods: Total of 80 subjects(40 male:40 female) ,aged35-65 years included in this study .About 5ml of fasting blood (8-12 h.) was collected from each individual. To determine serum FSH(Follicle-Stimulating Hormone),LH(Luteinizing Hormone) and sex hormone the quantitative sandwich enzyme immunoassay technique were used.FBG and Lipid profile were measured by an enzymatic colorimetric(GPO-POD) method.
Results: There were significant differences in physio-biochemical parameters between patients and control groups. There were significant elevation ($P<0.05$) in BMI(Body Mass Index), waist circumference (WC),Microalbuminuria (MA) ,Fasting blood glucose (FBG) , TG ,Testosterone ,Estradiol, FSH and LH in metabolic patients than control group, whereas the results of Systolic(SBP) and diastolic(DBP) blood pressure ,Cholesterol , HDL(High density lipoprotein) , LDL(Low density lipoprotein) and VLDL (Very low density lipoprotein) show no significant differences ($P > 0.05$) between metabolic groups and control. According to gender the results show significant elevation ($P<0.05$) in BMI ,HDL, Estradiol, FSH and LH in females than males and significant elevation ($P<0.05$) in Triglyceride and Testosterone in males than females , while other parameters show no significant differences ($p>0.05$) between males and females. Correlation analysis showed positive correlation between Estradiol with BMI in metabolic patients($r= 0.43$,$P= 0.05$), while in control group there was an inverse correlation between Estradiol and BMI was found($r= - 0.01$,$P= 0.03$) .
Conclusions: Disturbances in Sex hormones has been associated with metabolic and cardiovascular risk factors including diabetes, hypertension, dyslipidemia and obesity.
Keywords:Sex hormones, metabolic syndrome, lipid profile, BMI.

Introduction

Metabolic Syndrome (MS); also referred to as Syndrome X or Insulin Resistance Syndrome; describes a cluster of cardiovascular diseases (CVD) risk factors and metabolic alterations associated with excess fat weight. The MS which is associated with threefold increase in type 2-diabetes and twofold increase in cardiovascular diseases has become major public health challenge around the world . The incidence of MS is rising worldwide which is partly due to significant increase in the prevalence of obesity. The MS is a strong predictor of type 2 diabetes (Hunt *et al*.,2004;Bamashmoos *et al*.,2011;Marjani and Mojerloo,2011).Prevalence of type 2 diabetes is rapidly increasing world wide, primarily due to global increase in obesity & sedentary life style. Subjects with abnormal glucose metabolism are at increased risk for coronary artery disease(CAD) and they often exhibit various cardiovascular disease risk factors, like hyper triglyceredemia, dyslipidimia, hypertension, obesity and this MS is closely associated with type 2 diabetes mellitus and impaired glucose tolerance (Meigs, 2004; Sowjanya *et al*.,2011).

Adipose tissue for a long time was regarded as a comparatively passive side of energy storage (accumulated in the form of TG). However, recent studies show that adipose tissue is an endocrine organ producing various proteins (adipocytokines). Adipocytokines include leptin, angiotensinogen, tumor necrosis factor a, interleukin 6,plasminogen activator-inhibitor 1, transforming growth factor b, adipsin, adiponectin, resistin. These proteins are increased (with the exception of adiponectin, which decreases) in obesity , that link to the various components of metabolic syndrome and their cardiovascular effects while adiponectin decrease in obesity(Natah *et al*.,2013) .Central(Visceral) obesity, as measured by waist circumference or waist_ hip ratio, strongly correlates independently with insulin resistance and cardiovascular disease. Visceral adipocytes are metabolically more active than subcutaneous adipocytes. Visceral fat is a major source of free fatty acids and

adipocytokines to the liver which stimulates gluconeogenesis and inhibits hepatic insulin binding (Kolovou *et al*.,2005;Ferrannini *et al*., 2007 ; Muraleedharan and jones,2010).

