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Title: Serum Testosterone levels and Statin Therapy in normal, type 2 diabetic and hypertensive Libyan Male Subjects

BY

WALID M. EL-SHERIFF

SUPERVISED BY:

PROFESSOR DR. ABDALLA M JARARI

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Abbrevations:

T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
HMG-CoA reductase	β -hydrodxy-β-methylglutaryl Coenzyme A
LH	Leuteinizing hormone
FSH	Follicle stimulating hormone
SHBG	Sex hormone binding globulin
TNF-α	Tumor necrosis factor –alpha
IL	Interleukin
ED	Erectile dysfunction
HTN	Hypertension

Key words
Diabetes mellitus
Testosterone
Hypogonadism
Testosterone replacement therapy.
Statin

Abstract:

This study amid to assess and evaluate the effects of oral statin therapy on the testosterone serum levels in males with type 2 diabetes mellitus, hypertension patients and in normal.

Statins inhibit hydroxy methyl glutaryl COA reductase (HMG CO reductase),which is the rate limiting enzyme in cholesterol biosynthesis since statins decrease colesterol biosynthesis ,and cholesterol is the precursor of testosterone , there is some concern whether statins might impair testosterone production.

- hypogonadism in men is a clinical syndrome that results from failure of tests to produce testosterone.
- testosterone is the principle sex hormone in men.
- hypogonadism in men is one of the conditions that needs therapeutic attention and intervention.

It is reported to be associated with aging, diabetes and statin therpy,obesiy, diabetes and statin therapy are common in Libyan people there are few studies undertaken to study the prevalence association with diabetes and statin therapy in Libyan subjects.

Therefore, the present study was carried out to evaluate and measure serum testosterone levels on Libyan subject as following:

- in normal subjects using statin for dyslipidemia
- in diabetics
- in diabetic on statin therapy.
- in diabetic hypertensive
- in diabetic hypertensive on statin therapy.

Subject on statin therapy were grouped further into two catagories those who are going undergoing statin therapy for less than one year and those for more than one year

- Libyan subjects who attended Benghazi Center for Diagnosis and Treatment of Diabetes
- Libya from 2013-2014 were screened and 240 subjects were taken for the study.

They were divided into 8 groups: (30 subject in each group)

- Group I –controls
- Group II –patients with high cholesterol on statin therapy.
- Group III –type 2 diabetes.
- Group IV –type 2 diabetes on statin therapy for less than one year.
- Group V –type 2 diabetes on statin therapy for more than one year.
- Group VI –type 2 diabetic hypertensive
- Group VII –type 2 diabetic hypertensive on statin therapy for less than one year.
- Group VIII –type 2 diabetic hypertensive on statin therapy for more than one year.

In the present study, there was significant reduction in serum testosterone levels in patients treated with statin therapy.

The level of serum testosterone were significantly reduce compares to control subjects.

There was marked fall in serum testosterone, level in diabetic subject which was further reduced by statin therapy.

The presence of hypertension did not elicit greater fall in serum testosterone levels in hypertensive or diabetics with hypertension.

Statin therapy alone or statin therapy in type 2 diabetes mellitus (T2 DM) caused marked reduction in serum testosterone levels.

The reduction in serum testosterone level was more marked in patients who are on statin therapy for more than one year compared to those who are on statin therapy for less than one year.

The use of statins and its probable side effect is reported to be lowered testosterone levels.

It appeared that statin therapy is associated with hypogonadism,the finding of hypogonadism has resulted in reviewing statin therapy and has cautioned the physician to prescribe statins with care.

Therefore, there is a need of introspecting the use of drugs for therapy and its possible adverse effects.

Chapter 1

Introduction

1.1.Statins or HMG-CoA reductase inhibitors:

are widely used cholesterol lowering drugs which are effective in the primary and secondary prevention of cardiovascular disease (CVD),(Brugs et al 2009; Mihaylova et al.2012;Taylor et al.2013;4S study,1995). They competitively inhibit HMG-CoA reductase, mainly in the liver, which is the rate-limiting enzyme in the cholesterol biosynthesis pathway. By inhibiting cholesterol biosynthesis, the number of low-density lipoprotein (LDL) receptors in the hepatic membrane is increased. This leads to increased serum uptake of LDL-cholesterol, and thus decrease serum cholesterol concentration,(the Scandinavian Simvastatin Study(4S). Lancet. 1994; 344:1383-89.)

Testosterone is the main circulating androgenic hormone in men with important effects on libido, bone mass, fat distribution, muscle mass, strength and production of blood cells and sperm(Shalet 2009;Corona et al 2013). It is synthesized in the testes, and this process requires a continuous supply of cholesterol, which can be derived from plasma, mostly originating from the liver, or from de novo production within the gland (Miller and Bose,2011). In contrast, women have in general 8 to 9 times lower levels of serum total testosterone the hormone here plays a role in sexual function and libido (Redmond,1998). Circulating testosterone in men is for 40-65% bound to sex hormone-binding globulin (SHBG), which regulates the serum concentration of testosterone and its transport to target tissues. SHBG has a high binding affinity for testosterone and the serum concentrations of total testosterone and SHBG are strongly correlated. In contrast, the non-SHBG-bound fraction of testosterone, which is considered to be bioactive, is barely associated with the serum SHBG concentration (De Ronde etal.2005;Dunn et al.1981; Vermuelen 1996).This indicates that non-SHBG-bound testosterone, rather than total testosterone plays an important role in maintaining equilibrium in the negative feedback of the hypothalamo-pituitary-testicular axis and in other androgenic effects.

Since statins decrease cholesterol biosynthesis, and cholesterol is the precursor of testosterone, there is some concern whether statins might impair testosterone production. Statins decrease serum availability of the substrate cholesterol,and in

vitro studies showed that statins decrease cholesterol production in testicular Leydig cells (Klinefeltet al.2014;), or inhibit enzymes within the testosterone biosynthesis pathway (e.g. 17β-hydroxysteroid dehydrogenase), (Smals et al.1991). A lower testosterone level due to statins may be undesired in men with already low testosterone levels, since it may lead to symptoms such as a decrease in mood, libido, muscle strength, or bone mineral density. The 2013 American guidelines for cardiovascular disease prevention lowered the threshold for treatment with statins and widened the target population (Stone et al. 2014). Furthermore, the prevalence of diseases such as type 2 diabetes mellitus (T2DM) and CVD is increasing(Lieberman,2003;Gersh et al.2010).

Therefore, the already substantial use of statins in clinical practice may further increase, and this might come along with an increase in non-beneficial effects of statins (Ray et al.2014). Consequently, it is important to elucidate whether statins decrease serum testosterone levels, and more specifically non-SHBG bound testosterone, as potential undesired effect of their use.

1.2.Objective:

Hypogonadism in men is one of the conditions that needs therapeutic attention and intervention. It is reported to be associated with aging, diabetes and statin therapy.

Hypogonadism was defined as low serum total testosterone (<300 ng/dL) and free (<5 ng/dL) testosterone in combination with low libido, ED, osteoporosis or fracture, or 2 or more of the following symptoms: sleep disturbance, depressed mood, lethargy, or diminished physical performance.

Obesity, diabetes and statin therapy are common in Libyan subjects. There are few studies undertaken to study the prevalence, association with diabetes and statin therapy in Libyan subjects. Therefore the present study was carried out to evaluate and measure serum testosterone levels

- In normal subjects undergoing statin therapy for dyslipidemia
- In diabetes
- In diabetes with statin therapy

- In diabetic hypertensives
- In diabetic hypertensives on statin therapy

Subjects on statin therapy were grouped further into two categories–those who are undergoing statin therapy for less than one year and those for more than one year.

1.3.The obesity in Libya

The prevalence of obesity is increasing in Libya as well as all over the world (IASO,2012) as shown in the (Table2.1)below. Obesity is rampant in Libya as 30.5% of Libyan adults (IASO,2012) (Table2.1), 16.9% of children aged 5 or younger (Yang,Kelly and He,2007), and 6.1% of children aged between 10 and 18 are obese (Wells,2009). The rate of obesity progressively increases with age, from 4.2% in those aged between 10 and 12 to 46% in those aged between 55 and 64 (IASO,2012; Wells,2009) .

Table1.1. Prevalence of overweight and obesity in different countries

Country	Overweight			Obesity		
	Male (%)	Female (%)	All (%)	Male (%)	Female (%)	All (%)
Libya (IASO,2012)	36.1	29.7	33	21.4	40.1	30.5
USA 1999–2008 (FAO,2005)	40.1	28.6	34.2	32.2	35.5	33.8
KSA 1995–2002 (Hediger et al.2001)	42.4	31.8	36.9	26.4	44	35.6
Tunisia 1997 (Gilmann et al 2001)	23.3	28.2	27.4	6.7	22.7	14.4
Turkey 2001–2002 (Gilmann et al.2001)	46.5	28.6	36.8	16.5	29.4	23.5

.International Association for the Study of Obesity. Global prevalence of adult obesity (IASO)

The mean BMI in Libyan adults is 27.7 kg/m2 (26.4 kg/m2 in men and 29 kg/m2 in women), and the mean waist circumference is 93.3 cm. Obesity was almost two times more common among Libyan women than men (21.4% vs. 40.1%) (IASO,2012; Neel, 1962), whereas overweight was more prevalent among men than women, a trend being observed worldwide (FAO2005,Hediger et al2001;Gilmann et al 2001).

Table1.2 . Prevalence of obesity in Libya 1984 vs. 2008

Year	Obesity definition	Survey	Mean BMI (kg/m^2)	Obesity in Males	Obesity in Female	All
1984 (Neel,1962)	BMI≥27 M; BMI≥25 F	Subnational (Tripoli)	NR	7.7%	42.5%	12.6%
2008 (IASO,2012)	BMI≥30	National	27.7	21.4%	40.1%	30.5%

Globally, overweight and obesity are the fifth leading contributors to fatalities (Flegal et al.2010). Obesity and overweight result in major morbidity and premature death as they are predisposing factors for diabetes mellitus, hypertension and dyslipidemia (Benghazi Diabetes Center. 2009).

In Libya, some studies showed that obesity is more prevalent among people with Type 2 diabetics (T2DM)(Benghazi Diabetic Center 2009). hypertensives (Dakhil et al. 2000) and females with polycystic ovary disease (PCOD) (Najem et al.AOP.2000), (Table), which indirectly indicates that these diseases are more prevalent among obese than non-obese Libyans.

Table1.3 . Prevalence of obesity among Libyan patients with selected medical conditions in comparison to general Libyan population

Group	BMI (kg/m^2)	Obesity		
		Male	Female	All
General (IASO,2012) population	27.7	21.4%	40.1%	30.5%
Type 2 DM	33.7	52.67%	70.62%	63%
Hypertension (Dakhil et al 2000)	NR	87.4%	87.2%	87.3%
Polycystic ovary disease (Najem , Elmehdawi , Swalem,AOP)	34.4	NA	75%	NA

Diabetes mellitus is considered a CHD equivalent and, both CARE trial and Heart Protection Study found significant improvement in outcomes with statin therapy even

at LDL-cholesterol values below 100 mg/dL (2.6 mmol/l). The CARDS study found similar benefits of statin therapy in patients with an LDL-cholesterol above and below 120 mg/dL (3.1 mmol/L). Thus the ATP-III goal LDC-cholesterol is similar to that in patients with CHD: less than 100 mg/dL (2.6 mmol/l), and perhaps more aggressive target LDL-cholesterol goals of 75 to 80 mg/dL (1.9 to 2.1 mmol/l) may be appropriate in high risk groups Cardiologists declare that "cholesterol-containing lipoproteins are central to the pathogenesis of atherosclerosis,(ACC/AHA guidelines,2013).

1.4. Classification of LDL, Total, and HDL Cholesterol (mg/dL) (NIH, 2001)

1.4.1. LDL Cholesterol - Primary Target of Therapy

<100	Optimal
100-129	Near Optimal/Above Optimal
130-159	Borderline High
160-189	High
≥ 190	Very high

1.4.2. Total Cholesterol

<200	Desirable0
200-239	Borderline High0
≥ 240	High

1.4.3. HDL Cholesterol

< 40	Low
≥ 60	High

Statins, first approved for clinical use in 1987, are very effective in lowering cholesterol. High intensity statin therapy, rosuvastatin 20mg/day and atorvastatin (Lipitor) 40-80 mg, reduces LDL-C by 50 percent or greater. Moderate intensity therapy, rosuvastatin 10 mg, atorvastatin 10 mg, simvastatin (Zocor) 20-40 mg, and pravastatin (Pravachol) 40 mg/day, achieves a 30 to 50 percent reduction of LDL-C. [Miedema , Lopez , Blaha ,2015)].

The Middle East region has the highest dietary ene0rgy surplus among developing countries, and there is evidence of a rapid rise in non-communicable disease risk factors, especially obesity (Kelishadi, 2007) .

The prevalence of insulin resistance and metabolic syndrome is high in Libyan population. Type 2 diabetes affected >16% in Libya which is the highest prevalence in North Africa and among Arabic nations(Omran and Targ ,2006).

The prevalence of diabetes is rapidly increasing with the changes of life style and composition of meals. The high prevalence of diabetes has led to an increase in medical conditions that accompany obesity, hypertension, and cardiovascular disease (CVD) (Jazet, Pijl Meinders ,2003).

Type 2 diabetes (T2DM) develops through the stage of Impaired Fasting glucose(IFG) and/or impaired glucose tolerance (IGT), which are asymptomatic and unassociated with any manifested morbidity. Their sole significance, lies in the fact that they predict future diabetes or cardiovascular disease(Stern, Fatehi, Williams, Haffner ,2002). Recently, it has been found that insulin resistance and insulin secretory defect appears in the prediabetes stage i.e., before the onset of diabetes (Festa, D'Agostino Jr. Hanley et al.2004).

1.5. Statins: Mechanism of Action

Statins act by competitively inhibiting HMG-CoA reductase, the first and key rate-limiting enzyme of the cholesterol biosynthetic pathway. Statins mimic the natural substrate molecule, HMG-CoA, and compete for binding to the HMGCR enzyme. This competition slows the rate of mevalonate production, the next molecule in the serial steps to produce cholesterol. Hence, in the presence of statins, the precursor HMG-CoA is not efficiently processed forward to produce mevalonate, blocking the pathway.

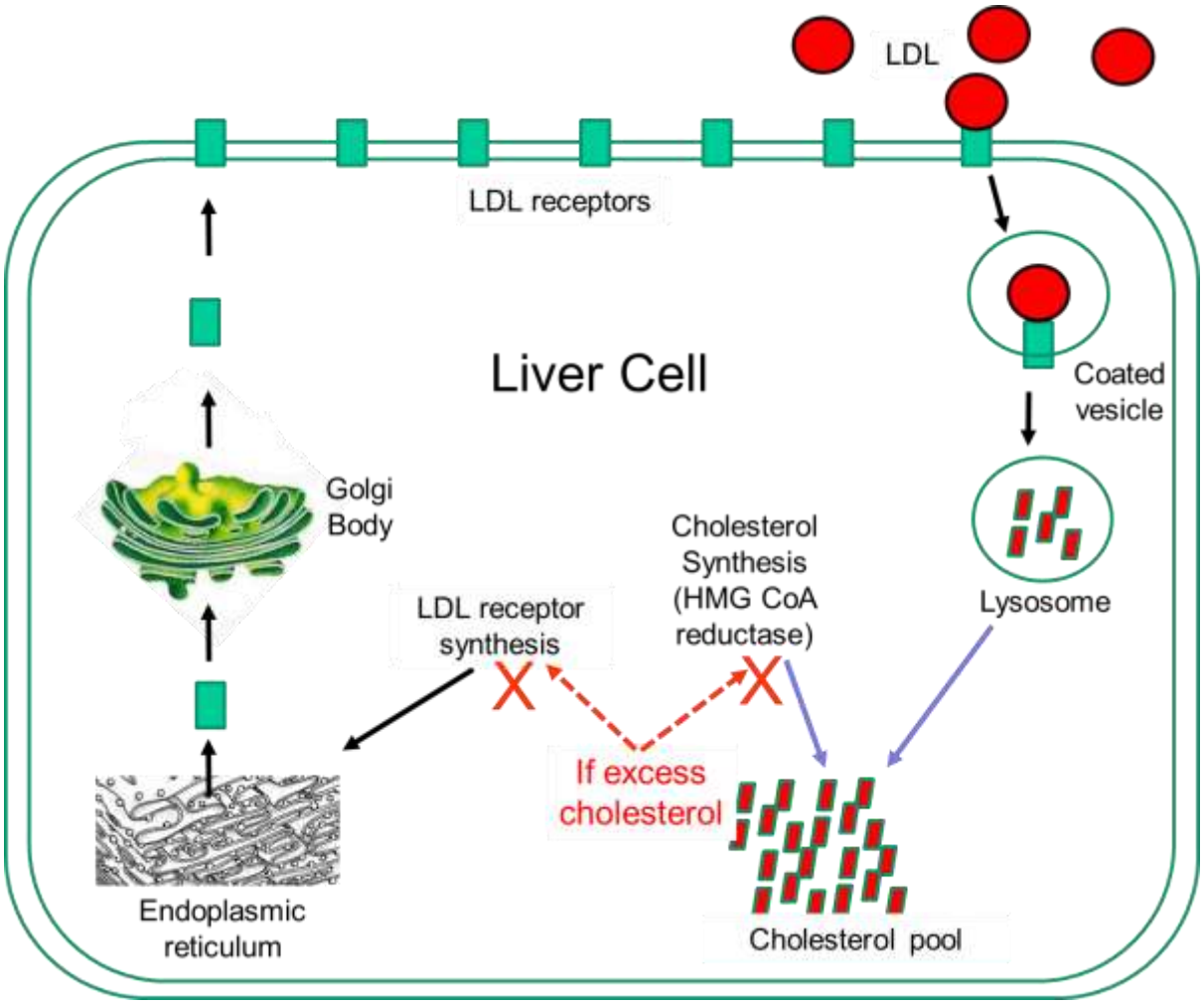


Figure 1.1: Statins act by competitively inhibiting HMG-CoA reductase

Statins inhibit cholesterol synthesis in the liver, significant because most circulating cholesterol comes from internal manufacture rather than the diet. If liver production of cholesterol falls, then so does the level in the blood. As cholesterol synthesis occurs mostly at night during fasting, statins with short biologic half-lives of activity are taken at night to maximize the inhibitory effect. Short-acting simvastatin taken at night shows greater LDL and total cholesterol reduction than if taken in the morning, whereas there is no such difference for the long-acting atorvastatin.

In addition, liver cells sense the reduced levels of liver cholesterol production with statin use and try to compensate by synthesizing more LDL receptors on the cell surface to increase cholesterol uptake from serum. The LDL and VLDL particles bind and are internalized into liver cells, where the cholesterol component is processed into bile salts. These are then excreted or recycled.

The molecules of statins vary from one another in their ring structure and chemical side group. These differences affect the pharmacologic properties of each statin by varying the:

- Affinity to the active site of the target enzyme, HMGCR
- Rates of entry into liver versus non-liver cells
- Systemic availability of the compounds in the body; and
- Biochemical metabolism and excretion pathways that affect the biologic half-life of the active compound (Goodman and Gilman, 2011).

Hepatoselectivity of statins is determined in large part by their hydrophilic properties. Hydrophobic statins tend to have higher exposure in non-hepatic tissues, while the hydrophilic statins are more liver specific. The reason for these selectivity differences is that lipophilic statins can passively diffuse through cell membranes into many cell types, while the hydrophilic statins make use of active transporters into hepatocytes, resulting in fewer unwanted side effects at other tissues.

