

CONTENTS

Introduction	1
Review of Literature	7
Subject and Methods	75
Results	87
Discussion	121
Summary & Conclusions	129
Recommendation	132
References	133
Arabic Summary	1

List of figure

Fig	Title	No
1	Adipose tissue, adipokines and insulin resistance	35
2	Comparison of BMI between males with and without metabolic syndrome (patients and controls), p value: 0.0001	94
3	Comparison of waist circumference between males with and without metabolic syndrome (patients and controls), p value: 0.0001	94
4	Comparison of SBP and DBP between males with and without metabolic syndrome (patients and controls), p value: 0.0001	95
5	Comparison of total cholesterol, LDL,HDL and TG between males with and without metabolic syndrome (patients and controls), P value: 0.0001	96
6	Comparison of fasting glucose between males with and without metabolic syndrome (patients and controls), p value 0.0001.	97
7	Comparison of fasting insulin between males with and without metabolic syndrome (patients and controls), p value 0.0001	97
8	Comparison of HOMA-IR between males with and without metabolic syndrome (patients and controls), p value 0.0001	98

9	Comparison of testosterone levels between males with and without metabolic syndrome (patients and controls) p value 0.0001	100
10	Statistically significant Inverse correlation between testosterone and weight.	102
11	Statistically significant Inverse correlation between testosterone levels and BMI.	103
12	Statistically significant Inverse correlation between testosterone levels and Waist-CR.	103
13	Statistically significant Inverse correlation between testosterone levels and FBS.	105
14	Statistically significant Inverse correlation between testosterone levels and Cholesterol.	105
15	Statistically significant Inverse correlation between testosterone levels and Fasting insulin	106
16	Statistically significant Inverse correlation between testosterone levels and HOMA_IR.	106
17	Statistically significant Inverse correlation between testosterone levels and Triglyceride.	107
18	Statistically significant direct correlation between testosterone levels and HDL.	107

19	Statisitcally significant Inverse correlation between testosterone levels and LDL.	108
20	Statistically significant Inverse correlation between testosterone levels and estradiol levels	109
21	Statisitcally significant Inverse correlation between Estradiol levels and AGE.	110
22	Statisitcally significant Direct correlation between Estradiol levels and LDL.	112
23	Statisitcally significant Direct correlation between Estradiol levels and FBS.	112
24	Statisitcally significant Direct correlation between Estradiol levels and Cholesterol.	113
25	Statisitcally significant Direct correlation between Estradiol levels and Fasting Insulin.	113
26	Statisitcally significant Direct correlation between Estradiol levels and HOMA_IR.	114
27	Roc Curve for sensitivity and specificity of estradiol mor than 16.78 The sensitivity was 92.5% and specificity was 82.5%	119
28	Roc Curve for sensitivity and specificity of testosterone less than 2.37% The sensitivity was 67.5% and specificity was 95%	120

List of table

No	Table	No
1	BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure; TG, triglycerides; WHR, waist/hip ratio	11
2	Causes of insulin resistance	23
3	Clinical and biochemical characteristics of the studied population	90
4	Prevalence of the metabolic syndrome components among males with metabolic syndrome	91
5	Prevalence of metabolic syndrome components among the males without metabolic syndrome	92
6	Comparison between males with and without metabolic syndrome regarding the clinical findings	93
7	Comparison between males with and without metabolic syndrome regarding the laboratory findings	95
8	Comparison between males with and without metabolic syndrome regarding sex hormone levels	99
9	Testosterone quartiles in the studied group	101
10	Estrogen quartiles in the studied patients	101
11	Correlation between testosterone levels and the clinical findings	102
12	Correlation between testosterone levels and the laboratory data	104
13	Correlation between testosterone levels and E2 levels	108
14	Correlation between estradiol levels and the clinical findings	109

15	Correlation between estradiol levels and the laboratory data	111
16	Correlation between T:E demographic characteristics	115
17	Correlation between T:E and different Laboratory parameters.	115
18	Association of estrogen levels to components of metabolic syndrome	116
19	Association of testosterone levels to components of metabolic syndrome	117

LIST OF ABBREVIATIONS

AACE	the American Association of Clinical Endocrinologists
ADA	American Diabetes Association
Pk	protein kinase
BMI	body mass index
BP	blood pressure
BPA	bisphenol A
CETP	cholesterol ester transfer protein
CNS	central nervous system
CRP	C-reactive protein
CVD	cardiovascular disease
DBP	diastolic blood pressure
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
E2	estradiol
EGIR	The European Group for the Study of Insulin Resistance
ERs	Estrogen receptors
ET-1	Endothelin-1
FFAs	free fatty acids
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes

FMD	flow-mediated dilation
GLUT4	glucose transporter 4
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HOMA	homeostatic model assessment
HOMA _{IR}	homeostatic model assessment of insulin resistance
HSL	hormone-sensitive lipase
IDF	International Diabetes Federation
IGT	impaired glucose tolerance
IL	interleukin
IRS	insulin receptor substrate
LDL	low-density lipoprotein
MetS	metabolic syndrome
NCEP	National Cholesterol Education Program Adult
NFκ-B	nuclear factor kappa-beta
NHANES	National Health and Examination Survey
NO	nitric oxide
NOS	nitric oxide synthase
PDE	Phosphodiesterase
PI3K	phosphoinositide 3-kinases
PRA	Plasma rennin activity
RAS	renal artery stenosis
RCT	randomized clinical trials
SBP	systolic blood pressure