Hadaegh *et al*. (2011) show that obesity consists of heterogeneous phenotypes resulting from interplay between genetic and environmental factors . Increased BMI has been associated with metabolic and cardiovascular risk factors including diabetes, hypertension, dyslipidemia .

After 8 years, men and women with either BMI above 30 kg/m^2 or waist circumference above "Action Level 2" (≥102 cm in men and ≥88 cm in women) were between three and eight times more likely to develop metabolic syndrome than those with BMI below 25 kg/m^2 or waist circumference below" Action Level 1"(≥ 94 cm in men and ≥ 80 cm in women). Up to one-third of the subjects with BMI above 30 kg/m^2 and waist above" Action Level 2" developed metabolic syndrome, compared with only one tenth of those who had both indices below these levels (Han *et al*.,2002).

Sheng *et al*.(2011) indicate that microalbuminuria is relatively common in patients with metabolic disorders, such as type 2 diabetes mellitus ,and has been incorporated into the definition of the metabolic syndrome of the World Health Organization. However, whether microalbuminuria should be an essential component of the metabolic syndrome remains controversial .

Hypertension is frequent in the metabolic syndrome, and more so is the BP abnormality, with values in the high normal range, that represents one of the five components that lead to the identification of this condition. Factors commonly associated with and partly dependent on obesity and insulin resistance, such as overactivity of the sympathetic , stimulation of the renin–angiotensin–aldosterone system , abnormal renal sodium handling , and endothelial dysfunction , need to be considered(Wilson and Grund,2003;Mule *et al*.,2005;Redon *et al*.,2008).

In study by Kolovou *et al*.(2005) refer that dyslipidaemia, the hallmark of the MS, is summarised as(a) increased flux of free fatty acids, (b) raised TG values, (c)low high density lipoprotein (HDL) cholesterol values, (d)increased small, dense low density lipoprotein (LDL) values, and (e) raised apolipoprotein (apo) B values .Dyslipidaemia is widely established as an independent risk factor for cardiovascular disease. Low HDL cholesterol and hypertriglyceridaemia have been found to be independently and significantly related to myocardial infarction/stroke in patients with MS. Additionally, a combination of high fasting glucose and low HDL cholesterol were shown to have primary predictive ability for coronary heart disease. The dyslipidaemia in MS patients may be caused by a combination of overproduction of very low density lipoprotein (VLDL) apo B-100,decreased catabolism of apo B containing particles, and increased catabolism of HDL-apo A-I particles .

Gonadal hormones have been associated with an increased cardiovascular risk and with severity of atherosclerosis in diabetes mellitus patients and healthy men. Furthermore, low levels of serum testosterone and sex-hormone–binding globulin (SHBG) have been associated with obesity, dyslipidemia, and insulin resistance (Nuver *et al*.,2005).

Also Muraleedharan and jones(2010) show that central fat deposits have a high aromatase activity thus converting more testosterone to oestrogen locally. This partially explains the higher level of oestrogens found in obese healthy men. Testosterone promotes myocyte and inhibits adipocyte development from pluripotent stem cells, thus increasing muscle mass, whereas a state of testosterone deficiency enhances greater fat mass . In addition testosterone increases the number of beta-adrenergic receptors which, in turn, promotes lipolysis and reduces fatty acid synthesis. Testosterone inhibits adipocytes lipoprotein lipase activity, the enzyme which breaks down circulating TG to absorbable free fatty acids which are taken up into the fat cells and converted back to TG for storage. The hypothesis suggests that low testosterone as a result of high aromatase activity leads to a cycle which promotes increasing adipocyte number and fat deposition which gradually leads to a lower testosterone levels.

Additionally, testosterone is perceived as a risk factor for cardiovascular disease accounting for the significantly higher prevalence of coronary heart disease (CHD) in men as compared to women. Mortality from CHD is at least twice as high in men as it is in women. This sex difference has been attributed to the difference in profiles of circulating sex steroids, with testosterone as the most obvious difference between the sexes. Men with diabetes have lower testosterone levels compared to men without a history of diabetes , and there is an inverse association between testosterone levels and glycosylated hemoglobin(Jones,2007;Saad,2009).