The **organic anion transporting polypeptide (OATP)** aids hepatic uptake of hydrophilic statins—such as rosuvastatin and pravastatin—to give them better potency and selectivity for liver.

Studies have shown that statins bind reversibly to the HMGCR enzyme. The binding affinity of statins for HMGCR enzyme is in the nanomolar range, about 10,000x higher affinity than the affinity for the natural substrate molecule (HMG CoA), in the micromolar range. The specificity and high binding affinity of statins is due to bonding interactions that form between the statin and the HMGCR enzyme active site.

1.5.1.Type 1 statins :

are those derived from natural sources or modifications of natural molecules, and include lovastatin, pravastatin, and simvastatin.

1.5.2.Type 2 statins

are those that are synthetic and can be made in relative abundance in the laboratory, after understanding the structures of various natural statins. These include fluvastatin, atorvastatin, rosuvastatin, and cerivastatin.

1.6.Steroidogenesis:

Formation of steroids and steroid hormones from cholesterol is called as steroidogenesis. The pathway is common with cell-specific variations depending upon in which gland steroidogenesis takes place. (adrenal, ovarian, testicular, placental).

The first and rate-limiting step in steroidogenesis is the conversion of cholesterol to pregnenolone by a single enzyme, P450scc (CYP11A1), but this enzymatically complex step is subject to multiple regulatory mechanisms, yielding finely tuned quantitative regulation. Qualitative regulation determining the type of steroid to be

produced is mediated by many enzymes and cofactors. Steroidogenic enzymes fall into two groups: cytochrome P450 enzymes and hydroxysteroid dehydrogenases. A cytochrome P450 may be either type 1 (in mitochondria) or type 2 (in endoplasmic reticulum), and a hydroxysteroid dehydrogenase may belong to either the aldo-keto reductase or short-chain dehydrogenase/reductase families. The activities of these enzymes are modulated by posttranslational modifications and by cofactors, especially electron-donating redox partners. The elucidation of the precise roles of these various enzymes and cofactors has been greatly facilitated by identifying the genetic bases of rare disorders of steroidogenesis. Some enzymes not principally involved in steroidogenesis may also catalyze extraglandular steroidogenesis, modulating the phenotype expected to result from some mutations. Understanding steroidogenesis is of fundamental importance to understanding disorders of sexual differentiation, reproduction, fertility, hypertension, obesity, and physiological homeostasis.

1.7. Cholesterol Uptake, Storage, and Intracellular Transport

De novo synthesis of cholesterol from acetate and from LDL cholesterol from the dietary total cholesterol form the precursors for adrenal steroid synthesis. 3-hydroxy-3-methylglutaryl co-enzyme A reductase (HMG Co A reductase) is the rate-limiting enzyme in cholesterol synthesis. LDL-cholesterol is taken up by the specific target organ by binding with apo-B 100 receptors through apo-B 100 present on the LDL. The uptake takes place clathrin coated pits by receptor-mediated reverse endocytosis. The cholesterol taken up by the cell is either stored as cholesterol ester or converted into specific steroid hormones.

1.7.1. Delivery of cholesterol to mitochondria

The initial step of steroid formation takes place inside mitochondria. StAR is the first-described member of a family of proteins that contain so-called START (StAR-related lipid transfer) domains, which are found in most metazoan organisms18. Free cholesterol is nearly insoluble (critical micellar concentration, ~25–40 nm) 21.

Cholesterol is solubilized by binding to proteins. StarD4, -5, and -6 that are structurally related to StAR, and appear to play major roles in intracellular cholesterol transport 19. Thus, the current view is that the family of proteins related to StarD4 are responsible for delivering cholesterol to the OMM from elsewhere in the cell (lipid droplets, endoplasmic reticulum) in most cell types, whereas StAR itself is responsible for delivery from the OMM to the IMM, but only acts in steroidogenic cells.

1.7.2.Key enzyme of Cholesterol Biosynthesis

Two acetyl-CoA molecules can be condensed to create acetoacetyl-CoA, the first step in the HMG-CoA/mevalonic cid pathway, leading to synthesis of isoprenoids like mevalonic acid and ultimately cholesterol.

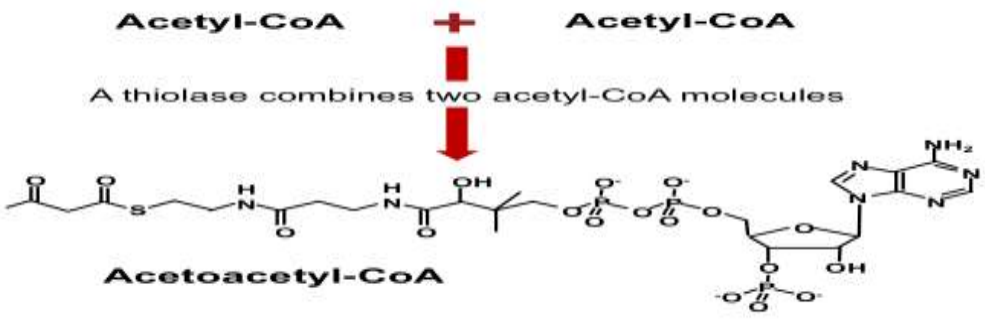


Figure 1.2: Acetoacetyl-CoA Biosynthesis

The molecule 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) is formed from acetyl CoA and acetoacetyl CoA via the action of the enzyme HMG-CoA synthase.

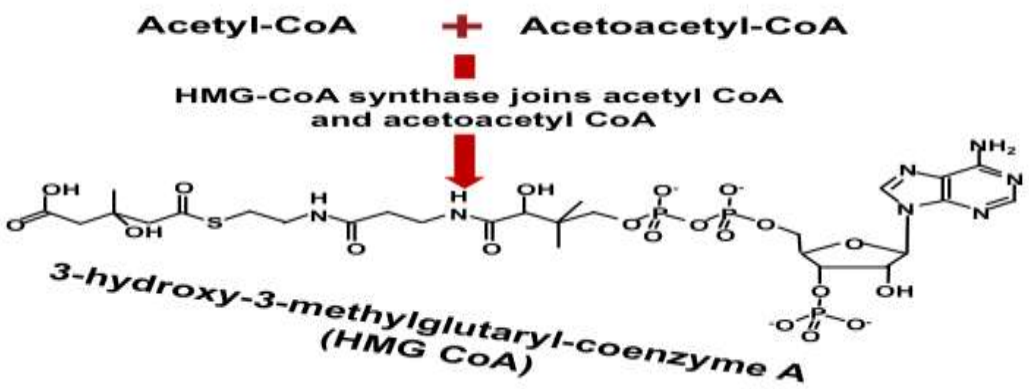


Figure 1.3.: HMG-CoA Biosynthesis

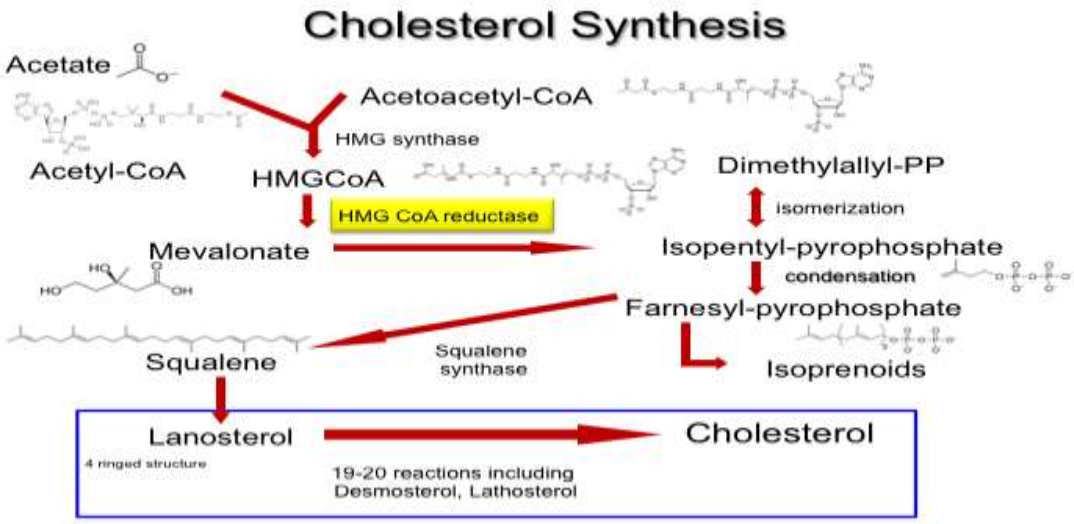


Figure 1.4: Cholesterol Biosynthesis

The HMG-CoA molecule, when acted upon by the enzyme HMG CoA synthase, leads to mevalonic acid the major precursor to **cholesterol** synthesis.

1.8.Androgen synthesis

The major circulating androgen is testosterone. Almost 95% is secreted by the Leydig cells in the testis, which synthesizes about 6-7 mg testosterone per day. The remaining derives form the adrenals (Saez, 1994).The precursor of the gonadal, as well as the adrenal steroids, is cholesterol (Figure). The conversion of cholesterol to

testosterone and DHT requires the action of five enzymes: side chain cleavage enzyme (SSC), 3β-hydroxysteroid dehydrogenase/ Δ5,4 isomerase (3β-HSD), 17α-hydroxylase/C17,20 lyase, 17β-hydroxysteroid dehydrogenase (17β-HSD) and 5α-reductase (SRD5A). Mutations in any of these enzymes, or associated proteins such as the steroidogenic acute regulatory (StAR) protein, affect both testosterone and cortisol synthesis. As result, either female or male androgen as well as adrenal insufficiency arises. These syndromes are known as congenital adrenal hyperplasia (Evenson et al., 1993; Lin et al., 1995). Since Leydig cells cannot store androgens, biosynthesis continually takes place and androgens are mainly secreted into the blood where testosterone is bound to albumin (54%) or sex hormone binding globulin (SHBG) (44%). Only 3% of total testosterone circulates in a free form.

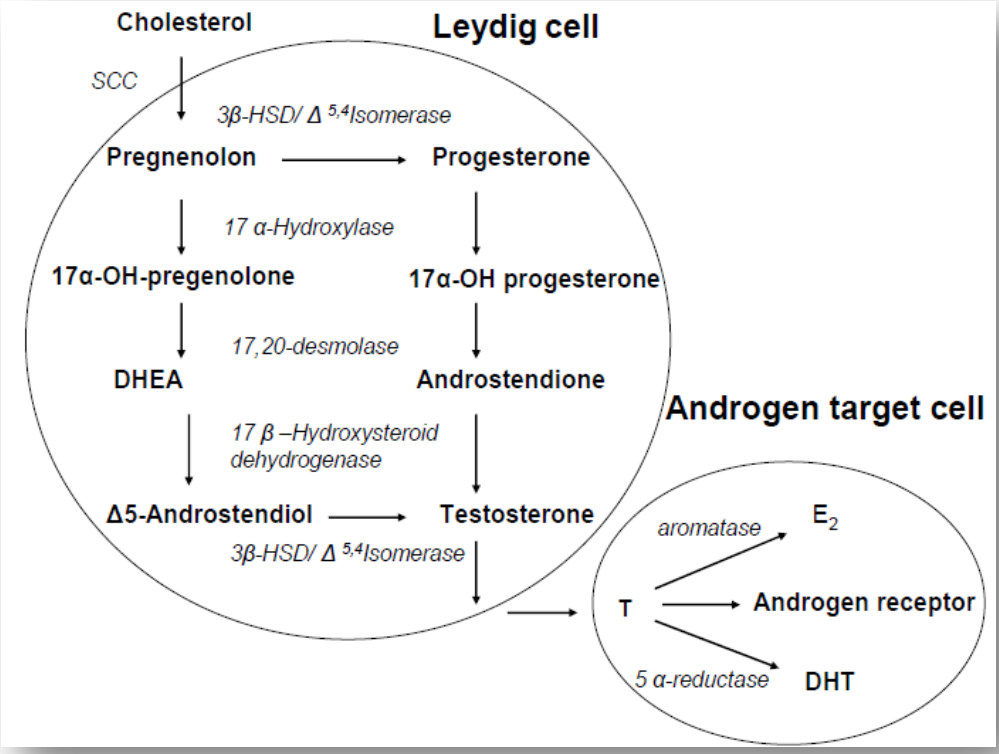


Figure 1.5. Androgen biosynthesis- Formation of Testosterone and its conversion to dihyrdo testosterone

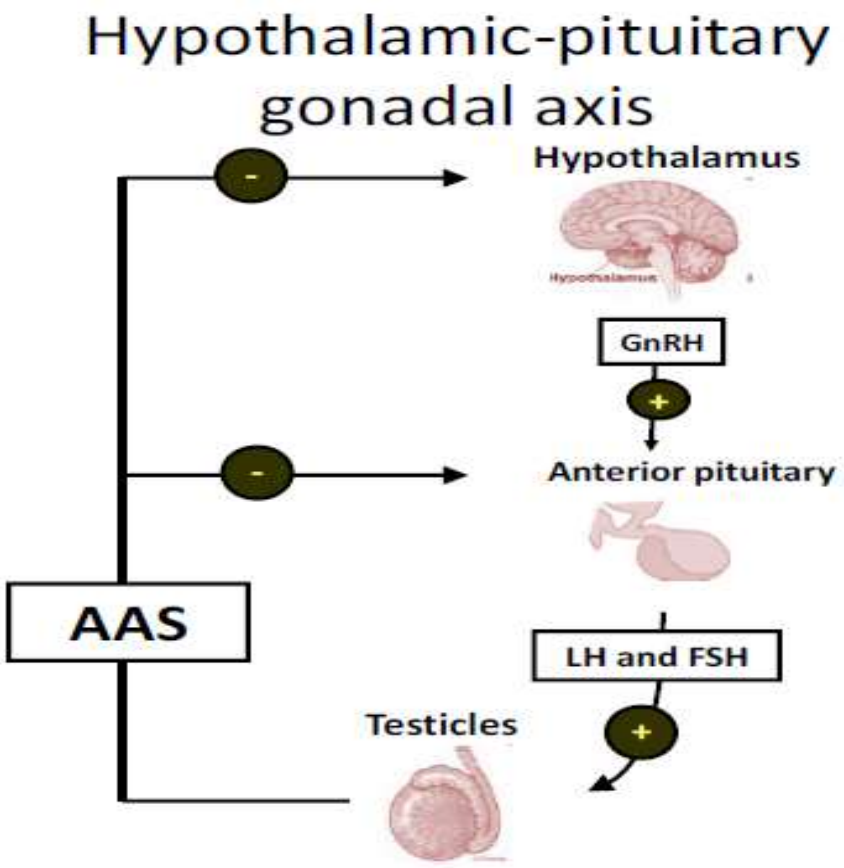


Figure 1.6:Hypothalamic –pituitary gondal axis

Testosterone circulates in the body both as free fraction (2%) and bound to albumin (54%) and sex hormone-binding globulin (44%). Free and albumin-bound testosterone comprises bioavailable testosterone (Mohr et al. 2005).

1.9.Testosterone

1.9. 1.Definition of Testosterone:

Derived from cholesterol, testosterone is a steroid hormone that is responsible for the development and maintenance of masculine characteristics. Testosterone is secreted in large amounts by the testes (testicles) in males, and to a lesser extent, by the adrenal cortex and ovaries in females (Mazur, A., & Booth, A. 1998).

Like all hormones, testosterone travels though the bloodstream and binds to other tissue in order to influence physiological activity. Testosterone belongs to a class of hormones called androgens, which are those steroid hormones that have masculinizing effects on individuals. Testosterone exerts its effects during three different life stages: the perinatal period (gestation and shortly after birth), puberty, and adulthood.

Not only does testosterone influence the growth and development of masculine physical features, such as the penis and the beard, but testosterone is also related to a variety of social behaviors of interest to social psychologists, including aggression, power, sexual behavior, and social dominance. In addition, social experiences such as competition can cause testosterone levels to rise or fall (Mazur, A., & Booth, A. 1998).

Androgens in the male are essential for the development and maintenance of specific reproductive tissues such as testis, prostate, epididymis, seminal vesicles and penis, as well as other characteristic male properties such as increased muscle strength, hair growth, etc. In order to maintain the androgen concentration at appropriate levels, the production rates of androgens must be in balance with the metabolic clearance and excretion. The action of androgens in target cells depends on the amount of steroid which can penetrate into the cells, the extent of metabolic conversions within the cells, the interactions with the receptor proteins and finally,

upon the action of the androgen receptors at the genomic level (Mooradian et al. 1987).

1.9.2.Perinatal Period :

During the perinatal period, testosterone release influences the development of the sexual organs, but animal studies show that greater perinatal testosterone release also masculinizes the nervous system and influences adult behaviors. The evidence in humans is less clear, but some studies have found an effect of perinatal testosterone exposure in females but not males (Haupt and Rovere. 1984).

For example, perinatal testosterone exposure in females has been associated with masculine or feminine behaviors in early childhood,and in adulthood, perinatal testosterone has been linked to personality traits such as sensation seeking and neuroticism. More research on perinatal testosterone exposure is necessary, but the existing humanevidence points to greater effects in females than in males (Haupt and Rovere. 1984).

1.9.3.Puberty:

Testosterone increases during puberty are related to the deepening of the voice, muscle growth, facial and body hair growth, and increased sex drive. There is also evidence in several animal species that testosterone elevations at the onset of puberty influence direct competitive behavior, including aggressive and dominant behavior, although the findings are less conclusive in humans (Loomba-Albrecht and Styne 2009).

1.9.4. Adulthood:

Across a number of animal species, higher testosterone concentrations in adult males seem to be associated with increased sex drive, and seasonal elevations in testosterone typically coincide with a greater frequency of reproductive behaviors. The few controlled studies that have been conducted in humans demonstrate that testosterone tends to increase sex drive and sexual behaviors among men with

abnormally low levels of testosterone, but not among men who already have testosterone levels within the normal range (Loomba-Albrecht and Styne 2009).

Testosterone has also been associated with aggression and competition over food and mates in a number of animal species. Seasonal elevations in testosterone are associated with increases in aggression and mate competition. In humans, there also seems to be a small relationship between testosterone and aggression. For example, several studies of male and female prisoners have found that prisoners with higher testosterone had conducted more violent crimes and tended to break more rules in prison.

Testosterone is also related to power and social dominance. In several animal species, higher testosterone is predictive of higher social status within status hierarchies. In humans, testosterone is associated with more masculine, dominant facial characteristics and with personality styles that align with power and dominance. In addition, high testosterone individuals are more reactive to and pay more attention to status threats, such as losing in a competition (Mazur, A., & Booth, A. 1998).

Testosterone levels fluctuate in both the short-term and the long-term. In humans, testosterone levels peak in the late teens to early twenties and decline slowly but steadily after that. Testosterone levels also change throughout the day - they are highest in the morning, decrease over the course of the day, and rise again in the evening. In a number of animal species, there are seasonal changes in testosterone, and testosterone levels are typically highest during the breeding season. Social experiences can also cause testosterone levels to change (Haupt and Rovere. 1984).

In nonhuman animals and humans, winners of competitions tend to increase in testosterone, and losers tend to drop in testosterone. In addition, testosterone can increase in response to sexual stimuli, such as the presence of a female. Most of the research on testosterone has focused on males, but more studies have begun examining females. Although females have only about one-seventh the testosterone levels as men, testosterone still seems to play a role. For example, research has found that higher testosterone females tend to smile less often, score higher on tests

of social dominance, and are more vulnerable to stereotype threat (Loomba-Albrecht and Styne 2009).