SHBG	sex hormone-binding globulin
ICAM-1	Intercellular Adhesion Molecule 1
sVCAM-1	vascular cell adhesion molecule-1
TAG	triacylglycerol
TG	Triglycerides
TNF- α	tumour necrosis factor alpha
tPA	tissue-type plasminogen activator
TRT	testosterone replacement therapy
VLDL	very low density lipoprotein
VSM	vascular smooth muscle
vWF	Von Willebrand factor
WC	Waist Circumference
WHO	the World Health Organization
WHR	waist/hip ratio

Association of sex hormones with metabolic syndrome among Egyptian males

Thesis

Submitted for partial fulfillment of the master degree in
endocrinology

By

**Eman Mohamed Abd EL- Azeam
M.B.B.CH**

Supervised by

Prof. Dr. Hussin Abd Elhay Aloraby

Professor of internal Medicine and Endocrinology
Faculty of Medicine – Ain Shams University

Dr. Iman Zaky Ahmed

Ass. Prof. of internal medicine and Edocrinology
Faculty of Medicine – Ain Shams University

Dr. Maram Mohammed Maher Mahdy

Lecturer of internal Medicine and Endocrinology
Faculty of Medicine – Ain Shams University

**Faculty of Medicine
Ain Shams University
2013**

Introduction

Metabolic syndrome is associated with increased risk of cardiovascular disease (CVD) and mortality (*Aijaz et al., 2008*). In fact, the presence of even 1 or 2 components of the metabolic syndrome increases overall mortality compared with the absence of any component of the metabolic syndrome. Metabolic syndrome even predicts the occurrence of sudden death, independent of the presence of other cardiovascular risk factors. (*Escobedo et al., 2009*).

Epidemiological studies have shown that low testosterone is associated with metabolic syndrome (MetS) in Caucasian and middle- aged Japanese men. (*Akishita et al., 2010*). In addition, numerous studies have found inverse associations between the severity of features of the metabolic syndrome and plasma testosterone (*Saad and Gooren., 2011*) .

Men show higher rates of cardiovascular morbidity and mortality than pre- menopausal women and this sexual dimorphism may be related to sex- specific effects of sex steroids on cardiovascular risk factors (*Tomaszewski et al ., 2009*).

Endogenous estrone levels among females have been linked to several components of the metabolic syndrome, including glucose tolerance, lipid metabolism and blood pressure, free estradiol levels were significantly higher among women with the metabolic syndrome than in women without metabolic syndrome in two separate studies (*Goulart et al., 2009*).

The increasing prevalence of metabolic syndrome (MS) with age in older men has been linked with decreasing testosterone levels. Interestingly, while testosterone levels decline with age, estradiol (E2) levels remain relatively stable, resulting in a decreased testosterone : E2 ratio. Because E2 levels tend to be elevated in morbid obesity, insulin resistance, and diabetes, it is reasonable to hypothesize that high E2 levels are associated with MS in older men. Whether changes in this hormonal pattern play a role in the development of MS should be further tested (*Maggio et al., 2008*).

It is likely that sex steroids are involved in the male and female patterns of fat deposition. The sex steroid- induced regional distribution is not an all- or- none mechanism. It is a preferential accumulation of excess fat. Obese men and women still show their sex- specific fat accumulation but store their fat also in the fat depots of the other a preferential accumulation of fat in the abdominal region is associated with an increased risk of type 2 DM and

cardiovascular disease , not only in obese subjects but even in non-obese subjects.(*Saad and Gooren, 2011*).

Sex hormone levels and androgen/estrogen balance may play an important role in determining MS and future cardiovascular risk among children and adolescents (*Agirbasli et al ., 2009*).

Androgens, estrogens were not extensively **investigated** in relation to cardiovascular phenotypes in men (*Tomaszeweski et al., 2009*).

Aim of the work

1-Examine the relation of endogenous sex hormone levels with components of metabolic syndrome in a cohort of apparently healthy males.

2-Comparison of the level of endogenous sex hormone levels between males with metabolic syndrome and healthy males.

THE METABOLIC SYNDROME

Definitions of Metabolic Syndrome

The clinical utility of identifying people with the metabolic syndrome (MetS) has raised concerns from many scientific groups. In particular, the use of the term “syndrome” was examined and discussed by the International Diabetes Federation (IDF) (*Alberti et al., 2006*). The IDF described a syndrome as “*a recognizable complex of symptoms and physical or biochemical findings for which a direct cause is not understood. When causal mechanisms are identified, the syndrome becomes a disease.*” Although insulin resistance is present in a majority of people with the MetS, the IDF found insufficient evidence for a causal link between the two, a statement that agreed with the American Diabetes Association (ADA), which published its concerns about the lack of certainty regarding the causative pathogenesis of insulin resistance and its utility as a marker for cardiovascular diseases (CVD) (*Kahn et al., 2005*).

In particular, the ADA emphasized the lack of clarity in the MetS definition and cautioned clinicians not to assume that the MetS is well characterized (*Kahn et al., 2005*). Although there are divergent criteria for the identification of the MetS, they all tend to agree that the MetS core components include obesity, insulin resistance, dyslipidemia, and hypertension (*Alberti et al., 2006*).