Hyperinsulinemia, as encountered in insulin resistance, might impair testosterone secretion by the Leydig cell, maybe directly since there are insulin receptors on the Leydig cell . Furthermore, testosterone reduces insulin levels and insulin resistance in men with obesity. Sex steroid hormones are involved in the metabolism, accumulation and distribution of adipose tissues. It is now known that there are estrogen receptors, progesterone receptors and androgen receptors in adipose tissues, so their actions could be direct. Sex steroid hormones carry out their function in adipose tissues by both genomic and nongenomic mechanisms. Activation of the cAMP cascade by sex steroid hormones would activate hormone-sensitive lipase leading to lipolysis in adipose tissues. In the phosphoinositide cascade, diacylglycerol and inositol 1,4,5-trisphosphate are formed as second messengers ultimately causing the activation of protein kinase C. Their activation appears to be involved

in the control of preadipocyte proliferation and differentiation. The role of testosterone in regulating lineage determination in mesenchymal pluripotent cells by promoting their commitment to the myogenic lineage and inhibiting their differentiation into the adipogenic lineage through an androgen receptor-mediated pathway has been convincingly demonstrated(Makhsida *et al*., 2005;Saad,2009).

Estrogens and estrogenic compounds have a major impact on the metabolism of lipids, but also on elements of the metabolic syndrome. Estrogens and estrogenic compounds act classically by binding to the estrogen receptors α and β (ERα and ERβ), which change their conformation and dimerize. The dimer in turn binds with or without recruitment of cofactors to an estrogen responsive element (ERE) and thereby activates transcription . In animal experiments it was shown that a lack of estrogen causes an increase of body fat resulting in obesity and hypercholesterolemia .The increase in body fat weight combined to a changed distribution of fat depots to a more central android distribution can be observed in postmenopausal women as well . Human patients with aromatase deficiency mean a complete lack of estrogen show also adiposity, elevated cholesterol levels, impaired bone maturation and for the male patients hyperinsulinemia. In a girl but not in a boy with aromatase deficiency a decrease of the negative feedback for both serum LH and FSH was observed (Starcke and Vollmer,2006).

Study by Sun and Ren(2012) indicate to several lines of evidence indicate that estrogen protects the cardiovascular system through modulation of neuronal and endothelial isoforms of NO synthase (NOS). However, it is also evident that estrogen may activate the renin-angiotensin aldosterone system (RAAS) and promote oxidative stress, which, in turn, may or may not depend on NOS and lead to cardiac injury. These observations are consistent with the finding that NOS serves as a key source of estrogen-stimulated superoxide production en route to deleterious cardiovascular effects of estrogen(Sun and Ren,2012).

Material and Methods

This study was performed in the Diabetic center in mergan hospital, Babylon province in 2013.The study group included 80 subjects (40 females and 40 males) with age average (35-65 year) ,as control group matched with patient group. At the point of study entry, all study participants were subjected to clinical and biochemical investigations. The exclusion criterion was the coexistence of any other serious illness. The metabolic syndrome was defined according to (WHO ,2004):

*Glucose intolerance, IGT or diabetes and/or insulin resistance together with two or more of the following:

*Raised arterial pressure ≥140/90 mmHg

*Raised plasma TG (≥1.7 mmol/L; 150 mg/dL) and/or low HDL cholesterol (<0.9 mmol/L, 35 mg/dL men;<1.0 mmol/L, 39 mg/dL women)

*Central obesity (WC ≥102 cm in men and ≥ 88 cm in female) and/or BMI >30 kg/m^2 *Microalbuminuria (urinary albumin excretion rate ≥20 g/min or albumin:creatinine ratio≥ 30 mg/g).