1.9.5.Biosynthetic pathways:

In the human male, testosterone is the major circulating androgen. More than 95% is secreted by the testis, which produces approximately 6–7 mg per day. The metabolic steps required for the conversion of cholesterol into androgens take place in approximately 500 million Leydig cells that constitute only a few percent of the total testicular volume. Although Leydig cells are of major importance for the generation of circulating androgenic hormones, the adrenal cortex also contributes to this production (Coffey 1988).

The production of steroids is not limited to endocrine glands but very small amounts, mainly pregnane derivatives, can also be produced in brain cells (Baulieu 1997). Although the contribution of cells in the nervous system to circulating hormones is very small, local production of steroids can be physiologically very important especially when transport and clearance are low. Since Leydig cells are most important for the production of androgens, the steroidogenic pathways in these cells will be described in some detail (King et al. 2002). The enzymes and intermediates involved in this reaction cascade are depicted in (Figure 1.7)

The source for the synthesis of steroids is cholesterol. This substrate may be synthesized de novo from acetate but it may also be taken up from plasma lipoproteins. For human Leydig cells the LDL lipoprotein fraction seems to be the predominant extracellular store of cholesterol. In addition, intracellular lipid droplets which contain cholesterol esters may function as intracellular stores of cholesterol (Freeman and Rommerts 1996).

The relative contribution of synthesis and cholesterol supply from lipoproteins or lipid droplets depends on the species and the extent of stimulation of steroid production. For high steroidogenic activity an ample supply of cholesterol is essential and sufficient hormone-sensitive lipase and enzyme activity for uptake of cholesterol (esters) must be present. For Leydig cells it appears that the cholesterol in the plasma

membranes acts as the main and most readily available pool of cholesterol (Rao et al. 2003).

A vesicle-mediated transport system involving an endosomal/lysosomal network seems to act as the conveyer belt for intracellular cholesterol transport to the mitochondria. The supply of cholesterol to the outer membrane of the mitochondria also requires transfer proteins and for this process sterol carrier protein2 (SCP2) could play an important role (van Noort et al. 1988).

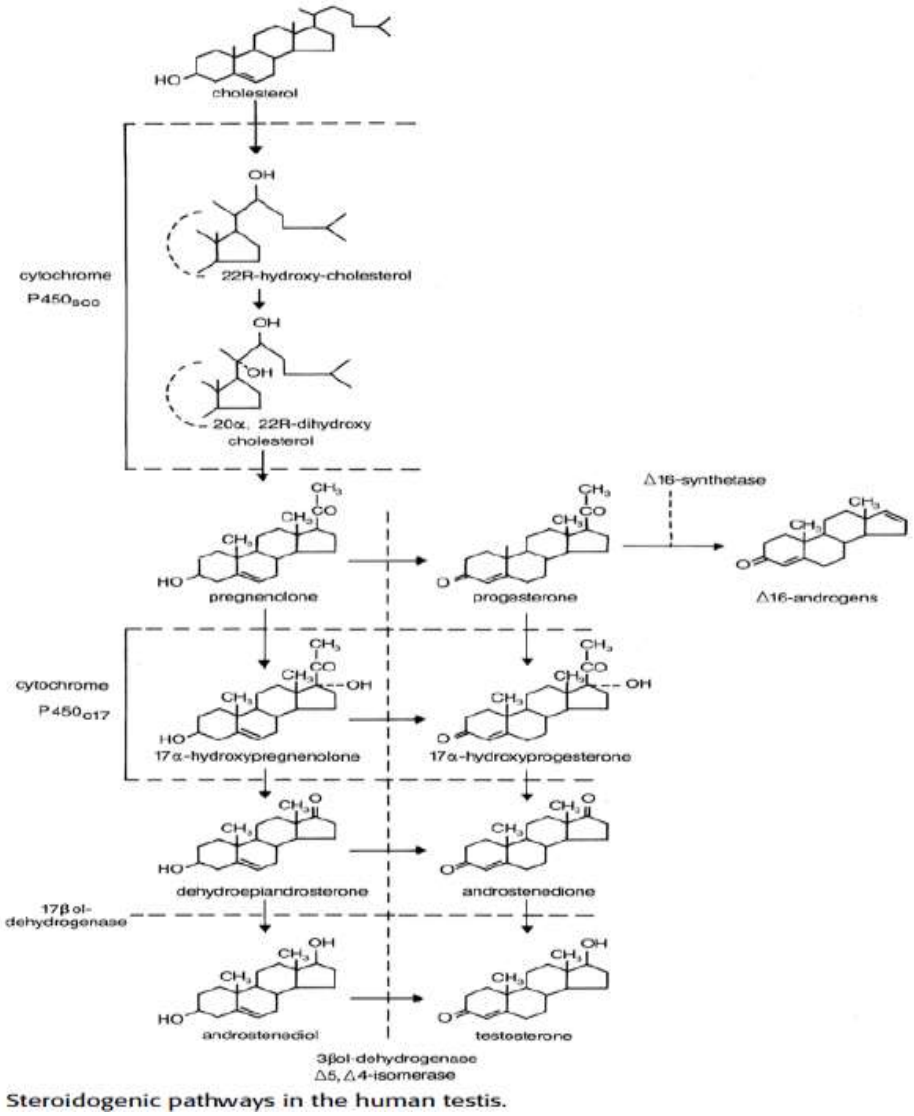
This protein could facilitate cholesterol trafficking inside the cell in conjunction with the cytoskeleton and the vesicular system, but although many suggestions have been made in this direction, there is still insufficient proof for this model. An important question in this respect is whether changes in intracellular cholesterol trafficking under the influence of LH are a consequence of utilization of cholesterol at the mitochondrial level followed by a re-equilibration process or whether LH actively directs cholesterol movement to the mitochondria (van Noort et al. 1988).

Whatever mechanisms operate, the ultimate result of the coupled intracellular transportmechanisms is regulation of the availability of cholesterol at the level of the mitochondria for production of pregnenolone (C21) from cholesterol (C27). Cleavage of the side chain of cholesterol and the formation of pregnenolone inside the mitochondria is the start of the steroidogenic cascade. Subsequently, pregnenolone is converted to a variety of C19-steroids by enzymes in the endoplasmic reticulum.

The biosynthesis of the biologically active androgens is thus the result of a stepwise degradation of biologically inactive pregnenolone. This process is catalyzed by oxidative enzymes, many of which are members of a group of heme-containing proteins called cytochromes P450.As can be seen in Figure 1.7, the specific steroidogenic P450 enzymes can catalyse different although related reactions. The precise pathways which are utilized for the formation of testosterone most probably depend on the properties and amounts of the various enzymes as well as on the composition of the membrane into which these steroid-converting enzymes are integrated.

Under normal conditions the total capacity of the pregnenolone-converting enzyme system in humans is insufficient to convert all available pregnenolone into testosterone.

As a result many intermediates in the form of progesterone derivatives leak out of the Leydig cells. This illustrates that the rate-limiting step for the production of testosterone is localized at the level of the endoplasmic reticulum, whereas the rate-determining step for steroidogenesis (short term regulated by LH) is at the level of the cholesterol side chain cleavage activity in the mitochondria (van Haren et al. 1989).



Steroidogenic pathways in the human testis.

Figure 1.7.:Steroidiogenic pathways .

1.9.6.Testosterone in blood

Testosterone circulates in serum largely bound to transport proteins. Like other steroids and thyroid hormones, both albumin and specific binding globulins are involved in testosterone binding. Testosterone binds to albumin with low affinity but, due to its high concentration, albumin displays a very high binding capacity.

The specific transport protein for testosterone, some other androgens and estradiol is sex hormone binding globulin (SHBG).

About 1.5–2% of serum testosterone is free and is believed to represent bioactive testosterone. According to the free hormone hypothesis, it is only the free hormone fraction that is accessible to all body compartments and can enter the cells, exerting its action where androgen receptors are available. The free diffusion of unbound testosterone in all cells and organs is demonstrated by the same free testosterone concentration in all body fluids, e.g. in blood and in saliva.

Free and protein bound testosterone and DHT are in equilibrium, so that when free hormone is subtracted from circulation because of entry into tissue, new testosterone dissociates from albumin and SHBG, a new equilibrium is promptly reached and the free hormone concentration in serum remains constant. Conversely, pathophysiological conditions causing changes in binding protein concentration (e.g. pregnancy, hyperthyroidism, growth hormone excess, treatment with antiepileptic drugs) or displacement of testosterone from SHBG by drugs (e.g. danazol) results in changes in total testosterone concentration in order to maintain constant free testosterone levels (Pugeat et al. 1981).

Measurement of SHBG is valuable for assessment of androgenization and of free testosterone. In earlier times SHBG was measured indirectly, by estimating its binding capacity. The classic method used tritiated DHT as ligand because of its higher affinity to SHBG and lack of binding to cortisol binding globulin (CBG).

Saturating amounts of labeled DHT were added to the samples and SHBG was then precipitated by ammonium sulfate (Ekins 1990).

The amount of labeled DHT precipitated provided a direct measurement of SHBG binding capacity. This method did not allow absolute changes in SHBG protein concentrations to be measured, which can now be assessed by modern immunoradiometric assays. Modern assays have demonstrated that, in general, SHBG binding capacity (expressed in terms of DHT binding) corresponds acceptably to the molar SHBG concentration (Ekins 1990).

The free hormone hypothesis has been repeatedly challenged in the scientific literature, mainly due to the difficulty of reconciling the existing experimental evidence with appropriate mathematical models of hormone transport (Mendel 1992). For instance, the low affinity of testosterone for albumin binding and some experimental data led to the idea that albumin-bound testosterone is readily available for delivery to the tissues (i.e. bioavailable) while only SHBG-bound testosterone is not biologically active (Manni et al. 1985).

In contrast, SHBG itself has been proposed to interact with cell surface receptors, thereby contributing to the biological activity of androgens (Rosner et al. 1999). This novel, putative function of SHBG is of particular interest in the light of the essential lack of any physiological explanation why primates, unlike all other species, possess such a protein.

SHBG seems to "buffer" serum testosterone levels, which, beside the physiological circadian rhythm, show only minor circhoral variations despite highly pulsatile LH secretion (Simoni et al. 1988 and 1992). On the contrary, serum testosterone levels oscillate widely in rodents, which do not have SHBG. In addition SHBG reduces the rate of hepatic testosterone degradation. There are no known cases of congenital absence of SHBG in humans but an analbuminemic strain of rats, a species which does not have circulating SHBG, is normally fertile and shows normal

free testosterone levels, arguing for a dispensable role of serum testosterone binding proteins (Mendel et al. 1989). Similarly, the congenital absence of thyroxin binding globulin (TBG) in humans is compatible with normal thyroid function (Dussault et al. 1977).

Since SHBG concentrations influence total and free testosterone levels, it is important to know which factors influence SHBG production. Of the hormones, estrogens stimulate and androgens inhibit SHBG secretion. Administration of 20 g daily of ethinyl estradiol to men for 5 weeks resulted in a 150% increase in SHBG and, as a consequence of the reduced free testosterone levels, in a 50% increase in total serum testosterone. The estrogen effect is evident in women, who have SHBG serum levels double of those in men, and during pregnancy, when SHBG rises to levels 5–10 times higher than in non-pregnant women (Anderson 1974).

In addition, SHBG levels are stimulated by thyroid hormones, resulting in high levels in thyrotoxicosis and low levels in hypothyroidism, and are reduced by growth hormone and cortisol, resulting in low levels in acromegaly and in Cushing syndrome (Dussault et al. 1977).

Finally, SHBG levels are higher in children than in adults and increase in men after the age of 50, contributing to the possible decline of free testosterones levels observed in aging men (Simoni et al. 1988).

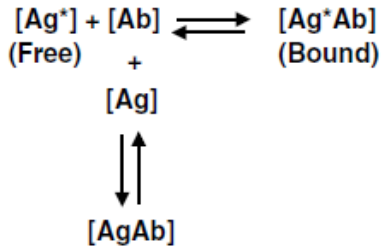
The most important bioactive metabolite of testosterone is DHT. The reduction of testosterone to DHT occurs in those tissues expressing 5α-reductase and DHT is well measurable in circulation. In eugonadal, adult men serum DHT concentrations are about 10–12 times lower than testosterone and DHT is mainly bound to SHBG. Given the role of DHT in prostate growth, the measurement of serum DHT is of relevance during testosterone treatment, especially when testosterone is administered via the trans-cutaneous route, (e.g. testosterone gel or patches) since the skin is the primary organ for 5α-reduction (Simoni et al. 1988).

1.9.7.Principles of immunological testosterone assays

As for all other hormones, the accurate measurement of testosterone in blood was made possible by the advent of radioimmunoassays (RIA). In immunological assays the hormone being measured (i.e. the antigen) competes with the labeled hormone (i.e. the tracer) for binding to an antiserum (the antibody). Since the amount of antibody available for reaction is limited, the higher the concentration of the hormone in blood, the lower the amount of tracer bound by the antibody (Furuyama et.al. 1970).

At the end of the reaction, the antibody bound to the hormone (B) is separated from the free fraction (F) and the radioactivity or the signal emitted by a non-radioactive tracer is measured (Fig. 3.2).

In case of testosterone RIA, the tracer can be tritiated or iodinated. 3H-testosterone can be tritiated in two or four positions (Fig. 3.2). Iodination, which can be achieved by oxidation (e.g. by reaction with chloramine-T) of a thyrosine or another amino acid residue in peptidic hormones, requires conjugation with a histamine residue in the case of a steroid molecule (Dechaud et. al. 1989).



Principle of immunological testosterone assay. Testosterone in the serum sample (Ag) and labeled testosterone (Ag*) competes for binding to a limited number of binding sites (Ab). The reaction is governed by the law of mass action. The asterisk indicates any type of label (e.g. an isotope, a non-radioactive label, an enzyme, etc.). At the end of the reaction the Free is removed and the Bound is counted.

Figure. 1.8. Principle of immunological testostreone assay

Both tritiated and iodinated testosterone tracers are commercially available. The half-life of the tracers depends on the isotope. Tritiated tracers can be stored and used for years but, since the slow but progressive decay results in impurities which reduce the assays' performance, they should be purified by chromatography at 6–12 months intervals (Morley et. al. 2002).

Iodinated tracers, e.g. testosterone-3-(O-carboxymethyl)oximino-(2-[125I] iodohistamine, show a much shorter half-life and can be used only for about one month, but they have a much higher specific activity than the tritiated tracers allowing the use of lower antiserum concentrations and improved assay sensitivity (Morley et. al. 2002).

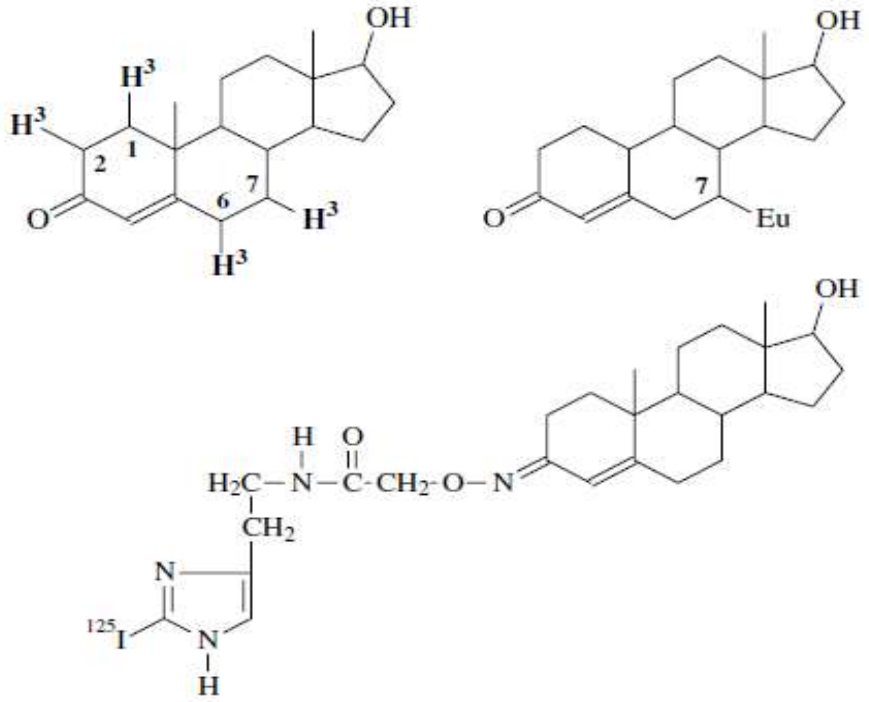
Iodinated testosterone is usually purified by high performance liquid chromatography (HPLC) by the manufacturer and does not require further cleaning before use. If the tracer is produced in-house, it should be purified by HPLC or other chromatographic technique (e.g. gel filtration on Sephadex) before use. In recent years non-radioactive testosterone tracers have been produced and are widely used in clinical routine measurements. They offer the advantage of a lower environmental impact, but the assays employing such tracer function according to the same principles of RIAs (Morley et. al. 2002).

Beside the specific activity of the tracer, the assays' sensitivity depends on the affinity of the antiserum, which should, if possible, be identical for both the antigen and the tracer. Since testosterone is not antigenic when injected in animals, a testosterone conjugate conferring aptene properties to the steroid must be used to obtain antisera (Raivio et. al. 2001).

As for iodination, position 3 in the A ring of testosterone is usually exploited for conjugation with the CMO (carboxymethyloximino) group, a spacer necessary for coupling the antigen to BSA which renders the conjugate antigenic. The antibodies for testosterone immunoassays are usually polyclonal antisera obtained in rabbits, but

monoclonal antibodies are used in some kits. Polyclonal antisera have the advantage of high affinity, but good monoclonal antibodies might have better specificity, obviating, at least in part, the problem of cross-reactivity of most polyclonal antisera with DHT (Raivio et. al. 2001).

After the antigen-antibody reaction has reached equilibrium, separation of the antibody-bound (B) from the free tracer (F) can be accomplished specifically by adding an antiserum directed against the immunoglobulins of the species from which the first antibody was obtained (e.g. goat antirabbit antiserum), together with preimmune serum (e.g. normal rabbit serum) to achieve complete precipitation of the immune complexes (Furuyama et.al. 1970).



Tracers used in testosterone immunoassays. RIAs are based on tritiated or iodinated (testosterone-3-(*O*-carboxymethyl) oximino-(2-[^{125}I]iodohistamine) tracers. The Europium-labeled testosterone is an example of non-radioactive tracer used in fluoroimmuno assays (FIA). Other non-radioactive immunoassays are based on testosterone molecules coupled with enzymes or luminescent substances.

Fig.1.9: Tracers uesd in testosterone immunoassays

The reaction tubes are then centrifuged and the radioactivity or the signal emitted by the non-radioactively-labeled tracer is counted. Alternatively, non-specific precipitating agents (e.g. ammonium sulphate, polyethylene glycol, [PEG]) or substances which absorb the free antigen (e.g. dextran-coated charcoal) can be used (Morley et. al. 2002).

In practice, in a testosterone RIA based on rabbit antiserum, B/F separation is performed very efficiently by addition of rabbit immunoglobulins, antirabbit antiserum and PEG (Morley et. al. 2002).

After counting the results can be calculated in several ways. The signal emitted by the unknown samples is compared to that of the samples with known testosterone concentrations, i.e. the calibrators of the standard curve, after logarithmic, semilogarithmic or logit/log transformation, using computer programs usually enclosed in the software of the counter. These mathematical transformations of the readouts permit linearization of the calibration curve over a wide range, allowing accurate calculation of the actual testosterone concentration in the unknowns (Morley et. al. 2002).

Since testosterone in serum is mostly bound to carrier proteins, which prevents the antibody-antigen reaction by competing with the antiserum, the steroid must be extracted with organic solvents prior to RIA or other immunoassays. Extraction is usually performed by adding 10–20 volumes of diethyl ether to the serum samples. This step is followed by vortexing (5 min) or agitation of the samples on a rotator (30 min) and freezing of the aqueous phase. Testosterone, which is lipophilic, remains in the organic phase which can be decanted, evaporated and reconstituted in assay buffer.

This extraction procedure is usually highly efficient (≈90%) and can be monitored by measuring the recovery of trace amounts of radiolabeled testosterone added beforehand. Both testosterone and DHT are extracted by this method. If an accurate

quantification of testosterone and DHT is desired, the extracted steroids can be reconstituted in the appropriate diluent and separated by a chromatographic procedure (e.g. HPLC or celite chromatography) before RIA (Morley et. al. 2002).

The calibrators used in the standard curve are serial dilutions of a sample with known testosterone concentrations dissolved in the same matrix (buffer or serum based) of the samples measured. In extraction methods, testosterone is weighed, dissolved in ethanol and further diluted in assay buffer. In non-extraction methods the standard is added to steroid-free sera. The maintenance of the same matrix is necessary to ensure parallelism between standards and unknowns.

These assay principles are common to RIA and non-radioactive methods. Unlike the most recent assays for peptidic hormones, the newest technologies which have highly improved sensitivity thanks to the two-site, sandwich approach, cannot be applied to the steroid hormone assays (Furuyama et.al. 1970).

In the immunoradiometric assays (IRMA) the large protein hormone is first reacted with a capture antibody (in molar excess) coated to the tube walls, the tubes are washed, and a labeled second antibody directed against a second epitope of the hormone is added. Steroid hormones are too small to be reacted simultaneously with two antibodies and the IRMA principle cannot be applied, so that the sensitivity of a testosterone assay can be improved only by increasing the specific activity of the tracer and/or the affinity and specificity of the antibody (Raivio et. al. 2001).

1.9.8.Measuring testosterone levels

Several laboratory assays and methods of calculation are used to assess the three testosterone measures: total testosterone (protein bound plus free), free testosterone (not bound to proteins), and bioavailable testosterone (free plus albumin bound). The methods used to conduct the measurements vary in their accuracy, standardization, the extent of validation, and the reproducibility of results. Additionally, there are issues regarding the timing and number of samples needed to provide accurate data

that can be compared across studies. Further complicating this issue are the fluctuations of an individual's testosterone levels during the day and the wide range of normal testosterone levels between individuals (Jockenhovel et. al. 1992).

Total testosterone (serum testosterone) is generally measured by radioimmunoassay, which is a validated, standardized, and reproducible assay. However, because the level of the high-affinity binding protein SHBG increases with age (and therefore a greater percentage of the total testosterone is bound to SHBG and is not available to the tissues), this measure may not be as useful in studies of aging populations as are measures of bioavailable testosterone (Gonzalez-Sagrado et. al. 2000).

Bioavailable testosterone (free plus albumin bound) is measured or calculated in several ways. SHBG in serum can be precipitated with ammonium sulfate and the bioavailable testosterone is then measured in the supernatant (SHBG is precipitated by a lower concentration of ammonium sulfate than albumin). Alternatively, bioavailable testosterone can be calculated using measures of total testosterone and immunoassayed SHBG concentrations (Rosner, 1972).

Measures of free testosterone are more controversial. Laboratory measurements of free testosterone have generally been conducted by equilibrium dialysis. This method is standardized and validated, but is only available through reference laboratories (Matsumoto, 2002) and is costly.

Direct non-dialysis measures of free testosterone using analog immunoassays are widely used in local laboratories; however, the results appear to be less accurate (Winters et al., 1998; Rosner, 2001) with either high or low SHBG levels. Free testosterone can also be calculated using measurements of total testosterone, albumin, and SHBG concentrations (Vermeulen et al., 1999).

1.9.9.Impact of life style related factors on reproductive function

Several life-style related factors including hot baths, tight clothing, caffeine intake, drugs, alcohol, snuffing, cigarettes (including mother's smoking during pregnancy) could potentially have some impact on the reproductive capability (Figure1.8) (Storgaard et al., 2003; Vine, 1996; Fagerström & Schildt, 2003; Shafik, 1993;Saikhun et al., 1998).

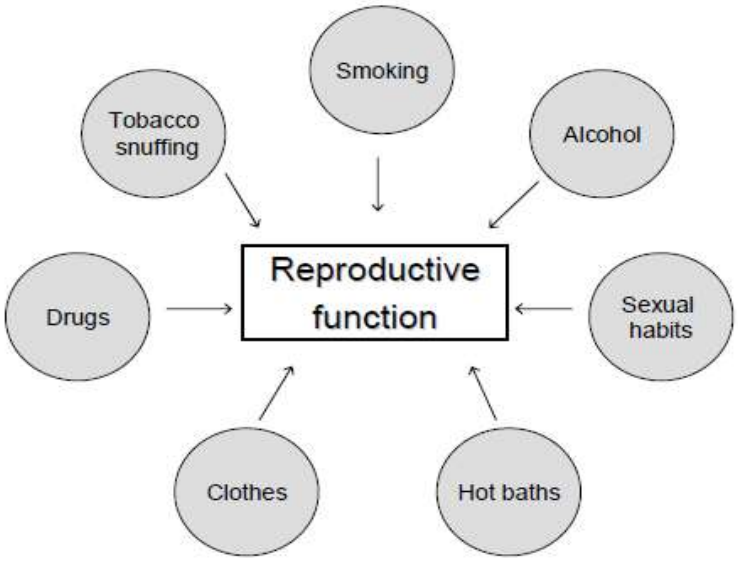


Figure 1.10: Effect of Environmental Factors on Reproductive functions

1.10.Diagnosis and Classification of Diabetes Mellitus

1.10.1 definition and Description of Diabetes Mellitues:

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels (Bell and Polonsky 2001).

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action (Bell and Polonsky 2001).

Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia.

Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome (Genuth et. al. 2003).

Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing

gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction (Robert, 1998).

Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes. The vast majority of cases of diabetes fall into two broad etiopathogenetic categories (Robert, 1998).

In one category, type 1 diabetes, the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers. In the other, much more prevalent category, type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response (Sicree et. al. 2003).

In the latter category, a degree of hyperglycemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period of time before diabetes is detected. During this asymptomatic period, it is possible to demonstrate an abnormality in carbohydrate metabolism by measurement of plasma glucose in the fasting state or after a challenge with an oral glucose load (Sicree et. al. 2003).

The degree of hyperglycemia (if any) may change over time, depending on the extent of the underlying disease process. A disease process may be present but may not have progressed far enough to cause hyperglycemia. The same disease process can cause impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) without fulfilling the criteria for the diagnosis of diabetes. In some individuals with diabetes, adequate glycemic control can be achieved with weight reduction, exercise, and/or oral glucose lowering agents.

These individuals therefore do not require insulin. Other individuals who have some residual insulin secretion but require exogenous insulin for adequate glycemic control can survive without it. Individuals with extensive β-cell destruction and therefore no residual insulin secretion require insulin for survival. The severity of the metabolic abnormality can progress, regress, or stay the same. Thus, the degree of hyperglycemia reflects the severity of the underlying metabolic process and its treatment more than the nature of the process itself.

1.10.2.Classification of Diabetes Mellitus and other Categories of Glucoes Regulation:

Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and many diabetic individuals do not easily fit into a single class. For example, a person with gestational diabetes mellitus (GDM) may continue to be hyperglycemic after delivery and may be determined to have, in fact, type 2 diabetes.

Alternatively, a person who acquires diabetes because of large doses of exogenous steroids may become normoglycemic once the glucocorticoids are discontinued, but then may develop diabetes many years later after recurrent episodes of pancreatitis. Another example would be a person treated with thiazides who develops diabetes years later. Because thiazides in themselves seldom cause severe hyperglycemia, such individuals probably have type 2 diabetes that is exacerbated by the drug. Thus, for the clinician and patient, it is less important to label the particular type of diabetes than it is to understand the pathogenesis of the hyperglycemia and to treat it effectively.Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

1.11.Aim of study:

The aim of this study was to assess the effects of oral statin therapy on the testosterone serum level in men with type 2 diabetes and Hypertension patients.

Chapter 2
Subjects and Methods

2.1. Subjects :

Libyan subjects who attended the Medicine Department, Faculty of Medicine, Benghazi University, Libya from 2013-2014 were screened and 240 subjects were taken for the study. They were divided into 8 groups: 30 subjects in each group

Group I – Controls

Group II- Patients with high cholesterol on statin therapy

Group III- Type 2 Diabetis

Group IV- Type 2 Diabetis on statin therapy for less than1 year

Group V- Type 2 Diabetis on statin therapy for more than one year

Group VI- Type 2 Diabetic hypertensives

Group VII- Type 2 Diabetic hypertensives on statin therapy for less than 1 year

Group VIII- Type 2 Diabetic hypertensives on statin therapy for more than year

The mean age and standard deviation (SD) of the patients with type 2 DM& HTN selected for this study was 45±8.5 years.

Diabetic patients included in the study were either diagnosed using the following criteria or those who are already under medications.

Diagnostic Tests for Diabetes: Diabetes weree diagnosed based on A1C criteria or plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-huor plasma glucose (2-h PG) value after a 75-gm oral glucose tolerance test (OGTT) .

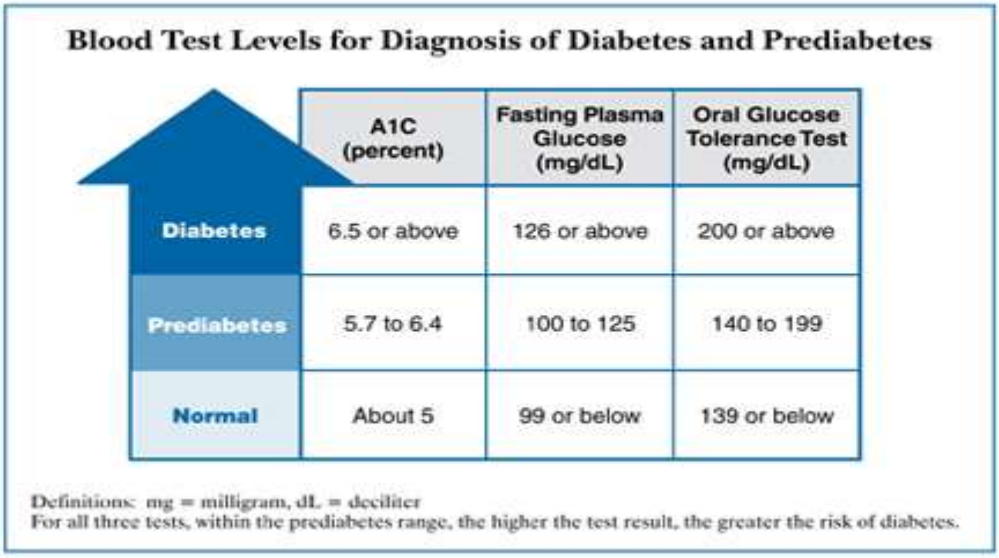
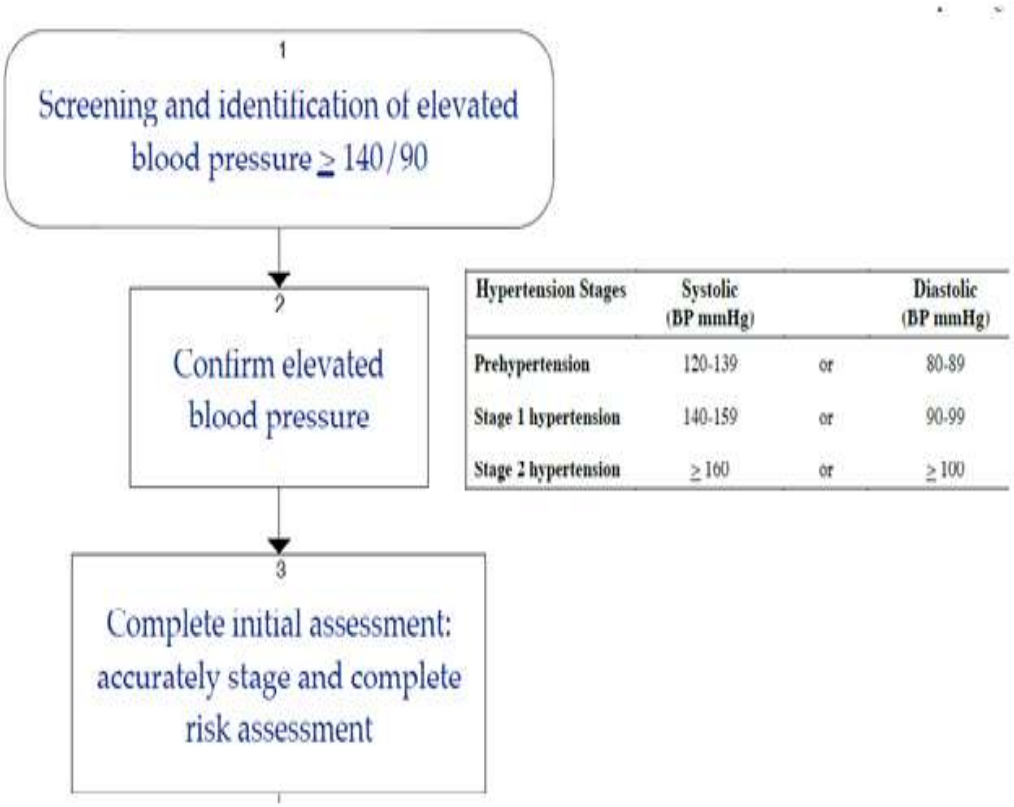


Figure 2.1 :blood test level.

Table2.1 Criteria for the diagnosis of diabetes
A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).



Hypertension Stages	Systolic (BP mmHg)		Diastolic (BP mmHg)
Prehypertension	120-139	or	80-89
Stage 1 hypertension	140-159	or	90-99
Stage 2 hypertension	≥ 160	or	≥ 100

Figure 2.2 : Diagnosis of Hypertension was done on the following basis (Kenning et al,2013)

2.2.Inclusion criteria:

1. Patients with high cholesterol
2. Patients with a history of type 2 Diabetes (T2DM)
3. Patients with diabetes and hypertension(HTN).

These subjects had no other secondary causes of hypercholesterolemia or with secondary causes of HTN or hyperglycemia.

Waist circumference is a better estimate of visceral fat, the dangerous internal fat which coats the organs. It is therefore a more accurate predictor of cardiovascular risk, type 2 diabetes in women and metabolic syndrome.

2.3.Waist circumference was measured as follows.

1) Place the tape measure directly on your skin, or over no more than one layer of light clothing.
2) The correct place to measure your waist is halfway between your lowest rib and the top of your hipbone. This is roughly in line with your belly button.
3) Breathe out normally and measure.
4) Make sure the tape is snug, without squeezing the skin.
5) risk is increased at ≥ 94 cm
6) risk is high at ≥ 102 cm for men

2.4.Methods

Serum total testosterone was measured by Enzyme immune assay. (testosterone enzyme immunoassay test KIT- A cobas e 411 analyzer)

2.4.1.Reagents I

Reagent rackpack *(ready for use)*

MStreptavidin-coated microparticles.

R1biotinylatedmonoclonal anti-Testosterone antibody .

R2Testosterone-peptide ~ Ru. Testosterone derivative, labeled with ruthenium complex

2.4.2.Reagents II

Calibrators *(lyophilisate)*

Cal 1 Testosterone calibrator (lyophilized) for 1.0 ml

Cal 2 Testosterone calibrator (lyophilized) for 1.0 ml

2.4.3.PreciControlUniversal *(lyophilisate)*

PCU 1 Testosterone control, (lyophilized) for each 1.0 ml

PCU 2 Testosterone control, (lyophilized) for each 1.0 ml

2.5.Reagent handling

Reagent rackpack (ready for use)

2.5.1.Calibrators:

Dissolve carefully by adding exactly 1.0 ml of distilled water, Mix carefully, avoid formation of foam. Reconstitute for 15 min. Transfer aliquots of the calibrators into empty labeled snap-cap bottles (CalSetVials). Attach the supplied labels.

☒ Store immediately at -20°C.

2.5.2.Controls:

Dissolve carefully by adding exactly 1.0 mLof distilled water, Mix carefully, avoid formation of foam. Reconstitute for 15 min. Transfer aliquots of the controls into appropriate vials.

☒ Store immediately at –20°C.

2.5.3.Calibrators and Controls:

Perform **only one**calibration or control procedure per aliquot.

☒ Stability at -20°C: 4 weeks (freeze only once).

2.6.Test principle I

Competition principle Total duration of assay: 18 minutes.

2.6.1.1st Incubation (9 minutes):

20 µL of the sample was incubated with abiotinylated monoclonal testosteronespecific antibody and 2-bromoestradiol (to release testosterone), with the amount of antibody binding sites subsequently occupied depending on the concentration of testosterone in the sample.

2.6.2. 2nd Incubation (9 minutes):

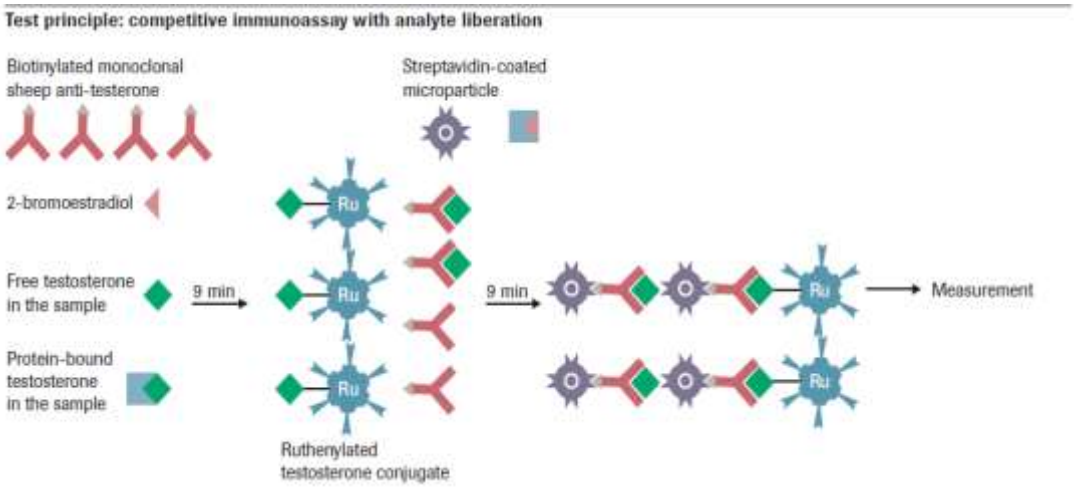
Streptavidin-coated microparticles and a ruthenylated testosterone derivative were added to the reaction mixture and the complexes bound to the solid phase via biotin-streptavidin bound to the solid phase via biotinstreptavidin

2.7. Measurement:

Testosterone bound to the solid phase via biotinstreptavidin and the microparticles were magnetically captured onto the surface of an electrode; unbound sample is washed away before a chemiluminescent reaction is induced by applying a voltage to the electrode.