Diabetes mellitus(DM) was defined as non ketosis diabetes by medical history and current treatment Type-2 DM with oral hypoglycaemic agents. None of the subjects had microvascular complications (diabetic nephropathy or retinopathy).Administration of insulin for glycaemic control was considered an exclusion criterion. A venous blood sample was collected from all the subjects who came after a 8-12-hours overnight fast. The samples were centrifuged for 10 minutes at 3000 rpm. The serum was used for estimating fasting blood glucose and lipid profile by biochemical kit using spectrophotometer techniques. Body mass index (BMI) was calculated using the formula BMI= weight (kg)/ $height^2$ $(m)^2$ and classifying under weight (BMI<18), normal (BMI 18 - 24.9), overweight (BMI 25 - 29.9) , obesity (BMI 30-39.9) and morbid obesity (BMI > 40) (WHO,2004).The waist circumference was measured while the subject standing up , at the narrowest point of the torso width-wise, usually just above the belly button ,which is ≤ 102 cm in male and ≤ 88 cm in female (WHO,2004).Systolic and diastolic blood pressures were measured using sphygmomanometer. Hypertension was defined as systolic ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg.

The analyses were performed using the statistical package for social sciences (SPSS version 17.0). Physiological and biochemical parameters data were analyzed using factorial experiment with completely randomized. Data were represented as mean ± SD. Bivaraite correlations were performed using the Pearson correlation coefficient .P value (P<0.05) was considered statistically significant .

Result

There were significant differences in physio-biochemical parameters between patients and control group(Table 1).There were significant elevation (P<0.05) in BMI, waist circumference ,Microalbuminuria (MA) ,Fasting blood glucose (FBG) , Triglyceride(TG) ,Testosterone ,Estradiol, FSH and LH in metabolic patients than control group, whereas the results of Systolic(SBP) and diastolic(DBP) blood pressure ,Cholesterol , HDL , LDL and VLDL show no significant differences (P > 0.05) between metabolic groups and control. According to gender the results show significant elevation (P<0.05) in BMI ,HDL, Estradiol, FSH and LH in females than males and significant elevation (P<0.05) in TG and Testosterone in males than females , while other parameters show no

significant differences (p>0.05) between males and females.
Correlation analysis showed positive correlation between Estradiol with BMI in metabolic patients(r= 0.43,P= 0.05), while in control group there was an inverse correlation between Estradiol and BMI was found(r= -0.01,P= 0.03) (Table 2).

Table(1): Comparison between metabolic syndrome and control subjects for both gender.

Parameter	Control N=40		Metabolic syndrome N=40		P value of group	P value of gender
	Male(N=20) Mean± SD	Female(N=20) Mean± SD	Male(N=20) Mean± SD	Female(N=20) Mean± SD		
BMI(kg/m^2)	28.09±4.96	31.14±6.26	31.04±4.70	34.13±5.95	0.01*	0.01*
WC(cm)	100.35±9.59	96.30±12.29	106.70±13.42	106.10±17.23	0.009*	0.44
FBG(mmol/l)	4.92±0.95	5.09±0.76	10.45±2.45	11.65±5.93	0.001*	0.35
Microalbuminuria (mg/l)	5±0.27	11±2.45	39±6.54	31±2.36	0.001*	0.86
SBP mm Hg	11.1± 1.31	12.3± 2.11	13.65± 1.35	14.11±2.19	0.07	0.43
DBP mm Hg	7.9± 0.61	8.1± 0.94	8.29± 0.74	8.47± 1.11	0.08	0.45
Cholesterol (mmol/l)	4.21±1.02	4.31±0.88	4.64±1.03	4.67±1.35	0.10	0.79
TG(mmol/l)	1.82±0.91	1.31±0.06	2.12±0.80	1.91±0.09	0.01*	0.04*
HDL(mmol/l)	1.07±0.24	1.16±0.15	1.07±0.19	1.19±0.29	0.78	0.04*
LDL(mmol/l)	2.51±0.98	2.59±0.88	2.96±0.14	2.85±0.30	0.15	0.95
VLDL(mmol/l)	0.56±0.08	0.48±0.02	0.62±0.01	0.60±0.02	0.25	0.54
Testosterone (ng/ml)	7.97±1.47		2.30±0.60		0.001*	
Estradiol(pg/ml)		21.06±2.42		43.38±3.90	0.01*	
FSH(mIU/ml)	9.03±1.66	30.34±3.79	13.09±4.39	52.66±8.96	0.01*	0.001*
LH(mIU/ml)	5.76±0.32	13.25±1.27	6.59±0.35	19.51±2.44	0.05*	0.001*