Chemiluminescence was measured by a photomultiplier and the concentration of Testosterone within the sample was calculated using a calibration curve.

4.7.1.Test principle II



2.8. Statistical analysis:

The data were analyzed using the statistical package for the social sciences (SPSSversion 17). Descriptive characteristics of the study participants were calculated as mean ± standard deviation (SD). Analysis of variance (T-TEST) was used to determine differences in subject characteristics , Pearson's correlation coefficient determination was done to evaluate the degree of association between Testosterone and Parameters in each group. *P* value < 0.05 was considered as statistically significant.

Chapter 3

Results

3.0. Result:

This study amid the effect of hypolipidemic drugs such statins family on the tsetosteron level in males with type 2 diabetes and hypertension There is a high prevalence of hypogonadism in men with type 2 diabetes which will lead to an increase in assessments of hypogonadism. Statins could potentially decrease testosterone levels by reducing the availability of cholesterol for androgen synthesis.

3.1. Controls & Patients with high cholesterol on statin therapy

The serum testosterone level was comparatively lower in patients with hig cholesterol under statin therapy compared to the controls ($p<0.05$).

There was a significant in the serum testosterone level between patients with high cholesterol under statin therapy and controls ($p= 0. 046$) .

There was no relation between the serum testosterone level with the age, weight and waist circumference.

These results showed that the serum testosterone level decreased with patients under statin therapy.

3.2. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus patients without statin therapy:

The serum testosterone level was comparatively lower in Type 2 Diabetes Mellitus patients without statin therapy compared to the controls ($p<0.05$).

There was a significant in the serum testosterone level between Type 2 Diabetes Mellitus patients without statin therapy and controls ($p= 0. 017$) .

There was no relation between the serum testosterone level with the age, weight and waist circumference .

These results showed the type 2 Diabetic plays a role in level of the serum testosterone .

3.3. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus patients use statin therapy for less than one year

The serum testosterone level was comparatively lower in Type 2 Diabetes Mellitus patients under statin therapy compared to the controls ($p<0.05$).

There was a significant difference in the serum testosterone level between Type 2 Diabetes Mellitus patients under statin therapy and controls ($p= 0. 00$) .

There was no relation between the serum testosterone level with the age, weight and waist circumference .

From these resultsappeared that the serum testosterone level decreased with type 2 Diabetes patients under statin therapy for less than one year.

3.4. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus patients use statin therapy for more than one year

The serum testosterone level was comparatively lower in type 2 Diabetes Mellitus patients under statin therapy compared to the controls ($p<0.05$).

There was a significant difference in the serum testosterone level between Type 2 Diabetes Mellitus patients under statin therapy and controls ($p= 0. 00$) .

There was no relation between the serum testosterone level with the age, weight and waist circumference .

Our studies clerly showed that the serum testosterone level decreased with Type 2 Diabetes patients under statin therapy for more than one year.

3.5. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus , The Hypertension patients without statin therapy

The serum testosterone level was comparatively lower in type 2 Diabetes Mellitus, the Hypertension patients without statin therapy compared to the controls ($p<0.05$).

There was a significant in the serum testosterone level between Type 2 Diabetes Mellitus, the Hypertension patients without statin and controls ($p= 0. 043$) .

There was no relation between the serum testosterone level with the age, weight and waist circumference .

Our results showed that the type 2 Diabetic and The Hypertension play a role in the level of the serum testosterone.

3.6. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus , The Hypertension patients using statin therapy less than one year

The serum testosterone level was comparatively lower in Type 2 Diabetes Mellitus , the Hypertension patients under statin therapy compared to the controls ($p<0.05$).

there was a significant in the serum testosterone level between type 2 Diabetes Mellitus, the Hypertension patients undert statin therapy and controls ($p= 0. 01$) .

There was no relation between the serum testosterone level with the age, weight and waist circumference .

We found that the serum testosterone level decreased with type 2 Diabetes Mellitus, the Hypertension patients under statin therapy for less than one year.

3.7. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus , The Hypertension patients using statin therapy more than one year

The serum testosterone level was comparatively lower in type 2 Diabetes Mellitus , the Hypertension patients under statin therapy compared to the controls ($p<0.05$).

There was a significant difference in the serum testosterone level between type 2 Diabetes Mellitus , the Hypertension patients under statin and controls ($p= 0. 00$)

There was no Relation between the serum testosterone level with the age, weight and waist circumference .

Our results showed that the serum testosterone level decreased with type 2 Diabetes Mellitus, the Hypertension patients under statin therapy for more than one year.

Table 3.1. Controls & Patients with high cholesterol on statin therapy			
Parameter	**Control N=30**	**patients on statin N=30**	**P value**
Testosterone (ng/ml)	**5.1±1.1**	**4.5±0.7**	**0.046**
Age (yr)	**46.7±8.2**	**45.4±7.2**	**0.596**
Weight (Kg)	**85.5±12.9**	**84.2±9.4**	**0.708**
Waist circumference (Cm)	**99.7±18.9**	**99.5±13.5**	**0.970**

Table 3.2. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus patients without statin therapy			
Parameter	**Control N=30**	**T2DM patient without statin N=30**	**P value**
Testosterone (ng/ml)	**5.1±1.1**	**4.4±1**	**.017**
Age (yr)	**45.5±8.2**	**44.4±4.9**	**0.611**
Weight (Kg)	**87.3±17.7**	**84.1±12.9**	**0.531**
Waist circumference (cm)	**99.5±18.9**	**96.4±18.2**	**0.596**

Table3.3.The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus patients use statin therapy for less than one year			
Parameter	**Control N=30**	**T2DM patient with statin <1yr N=30**	**P value**
Testosterone (ng/ml)	**5.1±1.1**	**3.8±0.5**	**0.00**
Age (yr)	**45.5±8.1**	**44.9±2.5**	**0.776**
Weight (Kg)	**91±16**	**84.2±12.9**	**0.141**
Waist circumference (Cm)	**99.5±18.9**	**97.5±11.9**	**0.725**

Table.3.4. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus patients use statin for more than one year			
Parameterr	**Control N=30**	**T2 DM patient with statin >1yr N=30**	**P value**
Testosterone (ng/ml)	**5.1±1.1**	**3.1±1.3**	**0.00**
Age (yr)	**46.4±8.2**	**45.4±31**	**0.612**
Weight (Kg)	**84.2±12.9**	**83.4±4.9**	**0.798**
Waist circumference (Cm)	**99.5±18.9**	**97.3±16.7**	**0.699**

Table.3.5. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus , The Hypertension patients without statin therapy

Parameter	Control N=30	T2DM & HTN patient without statin N=30	P value
Testosterone (ng/ml)	5.1±1.1	4.8±0.9	0.043
Age (yr)	45.4±8.2	44.6±4.5	0.686.
Weight (Kg)	84.1±12.9	79.4±10.4	0.205
Waist circumference (Cm)	99.5±18.9	97.2±18.3	0.701

Table.3.6. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus,the Hypertension patients using statin therapy less than one year

Parameter	Control N=30	T2DM & HTN patient with statin <1yr N=30	*P value*
Testosterone (ng/ml)	5.1±1.1	4.2±0.5	0.01
Age (yr)	45.+±8.2	44.3±3.7	0.554
Weight (Kg)	92.5±18.7	84.2±12.9	0.107
Waist circumference (Cm)	99.5±18.9	96.6±20.1	0.812

Table.3.7. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus,The Hypertension patients using statin therapy more than one year			
Parameter	**Control N=30**	**T2DM & HTN patient with statin >1yr N=30**	**P value**
Testosterone (ng/ml)	**5.1±1.1**	**3.4±1.3**	**0.00**
Age (yr)	**45.9±8.2**	**45.5±3.8**	**0.825**
Weight (Kg)	**87.4±12.9**	**984.2±12.**	**0.452**
Waist circumference (Cm)	**99.5±19**	**96.7±19.9**	**0.726**

Figure.3.1. Controls & Patients with high cholesterol on statin therapy

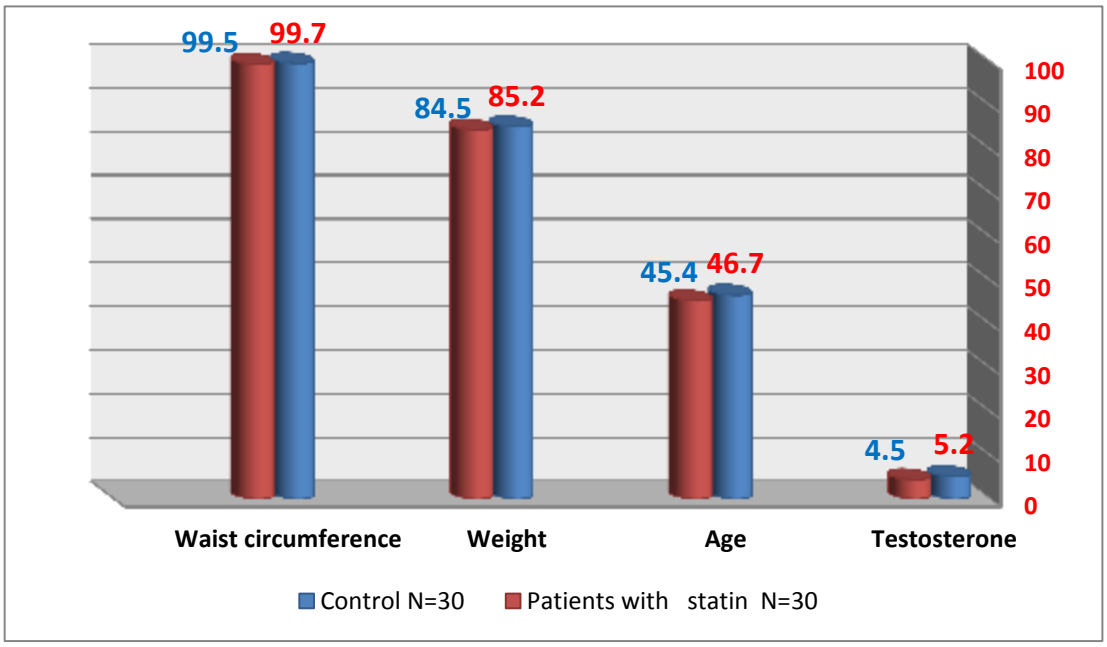


Figure.3.2. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus patients without statin therapy

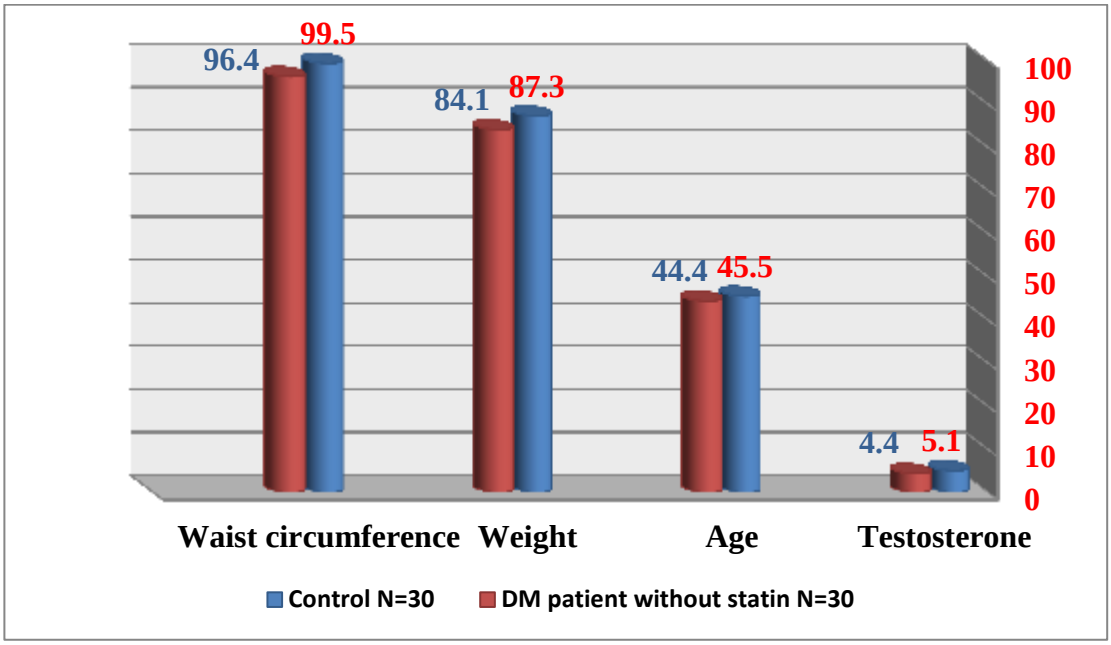


Figure.3.3.The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus patients use statin therapy for less than one year

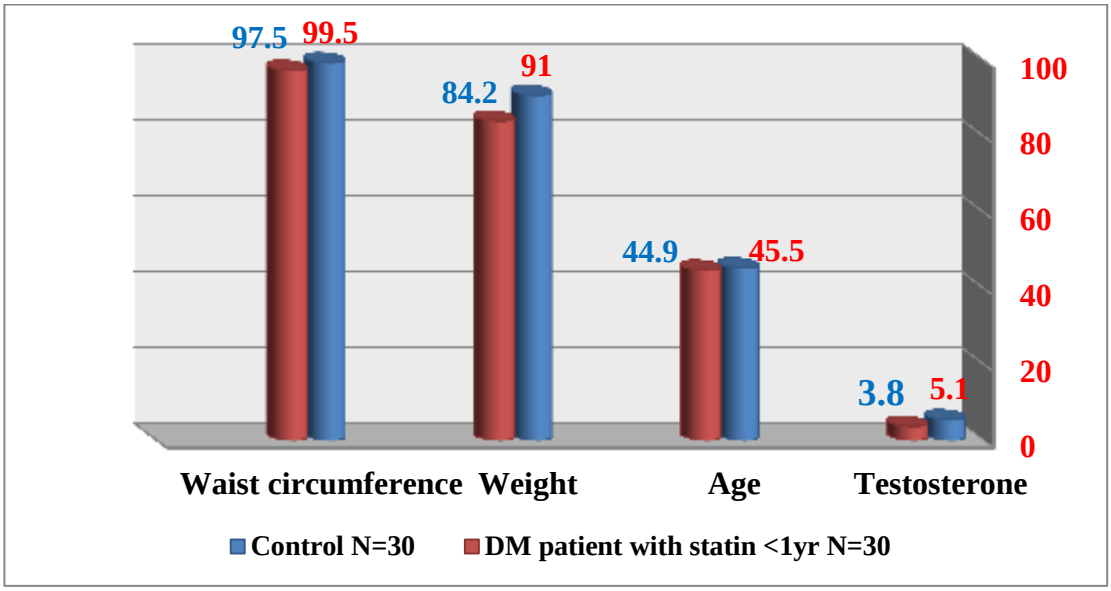


Figure.3.4. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus patients use statin therapy for more than one year

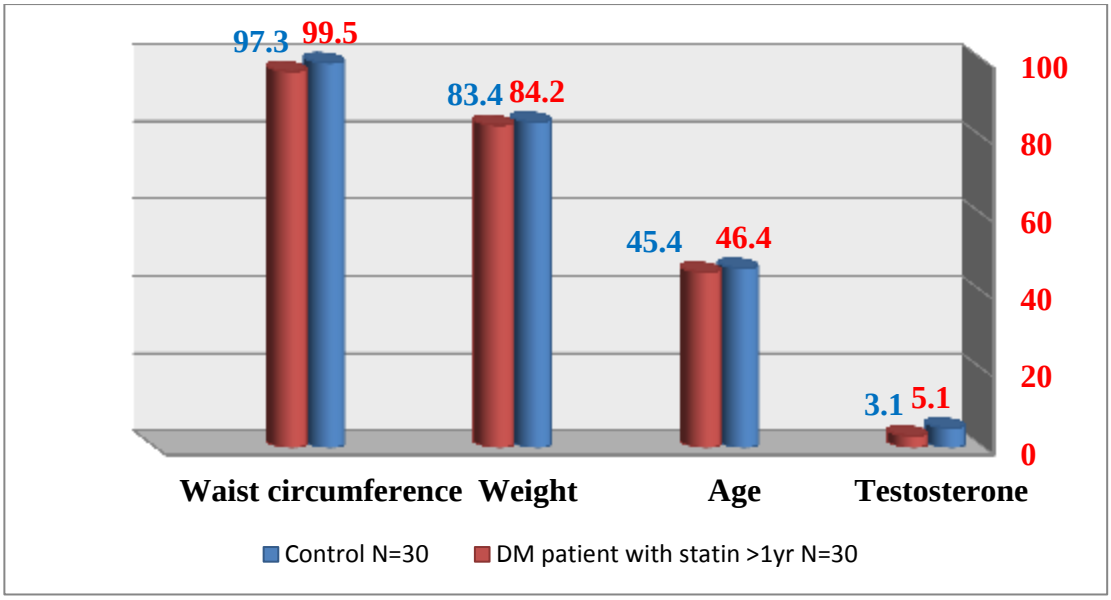


Figure.3.5. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus , The Hypertension patients without statin therapy

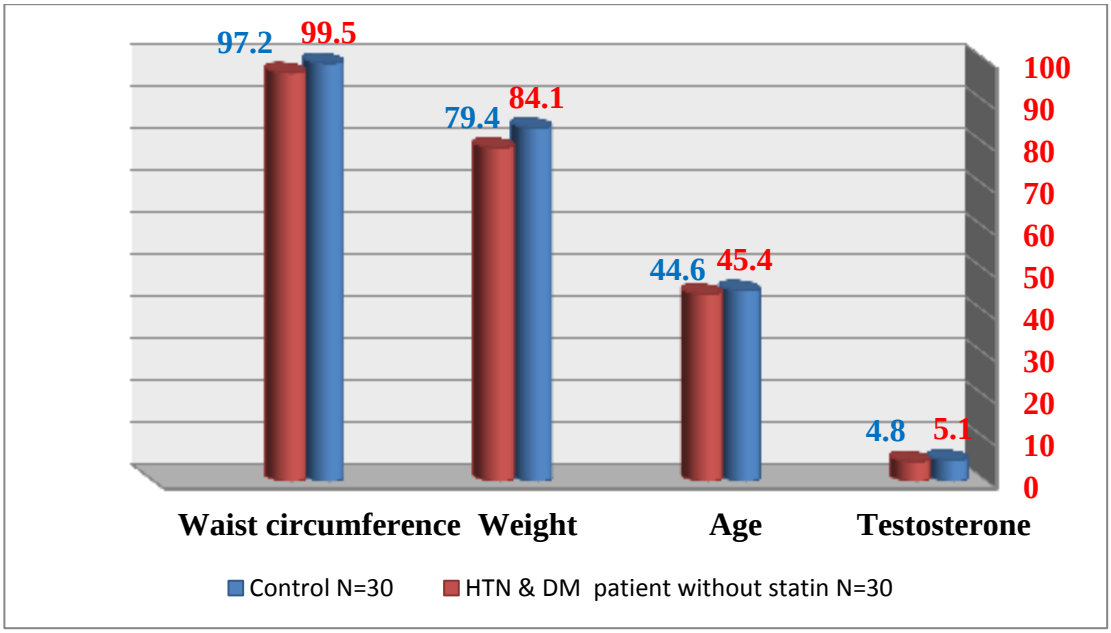


Figure.3.6. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus,the Hypertension patients using statin therapy less than oneyear

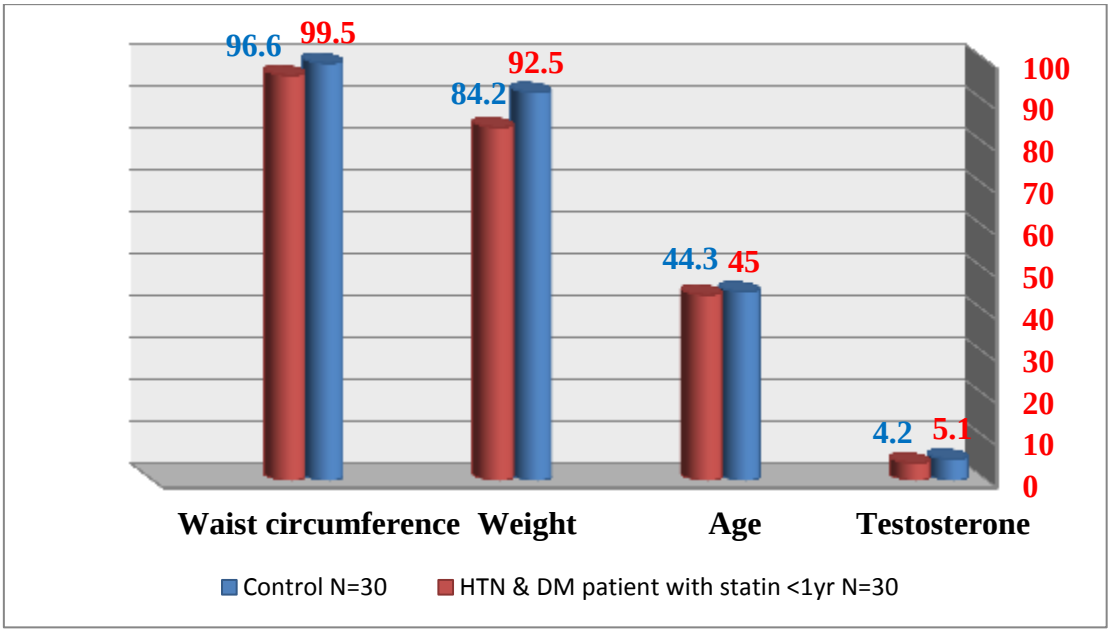


Figure.3.7. The Serum testosterone levels in normal control and Type 2 Diabetes Mellitus,The Hypertension patients using statin therapy more than one year

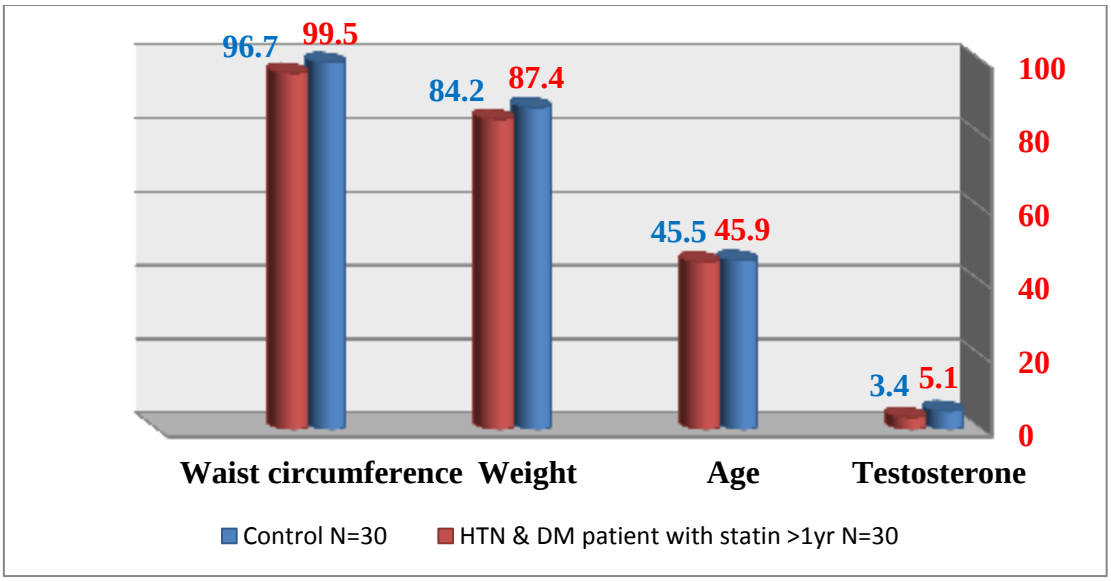
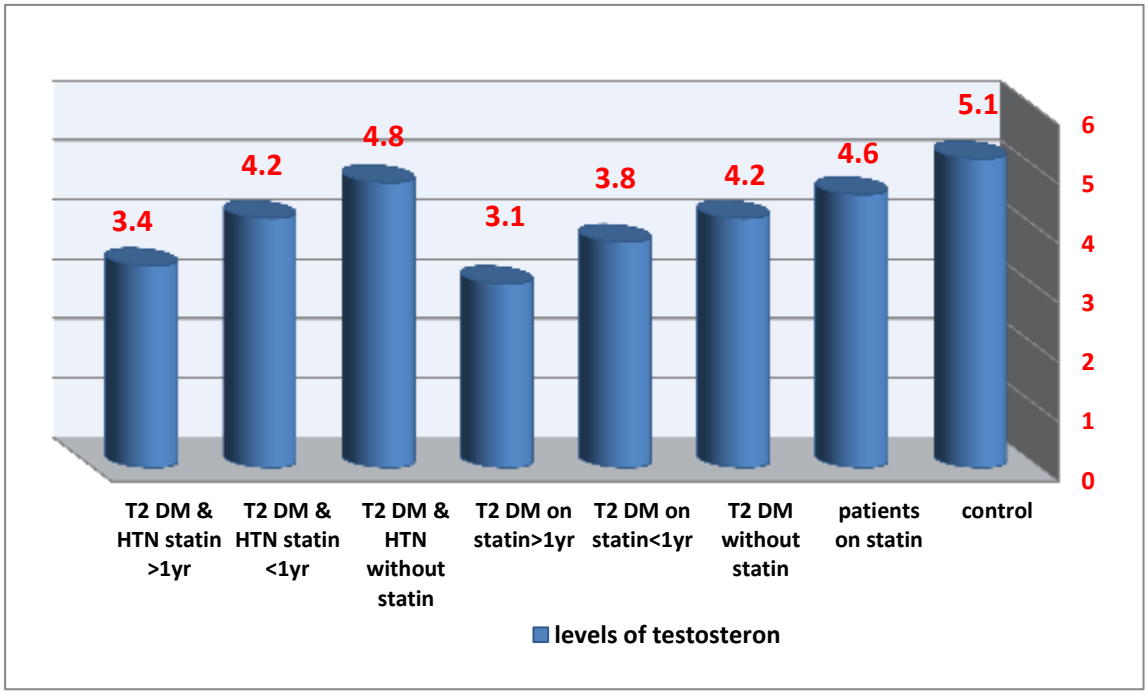


Figure.3.8.The levels of testosterone in the different groups (ng/ml)



3.8.Relationship between Serum Testosterone levels and Parameters in all gruops

Pearson's correlation analysis of Age weight waist circumference withe testosterone.

3.8.1.Parameters in Control (group I) showed that:

Age was negatively correlated with testosterone (r= -0.553 , $p < 0.05$), and Weight (r= -0.590, $p < 0.01$**).

Positive correlated between waist circumference (r= 0.11, $p > 0.05$) with testosterone.(Table 3.8)

3.8.2.Parameters in Patients on Statin Therapy (group II) showed that:

Age was negatively correlated with testosterone (r= -0.488 , $p < 0.05$), and Weight (r= -0.093, $p > 0.05$).

Positive correlated between Waist circumference (r= 0.412 , $p > 0.05$) with testosterone.(Table 3.9)

3.8.3.Parameters in T2DM patients without statin (group III) showed that:

Age was negatively correlated with testosterone (r= -0.490, $p < 0.05$), and Waist circumference (r= -0.461*, $p < 0.05$) .

Positive correlated between Weight (r= 0.263, $p > 0.05$),with testosterone.(Table 3.10)

3.8.4.Parameters in T2DM patient with statin <1yr (group IV) showed that:

Age was negatively correlated with testosterone (r=-0.459, $p < 0.05$*), and Waist circumference (r= -0.004 , $p > 0.05$) .

Positive correlated between Weight (r= 0.412, $p > 0.05$), with testosterone. (Table 3.11)

3.8.5.Parameters in T2 DM patient with statin >1yr (groupV) showed that:

Age was negatively correlated with testosterone (r=-0.641 , $p < 0.05$*), and Weight (r= -0.273, $p > 0.05$*).

Positive correlated between Waist circumference (r= 0.333, p >0.05*), with testosterone. (Table.3.12)

3.8.6.Parameters in T2DM & HTN patient without statin (group VI) showed that:

Age was negatively correlated with testosterone (r=-0.745 , p < 0.05*), and Weight (r= -0.529, p< 0.05) , Waist circumference (r= -0.151, p >0.05), with testosterone. (Table 3.13)

3.8.7.Parameters in T2DM & HTN patient with statin <1yr (group VII) showed that:

Age was negatively correlated with testosterone (r=-0.775 , p < 0.01**), and Weight (r= -0.383, p > 0.05).

Positive correlated between Waist circumference (r= 0.163, p >0.05), with testosterone. (Table 3.14.)

3.8.8.Parameters in T2DM & HTN patient with statin > 1yr (group VIII) showed that:

Age was negatively correlated with testosterone (r= -0.544, p < 0.05).

Positive correlated between Weight (r= 0.291, p >0.05), Waist circumference (r= 0.124 , p >0.05) with testosterone.(Table 3.15.)

Table.3.8. Correlations Control

Parameters	Pearson Correlation	*P value*
Age	-0.553	0.012*
Weight	-0.590	0.006**
Waist circumference	0.110	0.644

*. Correlation is significant at the 0.05 level.

**. Correlation is significant at the 0.01 level.

Table.3.9.Correlations Patients on Statin Therapy		
Parametres	**Pearson Correlation**	***P value***
Age	-0.488	0.029
Weight	-0.093	0.696
Waist circumference	0.412	0.071

*. Correlation is significant at the 0.05 level

Table.3.10. Correlations T2DM patients without statin.		
Parametres	**Pearson Correlation**	***P value***
Age	-0.490	0.028
Weight	0.263	0.357
Waist circumference	-0.461*	0.041

*. Correlation is significant at the 0.05 level.

Table.3.11. Correlations T2DM patient with statin <1yr		
Parametres	**Pearson Correlation**	***P value***
Age	-0.459	0.022
Weight	0.412	0.071
Waist circumference	-0.004	0.986

*. Correlation is significant at the 0.05 level .

Table.3.12. Correlations T2 DM patient with statin >1yr		
Parametres	**Pearson Correlation**	***P value***
Age	-0.641	0.002**
Weight	-0.273	0.245
Waist circumference	0.333	0.152

**. Correlation is significant at the 0.01 level .

*. Correlation is significant at the 0.05 level .

Table.3.13. Correlations T2DM & HTN patient without statin		
Parametres	**Pearson Correlation**	***P value***
Age	-0.745	0.00**
Weight	-0.529	0.017
Waist circumference	-0.151	0.526

**. Correlation is significant at the 0.01 level .

*. Correlation is significant at the 0.05 level .

Table.3.14. Correlations T2DM & HTN patient with statin <1yr .		
Parametres	**Pearson Correlation**	***P value***
Age	-0.775	0.00**
Weight	-0.383	0.095
Waist circumference	0.163	0.492

**. Correlation is significant at the 0.01 level .

Table.3.15. Correlations T2DM & HTN patient with statin > 1yr		
Parametres	**Pearson Correlation**	***P value***
Age	-0.544	0.013*
Weight	0.291	0.214
Waist circumference	0.124	0.601

*. Correlation is significant at the 0.05 level .

Chapter 4

Discussion

In the present study, Statin therapy in short had resulted in lowering serum testosterone levels in patients treated for hypercholesterolemia, in diabetics, diabetics treated with statin for one year or more than one year, hypertensives on statin therapy and hypertensives with diabetes. In general serum testosterone levels are lowered in diabetes as well as in cases without diabetes on statin therapy. Reductions in serum testosterone levels were more prominent in patients with diabetics and without hypertension on statin therapy. Patients with hypertension and hypertensive diabetics did not show marked reduction in serum testosterone levels though the effect is significant in diabetic hypertensives treated with statin for more than one year.

Diabetes mellitus is considered as a Congestive heart diseasr (CHD) equivalent and both CARE trial and Heart Protection Study found significant improvement in outcomes with statin therapy even at LDL-cholesterol values below 100 mg/dL (2.6 mmol/l). The CARDS study found similar benefits of statin therapy in patients with an LDL-cholesterol above and below 120 mg/dL (3.1 mmol/L). Thus the ATP-III goal of LDL-cholesterol for diabetics Patients similar to that in patients with CHD: less than 100 mg/dL (2.6 mmol/l), and perhaps more aggressive target LDL-cholesterol goals of 75 to 80 mg/dL (1.9 to 2.1 mmol/l) may be appropriate in high risk groups . Cardiologists declare that "cholesterol-containing lipoproteins are central to the pathogenesis of atherosclerosis (ACC/AH guidelines,2013). Statins, first approved for clinical use in 1987, are very effective in lowering cholesterol. High intensity statin therapy, rosuvastatin 20mg/day and atorvastatin (Lipitor) 40-80 mg, reduces LDL-C by 50 percent or greater. Moderate intensity therapy, rosuvastatin 10 mg, atorvastatin 10 mg, simvastatin (Zocor) 20-40 mg, and pravastatin (Pravachol) 40 mg/day, achieves a 30 to 50 percent reduction of LDL-C (Miedema , Lopez , Blaha ,2015).

Hypogonadism in men is a clinical syndrome that results from failure of testes to produce physiological levels of testosterone (androgen deficiency) and in some instances normal number of spermatozoa (infertility) due to disruption of one (or)

more levels of the hypothalamic pituitary testicular axis (TUE Physicians Guidelines ,2015).

Risk factors for male hypogonadism include diabetes, hypertension, heart disease, psychological stress, inflammatory illness, chronic obstructive pulmonary disease (COPD), chronic pain with Opioid use and obesity (Sarkar, 2009).

Testosterone is the principal sex hormone in men. It is important not only for normal sexual function but also for maintaining bone and muscle strength, mental and physical energy and for the overall well being. Low testosterone is associated with diminished libido, erectile dysfunction, increased fat mass, decreased muscle, bone mass and energy, depression and anemia (Paresh et al.2009).

Mild low testosterone was defined as a total testosterone level of <3.5ng/ml, and very low testosterone was defined as < 2.3ng/ml.(Standowrth et al.2009)

Statin like simvastatin, pravastatin, and lovastatin and atorvastatin are recommended to treat hyperlipidemia in military personnel. The use of statins and its probable side effect is reported to be lowered testosterone level along with myositis (Official Air Force Approved Aircrew Medications. Effective: 19 May, 2011).

4.1.Prevalence of Hypogonadism in diabetes

The prevalence of both hypogonadism and type 2 diabetes mellitus increases with age , Male hypogonadism is strongly associated with metabolic syndrome and may be a risk factor for the development of type2 diabetes and coronary artery disease (CAD). In the last decades concepts have developed on whether male hypogonadism and testosterone deficiency can lead to the development of insulin resistance and subsequent type 2 diabetes.

4.2.Hypogonadism is mostly hypothalamic in origin.

Hypogonadism / Androgen deficiency may be primary, due to a problem with testes (or) secondary, due to problem with hypothalamic pituitary-gonadal axis (or) combined both primary and secondary (TUE Physicians Guidelines,2015) .

Hypogonadism results from testicular failure, or is due to the disruption of one or several levels of the hypothalamic-pituitary-gonadal axis (Figure 6.3).

Male hypogonadism can be classified in accordance with disturbances at the level of:

• testes (primary hypogonadism);

• hypothalamus and pituitary (secondary hypogonadism);

• hypothalamus/pituitary and gonads (hypogonadism in adult men);

• androgen target organs (androgen insensitivity/resistance).

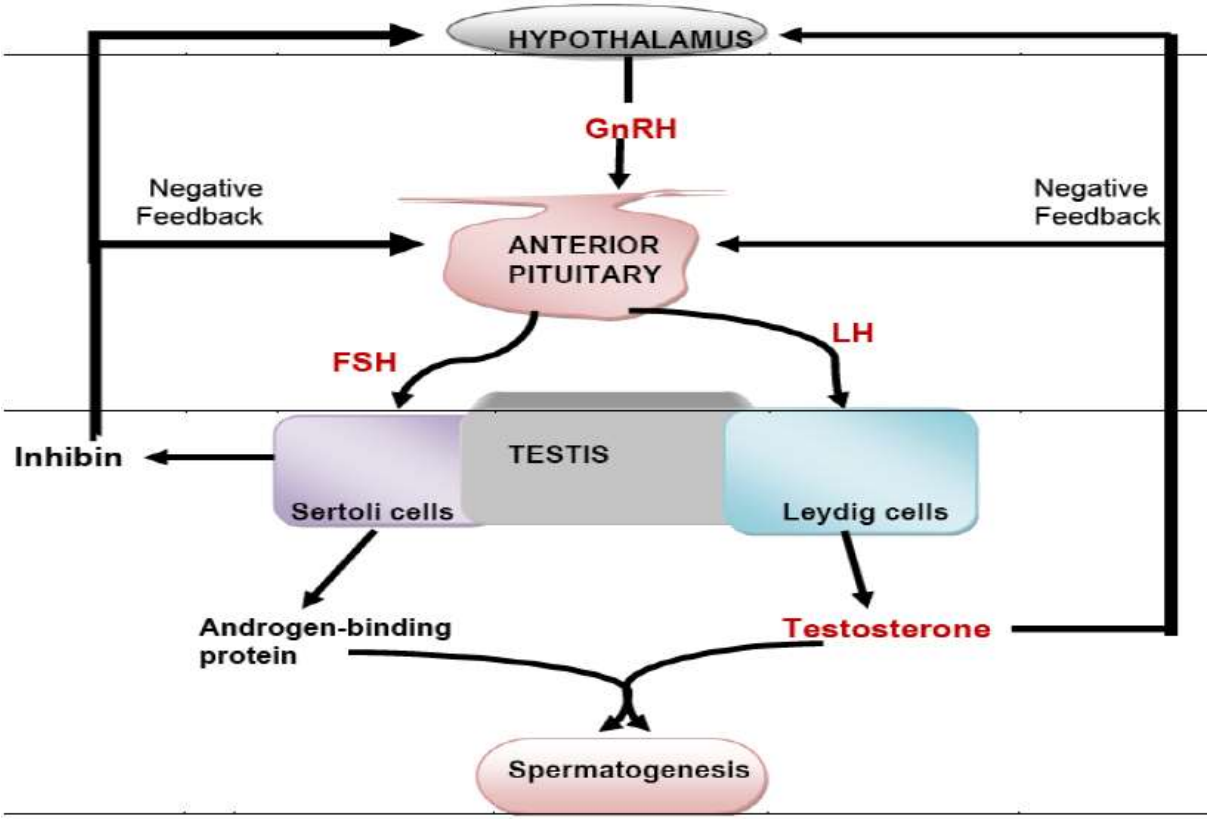


Figure 4.1: Hypothalamus –Pituitary-Testicular Axis, for Feedback regulation of secretion of Testosterone

4.3.Statin use and hypogonadism

The prevalence of hypogonadism among male veterans has been found to be as high as 38.7%. (Haffner et al.1993). In one study low testosterone was associated with increased mortality in male veterans (Haffner et al.1996). the percentage of patients was very high whoever on statins (Cermark et al. 1993). Thus, the evidence suggests that the use of statin is a significant contributor to decreased serum testosterone levels (Torzewski et al. 2000; Verma et al.2002; Mulligan et al;2006;Muhamad et al.2012).