BMI: Body Mass Index, WC: Waist Circumference, FBG: Fasting Blood Glucose ,SBP, systolic blood pressure, DBP, diastolic blood pressure ,TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein, FSH: Follicle-Stimulating Hormone, LH: Luteinizing Hormone.
*P value is significant ≤ 0 .05 level, SD :Standard deviation.

Table (2) The correlation between sex hormone with some physio-biochemical parameter in control and metabolic patients .

Index			BMI	WC	FBG	MA	Col.	TG	HDL	LDL	VLDL	FSH	LH
Testosterone	Con. N=20	r	-0.12	-0.18	-0.13	-0.14	0.17	-0.22	-0.13	0.32	-0.23	-0.13	-0.38
		p	0.96	0.44	0.58	0.55	0.46	0.34	0.57	0.16	0.32	0.57	0.09
	MS N=20	r	0.24	0.27	-0.06	0.04	0.11	0.05	-0.35	0.20	-0.16	-0.25	-0.29
		p	0.30	0.24	0.77	0.86	0.62	0.82	0.13	0.38	0.47	0.27	0.20
Estradiol	Con. N=20	r	-0.01	0.30	0.16	0.27	0.06	0.07	-0.07	0.04	0.45	0.07	0.60
		p	0.03*	0.19	0.47	0.24	0.78	0.75	0.74	0.86	0.06	0.77	0.15
	MS N=20	r	0.43	0.14	-0.04	-0.35	-0.36	-0.15	-0.15	-0.31	-0.11	-0.35	-0.33
		p	0.05*	0.53	0.86	0.12	0.11	0.51	0.50	0.17	0.63	0.12	0.14

Con: control, MS: Metabolic syndrome.
Correlation coefficient (r) ,* Correlation is significant ≤ 0.05 level (2-tailed).

Discussion

The results of the present study show that there were significant elevation in BMI and waist circumference in patients with metabolic syndrome compared to control and there were significant elevation in BMI in female than male (Table 1),this is may be due to a number of factors, the prevalence of abdominal obesity was remarkably higher among woman than men. This was partially explained by the difference in cut-points adopted for men and women, 102 and 88 cm, respectively. However, the actual waist circumferences were also higher in women than men (Al-Lawati *et al*.,2003).In our study, women had higher BMI than men. This finding is expected in our population because men are taller than women. Furthermore, BMI calculation is solely dependent on the net weight and height of the individual, and does not consider the distribution of muscle and bone mass. BMI also does not differentiate between body fat and muscle mass. This may result in misleading

information with regard to the amount of fat in an individual. Of all anthropometric indices, WC had the strongest association with each metabolic abnormality in men and women(Khader *et al*.,2010).

The greater proportion of women observed in the group with MS. It was explained by a greater prevalence of visceral obesity and of low HDL values in females than in males. The over-representation of women in the MS group may appear surprising in the light of the higher percentage of males reported in MS in previous papers , in which the WHO criteria were used to diagnose MS (Hunt *et al*.,2004;Mule *et al*.,2005; Bamashmoos *et al*.,2011;Marjani and Mojerloo,2011).