Statin users are older and have a higher prevalence of DM, CAD and hypertension (HTN) than non-users. Statin use persists as a significant factor when controlling for BMI, DM, CAD, HTN, age, dyslipidemia and Opioid use. Thus in patients with obese and DM high dose statin use may exacerbate the disorder of severe hypogonadism (Dhindsa et al.2007) .

Statin therapy in0duce overt primary hypogonadism which should be considered for the evaluation of low testosterone levels in patients with ED (Torzewski et al. 2000; Verma et al.2002; Mulligan et al;2006;Muhamad0 et al.2012). Effects of lipid lowering treatment on steroid synthesis in patients with type 2 diabetes,shch as 80 mg of atorvastatin decreased gonadal steroids (Tomar et al.2006). On the contrary another stu0dy showed high dose of atorvastatin seemed to be safe in terms of gonadal steroidogenesis.

The first study to report on the high prevalence of hypogonadism in type 2 diabetes mellitus based on free testosterone was published in 2004 (In contrast, hypogonadotropic hypogonadism does not occur in men with type 1 diabetes mellitus.(Tan and Pu,2008).

Age related fall in total testosterone with increase in SHBG and decrease in bio available free testosterone wear observed even if BMI does not exceed 26kg/m2 (Gray et al.1990).(Feldman, et al 2002). observed a decline of total testosterone by

0.8% per year of age, whereas as both free and albumin bound testosterone declined at about 2% per year. SHBG levels increased at 1.6% per year.

Tenover et al (1987) observed the fact that the major age related changes in testosterone levels are changes at testicular function and not due to hypothalamic pituitary axis pathway, which is not altered with age. They noted that treatment of aging men with clomiphene citrate, an anti-estrogen agent, could not increase the level of bio available testosterone as was seen in younger men even though LH pulse characteristics and bio available LH levels were similar in the two groups.

The mechanisms underlying hypogonadotropic hypogonadism in men with type 2 diabetes are not clear. It has been suggested that an excessive increase in fat mass may result in an increase in the activity of aromatase enzyme, which causes greater conversion of testosterone into oestrogen (the primary female sex hormone). An increase in oestrogen levels would lead to suppression of gonadotropin releasing hormone and impaired secretion of gonadotropin by the pituitary gland. This results in the reduction of both testosterone secretion and mature sperm production (Paresh et al 2009).

4.4. Diabetes and Hypertension:

High blood pressure is a very common disease in hypercholesterolemic and diabetic patients and contributes to the increase in cardiovascular risk. Inhibitors of 3-hdrox-3methyl-glutaryl-coenzyme A reductase (HMGCoAreductase) are the most effective and widely used cholesterol-lowering drugs. They significantly reduce the risk of cardiovascular events and death in both primary and secondary prevention of cardiovascular disease. Although the long-term benefit by statin treatment is largely attributed to their cholesterol-lowering action, increasing attention focuses on additional actions called "pleitropic effects" that might explain the cardiovascular protection seen shortly after the initiation of therapy. Very few and small studies have investigated the antihypertensive effect of statins in patients with hypertension associated with hypercholesterolemia, and the results of recently published large statin studies have attracted the interest on this subject. Many other studies, also not

specifically aimed at the evaluation of the statins (diabetes care volume32,number 4 april2009).

Antihypertensive effect, have provided information concerning changes in blood pressure during treatment with statins, but severe limitations such as inadequate study design, small or very small sample size, too short treatment period, and modification of concomitant antihypertensive therapy have prevented finding a definitive effect on blood pressure. From the available results, it appears consistent that statins may be useful in the reatment of hypertensives with high serum total cholesterol, in those whose hypertension is not well controlled with antihypertensive agents even without high serum total cholesterol, in hypertensive subjects well controlled with antihypertensives without high serum cholesterol. Future research could further characterize the impact of statin use alone or in combination with antihypertensive agents to delay the development of Stage 1 hypertension in prehypertension.

Chapter 5
References

Abbott, N. & Olness, K. (2001) Pediatric and Adolescent Health, p. 157-172. Handbook of Rural Health, New York: Kluwer Academic/Plenum Publishers

ACC/AHA (2013)Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.

Akkus E, Kadioglu A, Esen A, Doran S, Ergen A, Anafarta K, Hattat H, Turkish Erectile Dysfunction Prevalence Study Group. Prevalence and correlates of erectile dysfunction in Turkey: a population- based study. Eur Urol. 2002;41:298–304.

Allan CA, Strauss BJ, Burger HG, Forbes EA, McLachlan RI. Testosterone therapy prevents gain in visceral adipose tissue and loss of skeletal muscle in nonobese aging men. J Clin Endocrinol Metab. 2008b;93:139–146.

American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. DIABETES CARE 2011; 34(1): S62-S69.

Anderson DC (1974) Sex-hormone-binding globulin. Clin Endocrinol (Oxf) 3:69–96

Al-Arbah S. Tripoli: National Institute for Scientific Research; 1996. Food security, its limitation and achievement.

Al-Nozha MM, Al-Mazrou YY, Al-Maatouq MA, Arafah MR, Khalil MZ, Khan NB, et al. Obesity in Saudi Arabia. Saudi Med J. 2005;26:824–9.

Al-Nozha MM, Al-Mazrou YY, Al-Maatouq MA, Arafah MR, Khalil MZ, Khan NB, et al. Obesity in Saudi Arabia. Saudi Med J. 2005; 26: 824–9.

American Academy of Pediatrics Policy Statement (2007) Prevention of Pediatric Overweight and Obesity, Pediatrics Vol. 12, No 2, viewed online 2/21/2008 at http://aappolicy.aappublications.org/cgi/content/full/pediatrics;112/2/424.

Anderson, P. M., & Butcher, K. M. (2006) Childhood obesity, trends and potential causes The Future of Children:16 (1). Viewed online @ www.futureofchildren.org Androgen deficiency/Hypogonadism. TUE Physician Guidelines. Jan-2015; 4:1-8.

Anderson DC (1974) Sex-hormone-binding globulin. Clin Endocrinol (Oxf) 3:69–96
Furuyama S, Mayes DM, Nugent CA (1970) A radioimmunoassay for plasma testosterone. Steroids 16:415–428

Annie E. Casey Foundation Kids Count Special Report (2004) City and Rural, Kids Count Data Book. Anne E. Casey Foundation viewed at www.aecf.org/knowledgecenter/publications.

Baccush MM, Nayak CS. Breast feeding practice in an urban population of Tripoli, Libya. Garyounis Med J. 1992;15:35–42.

Barlow, S. F., Bobra, S. R., Elliott, M. B., Brownson, R. C. & Haire-Joshu, D. (2007) Recognition of childhood overweight during health supervision visits: Does BMI help pediatricians. Obesity 15:225-232. Retrieved 8/7/07 from http://www.obesityresearch.org/cgi/content/absract/15/1/225.

Barrett-Connor E, Khaw KT, Yen SS. Endogenous sex hormone levels in older adult men with diabetes mellitus. Am J Epidemiol 1990; 132:895-901.
Benghazi diabetes and endocrine center. Statistics; Benghazi: Ministry of Health-Libya; 2009.

Baulieu EE (1997) Neurosteroids: of the nervous system, by the nervous system, for the nervous system. In: Rec Prog Horm Res 52: pp 1–32

Berry, D. (2004). An emerging model of behavior change in women maintaining weight loss, Nursing Science Quarterly. 17:3, 242-252.

Betancout Albrecht M, Cunnihgham GR. Hypogonadism and diabetes. International Journal of Impotence Research 2002;15(suppl 4):S14-S20.

Bhatia V, Dhindsa S, Chaudhuri A, Ghanim H, Tomar R, Dandona P. Low testosterone and high C-reactive protein concentrations predict low hematocrit in Type 2 diabetes. Diabetes Care 2006; 28(10):2289-94.

Bibbins-Domingo, K., Coxson, P., Pletcher, M. J.., Lightwood, J., & Goldman L., (2007) Adolescent overweight and future adult coronary heart disease. New England Journal of Medicine 357:2372-9.

Borders, T. F., Rohner, K.M., Cardarelli, K. M. (2006) Gender specific Disparities in obesity, Journal of Community Health. 31 (1).

Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with Type2 diabetes, visceral obesity and partial androgen deficiency. Aging Male2003:1-7.

Bragg, S., & Leight, E,. (2003) The application of vulnerable populations conceptual model to rural health. Public Health Nursing, 20(6), 440-449. Retrieved October 1, 2006

Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RG, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ 2009; 338: b2376.

Ballester J, Mun˜oz MC, Domı´nguez J, Rigau T, Guinovart JJ, Rodrı´guez-Gil JE. Insulin-dependent diabetes affects testicular function by FSH- and LH-linked mechanisms. J Androl. 2004;25: 706–719.

Basaria S, Muller DC, Carducci MA, Egan J, Dobs AS. Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. Cancer. 2006;106:581–588.

Baulieu EE (1997) Neurosteroids: of the nervous system, by the nervous system, for the nervous system. In: Rec Prog Horm Res 52: pp 1–32

Bell GI, Polonsky KS. Diabetes mellitus and genetically programmed defects in b-cell function. Nature 2001;414:788–91.

Benitez A, Perez Diaz J. Effect of streptozotocin-diabetes and insulin treatment on regulation of Leydig cell function in the rat. Horm Metab Res. 1985;17:5–7.

Blouin K, Despres JP, Couillard C, Tremblay A, Prud'homme D, Bouchard C, Tchernof A. Contribution of age and declining androgen levels to features of the metabolic syndrome in men. Metabolism. 2005;54:1034–1040.

Bodie J, Lewis J, Schow D, Monga M. Laboratory evaluations of erectile dysfunction; an evidence based approach. J Urol. 2003;169:2262–2264.

Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male. 2003;6:1–7.

Braun M, Wassmer G, Klotz T, Reifenrath B, Mathers M, Engelmann U. Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. Int J Impot Res. 2000;12:305–311.

Brunton LL, Chabner BA, Knollmann BC. (Eds.). (2011). Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12 ed. Chapter 31, Drug Therapy for Hypercholesterolemia and Dyslipidemia. New York: McGraw-Hill.

Centers for Disease Control and Prevention (2007) Overweight and Obesity: About BMI for children and teens, retrieved online 9/27/07 at http://www.cdc.gov/nccdphp/dnpa/bmi/childrens_bmi/about_childrens_bmi..htm.

Centers for Disease Control and Prevention National Center for Health Statistics (2005) National survey of children's health The Health and Well-being Of Children: A Portrait of States and the Nation 2005 Viewed online 11/20007 At www.cdc.gov/nchs/about/major/slaits/nchs.htm.

Cermak J et al. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. Blood 1993; 82:513-20.

Cholesterol Treatment Trialists' (CTT) Collaborators. (2012). The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: Meta-analysis of individual data from 27 randomised trials. Lancet DOI:10.1016/S0140-6736(12)60367-5.

Chung, P. J., Lee, T. C., Morrison, J. L., & Schuster, M. A. (2006) Preventative care for children in the United States: quality and barriers. Annual Review of Public Health, 27:491-515. Viewed 2/18/2008 at cmwf@cmwf.org
CN Guide to Endocrine Testing . Diagnostic Division, ICN Biomedicals, Inc. pp. 2:33-35; 3:4-6.

Cohn JNet al. Surrogate markers for cardiovascular disease: functional markers. Circulation 2004; 109(25suppl1):V31-46.

Colhoun HM1, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004 Aug 21-27;364(9435):685-96.

Corona G, Rastrelli G, Maseroli E, Forti G, Maggi M. Sexual function of the ageing male. Clin Endocrin & Metab 2013; 27(4): 581‑601.

Caprio M, Isidori AM, Carta AR, Moretti C, Dufau ML, Fabbri A. Expression of functional leptin receptors in rodent Leydig cells. Endocrinology. 1999;140:4939–4947.

Cersosimo E, DeFronzo RA. Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. Diabetes Metab Res Rev. 2006;22:423–436.

Chen RYT, Wittest GA, Andreson GR. Relative androgen deficiency in relation to obesity and metabolic status in older men. Diabetes Obes Metab. 2006;8:429–435.

Coffey DS (1988) Androgen action and the sex accessory tissues. In: Knobil E, Neill (eds) The physiology of reproduction. J. Raven Press, New York, pp 1081–1119
Corona G, Mannucci E, Mansani R, Petrone L, Bartolini M, Giommi R, Forti G, Maggi M. Organic, relational and psychological factors in erectile dysfunction in men with diabetes mellitus. Eur Urol. 2004;46:222–228.

Corona G, Mannucci E, Petrone L, Balercia G, Paggi F, Fisher AD, Lotti F, Chiarini V, Fedele D, Forti G, Maggi M. NCEP-ATPIIIdefined metabolic syndrome, type 2 diabetes mellitus, and prevalnce of hypogonadism in male patients with sexual dysfunction. J Sex Med. 2007;4:1038–1045.

Corona G, Mannucci E, Petrone L, Ricca V, Balercia G, Mansani R, Chiarini V, Giommi R, Forti G, Maggi M. Association of hypogonadism and type II diabetes in men attending an outpatient erectile dysfunction clinic. Int J Impot Res. 2006;18:190–197.
Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477–2486

Crawford, P.B., Story M. Wang M. C., Ritchie, L.D., & Sabry, Z. (2001) Ethnic Issues in the epidemiology of childhood obesity. Pediatric Clinics of North America 48(4): 855-78.

Dakhil FO, Zew M, Ahmad M, Aboudabus F, El Jaroushi A, El Badri A, et al. Pattern of hypertension in Ibn Sina hypertension clinic, benghazi-libya. Garyounis Med J. 1998–2000; 19: 56–60.

Daniels, S. R. (2006) the consequences of childhood overweight and obesity. The Future of Children, vol. 16(1). Viewed online @ www.futureofchildren.org

Daniels, S. R., Arnett, D. K., Eckel, R. H., Gidding, S. S., Hayman, L. L., Kumanyika, S., Robinson, T. N., Scott, B. J., Jeor, S. S., & Williams, C. L. (2005) Prevention, and treatment of overweight in children and adolescents: pathophysiology and Consequences Circulation 2005;111,1999-2012

Davidson, M. & Knafl, K. A. (2006) Dimensional analysis of the concept of obesity. Journal of Advanced Nursing 54(3):342-350. Retrieved online at http://wwwingentaconnect.com/content/bsc/jan/2006

De Graaf L, Brouwers AHPM, Diemont WL. Is decreased libido associated with the use of HMG CoA- reductase inhibitors? Br J Clin Pharmacol.2004; 58(3):326-28.

de Ronde W, van der Schouw YT, Muller M, Grobbee DE, Gooren LJ, Pols HA, et al. Associations of sex hormone- binding globulin (SHBG) with non-SHBG-bound levels of testosterone and estradiol in independently living men. J Clin Endocrinol Metab 2005; 90(1): 157‑162.

Dennis, L. K., & Pollotta, S. L., (2001) Chronic disease in rural health, Handbook of Rural Health, p 189-207 New York: Kluwer Academic Plenum Publishers

Dhindsa S, Bhatia V, Dhindsa G, Chaudhuri A, Murthigollapudi G, Dandona P. The Effects if Hypogonadism on Body composition and bone mineral density in type 2 diabetic patients, Diabetes Care 2007; 30:7.

Dhindsa S, Prabhakar S, Sethi M, et al. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J.Clin Endocrinol Metab 2004; 89: 5462-8

Diabetes. TUE Physician guidelines medical information to support the decisions of TUE committees; June 2015.

Dilley, K. J., Martin, L.A., Sullivan, C., Seshadri, R., & Binn, H.J,. (2007) Identification of overweight status is associated with higher rates of screening for comorbidities of overweight in pediatric primary care. Pediatrics 119:148-155. Viewed online at http://www.pediatrics.org/cgi/content/full/ll9/1/e148

Dillman, D.A. (2007) Mail and internet Surveys: The Tailored Design Method 2007 Update with New Internet, Visual and Mixed Mode Guide. John Wiley & Sons, Viewed online 9/1/07 at http://www.diesel-ebooks.com/cgi-bin/chapter.

Dobs AS, Schrott H, Davidson MH, et al. Effects of high-dose simvastatin on adrenal and gonadal steriodogenesis in men with hypercholesterolemia. Metabolism.2000; 49(9):1234-38.

Dockery F, Bulpitt CJ, Agarwal S, Donaldson M, Rajkumar C, Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and Hyperinsulinaemia. Clinical Science 2003; 195-201.

Dorsey, K. B., Wells, C., Krumholtz, H. M., & Concato, J. C. (2005) Diagnosis, evaluation and treatment of childhood obesity in pediatric practice. Archive Pediatric and Adolescent Medicine 15(9):632-638.

Dunn JF, Nisula BC, Rodbard D. Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metab 1981; 53(1): 58‑68.

Dechaud H, Lejeune H, Garoscio-Cholet M,Mallein R, PugeatM(1989) Radioimmunoassay of testosterone not bound to sex-steroid-binding protein in plasma. Clin Chem 35:1609–1614

Derweesh IH, DiBlasio CJ, Kincade MC, Malcolm JB, Lamar KD, Patterson AL, Kitabchit AE, Wake RN. Risk of new-onset diabetes mellitus and worsening glycemic variables for established diabetes in men undergoing androgen-deprivation therapy for prostate cancer. BJU Int. 2007;100:1060–1065.

Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab. 2004;89: 5462–5468.

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;295:1288–1299.

Dockery F, Bulpitt CJ, Agarwal S, Donaldson M, Rajkumar C. Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. Clin Sci. 2003;104:195–201.

Droumaguet C, Balkau B, Simon D, Caces E, Tichet J, Charles MA, Eschwege E, the DESIR Study Group. Use of HbA1c in predicting progression to diabetes in French men and women: data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) Diabetes Care 2006; 29:1619–1625.

Dussault JH, Letarte J, Guyda H, Laberge C (1977) Serum thyroid hormone and TSH concentrations in newborn infants with congenital absence of thyroxine-binding globulin. J Pediatr 90:264–265.

Ekins R (1990) Measurement of free hormones in blood. Endocr Rev 11: 5–46
Esposito K, Ciotola M, Giuliano F, Schisano B, Improta L, Improta MR, Beneduce F, Rispoli M, DeSio M, Giuliano D. Endothelial microparticles correlate with erectile dysfunction in diabetic men. Int J Impot Res. 2007;19:161–166.

Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183–1197.

Ebrahim S, Casas JP. (2012, May 17). Statins for all by the age of 50 years? Lancet. Early Online Publication. Retrieved May 25, 2012 from this link.

Eissa, M. A. H., & Gunner, K. B., (2004) Evaluation and management of obesity in children and adolescents, Journal of Pediatric Health Care 18(1):35-38.
Evenson et al., 1993; Lin et al., 1995

Ford ES, Li C, Zhao G, Pearson WS, Mokdad AH. Prevalence of the metabolic syndrome among US adolescents using the definition from the international diabetes federation. Diabetes Care. 2008;31:587–589.

Freeman DA, Rommerts FFG (1996) Regulation of Leydig cell cholesterol transport. In: Payne AH, Hardy MP, Russell LD (eds) The Leydig cell. Cache River Press, Vienna, Il pp 232–239.