Abdominal fat accumulation, as measured by WC, has been shown to be associated with metabolic and CVD risk, type 2 diabetes mellitus, hypertension, coronary artery disease, and stroke, and a stronger association was found with abdominal adiposity than with overall adiposity as measured by BMI (Baynouna *et al*.,2009;Khader *et al*.,2010).

There was significant elevation in microalbuminurea (MA) in metabolic patients than control group while there was no significant differences between males and females in both groups (Table 1), this is because the hyperglycemia may directly induce mesangial expansion and injury, perhaps in part via increased matrix production or glycosylation of matrix proteins .Also hyperglycemia increases the expression of transforming growth factor-beta (TGF-beta) in the mesangial cells which causes increased vascular permeability. This abnormality permits the leakage of low molecular weight proteins (albumin). This is the stage of microalbuminuria (incipient nephropathy) which could be reversible with good glycaemic control (Idogun and Kasia ,2011 ; Naveen *et al*., 2012).

There were no significant differences in blood pressure between metabolic patients and control group in both gender (Table 1), this may be due to hypertension is not strongly linked to the metabolic syndrome (Ford *et al*.,2002).

The results revealed significant elevation in triglyceride in metabolic patients than control group, whereas the results of cholesterol, HDL, LDL and VLDL showed no significant differences between control and diabetes group ,while significant differences in HDL levels between males and females for both group(Table 1). The primary defect is probably focused in the inability to incorporate the free fatty acids to TGs by the adipose tissue (inadequate esterification).This results in reduced fatty acid trapping and consequent retention by the adipose tissue. The insulin resistance also causes reduced retention of free fatty acids by the adipocytes. Both these abnormalities lead to increased flux of free fatty acids back to the liver (Kolovou *et al*.,2005).

Insulin resistance at the level of adipose tissue is the initiating event for dyslipidemia in MS. Due to IR, Free fatty acids(FFA) are released from adipose tissue .Thus there will be increased availability of FFA to liver ,this leads to increased triglyceride (TG) synthesis & overproduction of VLDL. CETP (cholesteryl ester transfer protein)mediates the exchange of TG-CE between LDL, VLDL and HDL forming TG rich HDL. These TG rich HDL are prone to be catabolised leading to low HDL levels in MS (Ferrannini *et al*.,2007;Sowjana *et al*.,2011).

In the insulin resistant state, the LDL levels are usually within normal limits or only mildly raised; however the LDL particle is often of abnormal composition (small, dense LDL). The underlying abnormality causing small dense LDL is hypertriglyceridaemia. TG rich LDL is a good substrate for hepatic lipase that finally generates small dense LDL, which is associated with increased cardiovascular risk because reduced LDL receptor mediated clearance, (b) increased arterial wall retention, (c) increased susceptibility to oxidation (Kolovou *et al*.,2005).

Low HDL cholesterol in patients with the MS is often considered as secondary to raised TG. In the presence of increased plasma TG levels, the cholesteryl ester transfer

protein mediates TG-cholesteryl ester exchange between LDL and VLDL. Similar lipid exchange is taking place between VLDL and HDL particles, forming TG rich HDL . These TG rich but cholesterol depleted HDLs are more prone to be catabolised. They undergo hydrolysis of their TG component and dissociation of their protein component, apo A (the main protein of HDL).There are additional mechanisms that contribute to the low HDL cholesterol levels. One possibility is that changed lipid flux in the liver attributable to insulin resistance may reduce the hepatic production of apo A (Kolovou *et al*.,2005).

Levels of FSH and LH (Interstitial cell stimulating hormone ICSH in males) were significantly higher in metabolic group than control ($P<0.05$), while the levels of estradiol in female and testosterone in male show significant differences between groups (Table 1).Estradiol at physiological concentrations enhances glucose uptake in adipocytes at least in part at the step of insulin-induced tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1). At higher concentrations estradiol inhibits insulin-induced glucose metabolism which might be a possible explanation of insulin resistance in late pregnancy . The mechanism of this effect could be the inhibition of insulin signaling through phosphorylation of IRS-1 at Ser307. This serine307 is known to be phosphorylated by JNK, which is a crucial mediator of insulin resistance. Hyperinsulinemia also might increase the risk of developing colorectal cancer since high insulin levels exhibited growth factor and tumor promoting properties in vitro . At the same time estradiol causes an up regulation of IGF-1R and IRS-1. This enhanced

presence of IRS-1 seems to involve an IGF-1R mediated increased proliferation. At least two signal cascades are involved in these effects: the phosphatidylinositol 3 (PI-3)-kinase-cascade and the MAP-kinase-cascade (Starcke and Vollmer,2006) .

Visceral obesity is an independent risk factor for cardiovascular disease . Total testosterone levels are lower in men with obesity. The San Antonio Heart Study found that both total and free testosterone levels inversely correlated with body mass index and waist-to-hip ratio . Visceral adiposity correlates positively with the degree of insulin resistance. Aromatase has a high activity in adipocytes and metabolism of testosterone to oestradiol. The higher the number and volume of adiposities, the greater is the breakdown of testosterone. Testosterone inhibits the enzyme lipoprotein lipase, which is situated on the outer surface of the fat cell that regulates the conversion of free fatty acids into triglyceride . Lower testosterone levels would enhance the enzyme activity leading to greater uptake of triglyceride into the adipocytes, increasing fat storage and also stimulating the formation of new fat cells from pre-adipocytes. This exacerbates insulin resistance and drives the cycle to further reduce testosterone levels. The normal homeostatic response is that the hypothalamic-pituitary axis would detect the falling testosterone level and increase gonadotrophin secretion to stimulate the testis. The relationship between testosterone and lipid parameters is not fully clear, but the majority of reports have found that hypogonadism is associated with higher levels of total and low-density lipoprotein (LDL) cholesterol, and triglycerides and low levels of high-density lipoprotein (HDL) cholesterol (Jones,2007; Saad,2009; Wang *et al*.,2011).

There were inverse correlations between plasma testosterone and triglycerides (TG), total cholesterol, LDL, fibrinogen and plasminogen activator type I(Makhsida *et al*., 2005).Other study have shown inverse correlations between plasma testosterone and BMI, waist circumference, the waist-to-height ratio, amount of visceral fat, serum leptin, serum insulin and serum-free fatty acid concentrations(Tsai *et al*., 2000).

Hypogonadal men exhibit an increased body fat mass. HDL-C and TG levels comprise two central components of the metabolic syndrome whereas total and low-density lipoprotein (LDL) cholesterol (LDL-C) are not. Raised total cholesterol, LDL-C and TG confer risk for future cardiovascular events whilst HDL-C is protective against atherosclerosis and low levels are associated with increased cardiovascular risk. HDL-C presents a complicated picture and the effect seems to be gender specific . Low HDL correlates with CHD more in men than women. There is a strong inverse correlation between body fat and testosterone levels in men (Muraleedharan and jones,2010).

Correlation analysis showed an inverse correlation between estradiol with BMI in control group, while positive correlation between estradiol with BMI in metabolic group . This result is supported by Ren and Kelley (2007) that found inverse correlation between estrogen and metabolic syndrome suggests that estrogen deficiency that accompanies menopause may play a role in the onset and development of metabolic syndrome. Also study by Ali and Al-Zaidi (2011) revealed an inverse correlation between serum estradiol level and BMI.

Obesity is aproinflammatory state resulting in increased release and secretion of proinflammatory cytokines and adipokines, free fatty acid and estrogen from adipose tissue. These increases are important risk factors that may contribute to the development of metabolic syndrome and type 2 diabetes as well as androgen deficiency(Wang *et al*.,2011).

Conclusions: Disturbances in Sex hormones has been associated with metabolic and cardiovascular risk factors including diabetes, hypertension, dyslipidemia and obesity. While these hormone in physiological concentration protect the cardiovascular system.

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