Fukui M, Soh J, Tanaka M, Kitagawa Y, Hasegawa G, Yoshikawa T, Miki T, Nakamura N. Low serum testosterone concentration in middle-aged men with type 2 diabetes. Endocr J. 2007;54:871–877.

Furuyama S, Mayes DM, Nugent CA (1970) A radioimmunoassay for plasma testosterone. Steroids 16:415–428

Farewell WR, Scranton RE, Lawler EV, et al. The association between statins and cancer incidence in veteran's populations. J Nal Cancer Inst.2008; 100(2): 134-39.

Feldman HA, et al. Age trends in the level of serum testosterone and other hormones in middle -aged men: Longitudinal results from the Massachusetts Male Aging Study. J Clin Endocrinoal Metab 2002; 87:589-98.

Festa A, D'Agostino Jr. R, Hanley AJG, Karter AJ, Saad MF, Haffner SM. Differences in Insulin Resistance in Nondiabetic Subjects With Isolated Impaired Glucose Tolerance or Isolated Impaired Fasting Glucose. Diabetes 2004, 53:1549-1555.

Fierro, M. P. with National Governors Association Center for Best Practices (2002) The Obesity Epidemic: how states can trim the fat. Viewed online @ www.nga.org

Fleqal KM, Carroll MD, Oqden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. JAMA. 2010;303:235–41.

Fleqal KM, Carroll MD, Oqden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. JAMA. 2010; 303: 235–41.

Flower, K. B., Perrin, E. M., Viadro, C. L., & Ammerman, A. S. (2007) Using body mass index to identify overweight children: barriers and facilitators in primary care. Ambulatory Pediatrics 7(1):38-44. Viewed 2/18/08 at http://www.pubmedcentral.nih.gov

Fontaine, K.R., & Barofsky, I,. (2001) Obesity and health-related quality of life, the International Association for the Study of Obesity: Obesity Reviews 2, 173-182. Retrieved octobe 1, 2006 from: http://www.lib.montan.edu/epubs/indexes/health.html

Food and Agriculture Organization of the United Nations – Food and Nutrition Division. Libyan Arab Jamahiriya; 2005. Nutrition Profile.

Food and Agriculture Organization of the United Nations – Food and Nutrition Division. Libyan Arab Jamahiriya. Nutrition Profile; 2005.

Food and Drug Administration (FDA). (2008). Making Sense of Vytorin Concerns. Retrieved May 19, 2012 from this link.

Food and Drug Administration (FDA). (2010). Controlling Cholesterol with Statins. Retrieved May 6, 2012 from this link.

Food and Drug Administration (FDA). (2012a). Zocor (simvastatin) tablets. Retrieved May 12, 2012 from this link.

Food and Drug Administration (FDA). (2012b). FDA Drug Safety Communication: Interactions between certain HIV or hepatitis C drugs and cholesterol-lowering statin drugs can increase the risk of muscle injury. Retrieved May 12, 2012 from this link.

Fowler-Brown, A., & Kahwati, L. C., (2004) Prevention and treatment in overweight in children and adolescents, American Family Physician 69:11 2591-2598. Viewed Online at http://www.aafp.org/afp.

Freedman, D.S., Dietz, W. H., Srinivasan, S.R., & Berenson, G. S., (1999) The relation Of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa heart study. Pediatrics 103:1175-1182. Viewed online at http://www.pediatrics.org/csi/content/full/103/6/1175

Gersh BJ, Sliwa K, Mayosi BM, Yusuf S. Novel therapeutic concepts: the epidemic of cardiovascular disease in the developing world: global implications. Eur Heart J 2010; 31(6): 642‑648.

Gillman MW, Rifas-Shiman SL, Camargo CA, Jr, Berkey CS, Frazier AL, Rockett HR, et al. Risk of overweight among adolescents who were breastfed as infants. JAMA. 2001; 285: 2461.

Giovanni Corona, Edoardo Mannucci, Luisa Petrone, Giancarlo Balercia, Francesco Lotti, Valerio Chiarini, Domenico Fedele, Gianni Forti, Mario Maggi, NCEP-ATPIII-Defined Metabolic syndrome, Type2 Diabetes Mellitus and Prevalence of Hypogonadism in male patients with sexual Dysfunction. Sex Med 2007; 4:1038-45.

Golan M., & Crow S. (2004) Targeting parents exclusively in the treatment of childhood obesity: Long term results. Obesity Research 12:357-361. Viewed online 8/28/07 http://www.obesityresearch.org/cgi/content/abstract/12/2/357.

Gray A, Feldman HA, McKinaly JB, Longcope C. Age, disease and changing sex hormone levels in middle- aged men: results of Massachusetts Male Aging Study. J Clin Endocrinol Metab 1991; 73:1016-25.

Geiss LS, Pan L, Cadwell B, Gregg EW, Benjamin SM, Engelgau MM. Changes in incidence of diabetes in U.S. adults, 1997– 2003. Am J Prev Med 2006;30:371–377

Genuth S, Alberti KG, Bennett P; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003; 26: 3160–7.

Ginsberg HN. Insulin resistance and cardiovascular disease. J Clin Invest. 2000;106:453–458.

Giuliano FA, Leriche A, Jaudinot EO, de Gendre AS. Prevalence of erectile dysfunction among 7689 patients with diabetes or hypertension, or both. Urology. 2004;64:1196–1201.

Gonzalez-Sagrado M, Martin-Gil FJ, Lopez-Hernandez S, Fernandez-Garcia N, Olmos-Linares A, Arranz-Pena ML (2000) Reference values and methods comparison of a new testosterone assay on the AxSYM system. Clin Biochem 33:175–179

Grossman M, Thomas MC, Panagiotopoulos S, Sharpe K, Macisaac RJ, Clark S, Zajac JD, Jerums G. Low testosterone levels are common and associated with insulin resistance in men with diabetes. J Clin Endocrinol Metab. 2008;93(5):1834–1840.
Gruenewald DA, Matsumoto AM. Testosterone supplementation therapy for older men: potential benefits and risks. J Am Geriatr Soc. 2003; 51:101–115.

Gustafson B, Hammarstedt A, Andersson CX, Smith U. Inflamed adipose tissue: a culprit underlying the metabolic syndrome and atherosclerosis. Arterioscler Thromb Vasc Biol. 2007;27:2276–2283.

Haffner SM, Shaten J, Stern MP, Smith GD, Kuller L. Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. MRFIT Research Group. Multiple Risk Factor Intervention Trial. Am J Epidemiol. 1996;143:889–897.

Haidar A, Yassin A, Saad F, Shabsigh R. Effects of androgen deprivation on glycaemic control and on cardiovascular biochemical risk factors in men with advanced prostate cancer with diabetes. Aging Male. 2007;10:189–196.

Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. J Clin Endocrinol Metab. 2001;86:724–731.

Haupt HA, Rovere GD (1984) Anabolic steroids: A review of the literature. Am J Sports Med 12:469–484

Hong CY, Park JH, Ahn RS, Im SY, Choi HS, Soh J, Mellon SH, Lee K. Molecular mechanism of suppression of testicular steroidogenesis by proinflammatory cytokine tumor necrosis factor alpha. Mol Cell Biol. 2004;24:2593–2604.

Hutson JC, Stocco DM, Campbell GT, Wagoner J. Sertoli cell function in diabetic, insulin-treated diabetic, and semi-starved rats. Diabetes. 1983;32:112–116.

Haffner SM, et al. Decreased sex hormone-binding globulin predicts non insulin-dependent diabetes mellitus in women but not in men. J Clin Endocrinol Metab 1993; 77:56-60.

Haffner SM, et al. Low levels of sex hormone- binding globulin and testosterone predict the development of non insulin dependent diabetes mellitus in men. MRFIT Research Group. Multiple Risk Factor Intervention Trial. Am J Epidemiol 1996; 13:889-97.

Halperin RO, Sesso HD, Ma J, Buring JE, Stampfer MJ, Gaziano M. Dyslipidemia and the risk of incident hypertension in men. Hypertension 2006; 47: 45–50.

Harder T, Bergmann R, Kallischnigg G, Plagemann A. Duration of breastfeeding and risk of overweight: a meta-analysis. Am J Epidemiol. 2005;162:397.

Hawley, S. R., Bishop, H. and Beckman, J. (2006) Development of obesity prevention and management program for children and adolescents in rural setting. Journal of Community Health Nursing, 23(2), 69-80.

Heart Protection Study Collabrative Group. MRC/BHF Heart Protection Study (HPS) of cholesterol lowering with simvastatin in 20,536 high- risk individuals: a randomized placebo-controlled trial. Lancet 2002; 360:7-22.

Hediger ML, Overpeck MD, Kuczmarski RJ, Ruan WJ. Association between infant breastfeeding and overweight in young children. JAMA. 2001;285:2453.

Hedley, A.A., Ogden, C.L., Johnson, C.C., Carroll, M. B., Curtin, L. R., Flegal, K.M (2004) Prevalence of overweight and obesity among US children, adolescents and adults 1999-2000. JAMA 291: 2847-2850.

Hofman A, Darwish Murad S, van Duijn CM, Franco OH, Goedegebure A, Ikram MA, et al. The Rotterdam Study: 2014 objectives and design update. Eur J Epidemiol 2013; 28(11): 889‑926.

Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol 1991; 7(4): 403‑422.http://www.quirks.com/articles/a2001/20010703

International Association for the Study of Obesity. Global prevalence of adult obesity.http://www.iaso.org/site_media/uploads/GlobalPrevalence_of_Adult_Obesity_January_2011.pdf[cited 30 June 2012].

International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327– 1334

Isidori AM, Caprio M, Strollo F, Moretti C, Frajese G, Isidori A, Fabbri A. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. J Clin Endocrinol Metab. 1999;84:3673–3680.

Isidori AM, Strollo F, More M, Caprio M, Aversa A, Moretti C, Frajese G, Riondino G, Fabbri A. Leptin and aging: correlation with endocrine changes in male and female healthy adult populations of different body weights. J Clin Endocrinol Metab. 2000;85:1954–1962.

Jackson, J. E., Doescher, M. P., Jerant, A. F., & Hart, L. G. (2005) A national study of obesity prevalence and trends by type of rural county. Journal of Rural Health, 21(2), p.140-148.

Jackson, J. E., Doescher, M. P., Saver, B. G., & Hart, L. G. (2005) Trends in professional advice to lose weight among obese adults 1994-2000. Journal of General Internal Medicine, 20:814-818. 84 JAMA 295:1549-1555. Retrieved online 8/15/07. at http://www.jama.ama-ssn.org/cgi/content/abstract/295/13/1549?maxtoshow .

Jockenhovel F, Krusemann C, Jaeger A, Olbricht T, Reinwein D (1992) Comparability of serum testosterone determinationwith the ten most commonlyused commercial radioimmunoassays and with a new enzyme immunoassay. Klin Lab 38: 81–88.

Jazet IM, Pijl H, Meinders AE. Adipose tissue as an endocrine organ: impact on insulin resistance. Neth J Med 2003, 61:194-212.

Jockenhovel F,Blun WF, Vogel E, E nglaro P, Muller Wieland D, Reinvein D, et al. Testosterone substitution normalizes elevated serum leptin levels in hypogonadal men. Journal of Clinical Endocrinology and Metabolism 1997; 82:2510-13. Kaiser State Health Facts@www.statehealthfacts.org

Kenning I, Kerandi H, Luehr D, Margolis K, O'Connor P, Pereira C, Schlichte A, Woolley T. Institutefor Clinical Systems Improvement. Hypertension Diagnosis and Treatment. Updated November 2014 Abate N, et al. Sex steroid hormones, upper body obesity, and insulin resistance. *J* Clin Endo Metab 2002; 87:4522-27.

Kanat M, Serin E, Tunckale A, et al. A multi-center, open label, cross over designed prospective study evaluating the effects of lipid lowering treatment on steroid synthesis in patients with type 2 diabetes (MODEST Study) J Endocrinol Invest. 2009; 32(10):852-56.

Kapoor D, Aldred H, Clark S, Kevin S. Channer, Hugh JT, Clinical and Biochemical Assessment of Hypogonadism in men with type 2 diabetes, Diabetes Care 30 (4) April 20.

Kapoor D, Clarke S, Stanworth R, Channer KS, Jones TH. The effect of testosterone replacement therapy on adipokines and C-reactive protein in hypogonadal men with Type 2 diabetes. European Journal of Endocrinology 2007;156:595-602.

Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance glycemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. European Journal of Endocrinology 2006; 154:899-906.

Kapoor D, Malkin CJ. Channer KS, Jones TH. Androgens insulin resistance and vascular disease in men. Clinical Endocrinology 2005:239-50.

Kelishadi R. Childhood overweight, obesity and the metabolic syndrome in developing countries. Epidemiologic Reviews, 2007, 29:62–76.

Kenning I, Kerandi H, Luehr D, Margolis K, O'Connor P, Pereira C, Schlichte A, Woolley T. Institute for Clinical Systems Improvement. Hypertension Diagnosis and Treatment. Updated November 2014.

Khan T, Hamilton MP, Mundy DI, Chua SC, Scherer PE. Impact of simvastatin on adipose tissue: pleiotropic effects in vivo. Endocrinology 2009;150:5262e5272.

Kimbro, R. T., Brooks-Gunn, J. & McLanahan, S. (2007) Racial and ethnic differential in overweight and obesity among 3 year old children. American Journal of Public Health. 97(2):298-305.

Klinefelter GR, Laskey JW, Amann RP. Statin drugs markedly inhibit testosterone production by rat Leydig cells in vitro: Implications for men. Reprod Toxicol 2014; 45C: 52‑58.

Kocum TH, Ozcan TI, Gen R, et al. Does atorvastatin affect androgen levels in men in the era of very –low LDL targeting therapy? Exp Clin Endocrinol Diabetes. 2009; 117(2):60-63.

Krishnamoorthy, J. S., Hart, C., & Jelalian, E. (2006) The epidemic of childhood obesity: Review of research and implications for public policy. Society for Research in Child Development, Social Policy Report XX(II).

Krysiak R, Labuzek K, Okopien B. Effect of atorvastatin and fenofibric acid on adipokine release from visceral and subcutaneous adipose tissue of patients with mixed dyslipidemia and normolipidemic subjects. Pharmacol Rep 2009;61:1134e1145.

Kumanyika, S., & Grier, S. (2006) Targeting interventions for ethnic minority and low income populations. The Future of Children 16:1. Retrieved online 3/20/07 from www.futureofchildren.org.

Kalinchenko SY, Kozlov GI, Gontcharov NP, Katsiya GV. Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. Aging Male. 2003;6:94–99.

Kapoor D, Aldred H, Clark S, Channer K, Jones T. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes. Diabetes Care. 2007;30:911–917.

Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol. 2006;154: 899–906.

Khaodhiar, L., S. Cummings, and C.M. Apovian, Treating diabetes and prediabetes by focusing on obesity management. Curr Diab Rep, 2009. 9(5): p. 348-54.

King SR, Manna, PR, Ishii T, Syapin PJ, Ginsberg SD, Wilson K, Walsh LP, Parker KL, Stocco DM, Smith, RG, Lamb DJ (2002) An essential component in steroid synthesis, the steroidogenic acute regulatory protein, is expressed in discrete regions of the brain. J Neurosci 22: 10613–10620.

Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.

Kovanecz I, Ferrini MG, Vernet D, Nolazco G, Rajfer J, Gonzalez- Cavadid NF. Pioglitazone prevents corporal veno-occlusive dysfunction in a rat model of type 2 diabetes mellitus. BJU Int. 2006;98:116–124.

L. A. Loomba-Albrecht and D. M. Styne. "Effect of puberty on body composition," Current Opinion in Endocrinology. Diabetes and Obesity, vol. 16, no. 1, pp. 10–15, 2009.

Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Salonen R, Rauramaa R, Salonen JT. Sex hormones, inflammation and the metabolic syndrome: a population-based study. Eur J Endocrinol. 2003;149:601–608.

Lage MJ, Barber BL, Markus RA. Association between androgendeprivation therapy and incidence of diabetes among males with prostate cancer. Urology. 2007;70:1104–1108.

Landon MB, Spong CY, Thom E, CarpenterMW, Ramin SM, Casey B, Wapner RJ, Varner MW, Rouse DJ, Thorp JM, Jr., Sciscione A, Catalano P, Harper M, Saade G,

Lain KY, Sorokin Y, Peaceman AM, Tolosa JE, Anderson GB. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009; 361:1339–1348.

Lebovitz, H.E., Present recommendations in type 2 diabetes treatment. Endocrinol Nutr, 2009. 56S4: p. 46-49.

Lee, H. J., & Winters, C. A. (2006) Rural nursing: concepts, theory, and practice . New York: Springer Publishing Company.

Leite-Moreira AF, Castro-Chaves P. Heart failure: statins for all? Heart 2006; 92: 1537-38.

Leslie, W. S., Hankey, R., McCombie, L., & Lean, M. J., (2004) Weight management: a survey of current practice in secondary care NHS setting in 2004. Journal of Evaluation in Clinical Practice, 11(5):462-467.

Lewis, R. D., Meyer, M. C., Lehman, S. C., Trowbridge, F. L., Bason, J. J., Yurman, K. H., & Yin, Z., (2006) Prevalence and degree of childhood and adolescent overweight in rural, urban and suburban Georgia. Journal of School Health .

Licinio J, Caglayan S, Ozata M, Bulent O Yildiz, Particia B, De Miranda, Fiona O' Kirwan Phenotypic effects of leptin replacement on morbid obesity, diabetes mellitus, hypogonadism and behavior in leptin-deficient adults. PNAS; March 30, 2004; 101:4531-6.

Lieberman LS. Dietary, evolutionary, and modernizing influences on the prevalence of type 2 diabetes. Annu Rev Nutr 2003; 23: 345‑377.

Lobstein T., Baur L., & Uauy R., (2004) International obesity task force, obesity in Children and young people: a crisis in public health. Obesity Review Suppl.1:4- 104.

Lombard, K. A., Forster-Cox, S., & O'Neil, M. K. (2006) Diabetes on the Navajo Nation: what role can gardening and agriculture extension play to reduce it. Remote and Rural Health, 6:640

Loue, S., & Quill, B.E., (2001) Handbook of Rural Health New York :Kluwer/Plenum Publishers

Ludwig, D. S. (2007) Childhood obesity the shape of things to come. New England Journal of Medicine 357:23. Viewed at www.nejm.org

Lindmark S, Burein J, Ericksson JW. Insulin resistance, endocrine function and adipokines in type 2 diabetes patients at different glycemic levels: potential impact for glucotoxicity in vivo. Clin Endocrinol. 2006;65:301–309.

Luukkaa V, Pesonen U, Huhtaniemi I, Lehtonen A, Tilvis R, Tuomilehto J, Houlu M, Huupponen R. Inverse correlation between serum testosterone and leptin in men. J Clin Endocrinol Metab. 1998;83:3243–3246.

M. A. Boyanov, Z. Boneva* and V. G. Christov Endocrinology Clinic, Alexandrovska Hospital, Medical University of Sofia, Sofia; *Endocrinology Unit, InternalDepartment, Central Police Hospital, Sofia, BulgariaThe Aging Male 2003;6:1–7

Maggio M, Basaria S, Ceda GP, Ble A, Ling SM, Bandinelli S, Valenti G, Ferrucci L. The relationship between testosterone and molecular markers of inflammation in older men. J Endocrinol Invest. 2005;28(11 suppl proceedings):116–119.

Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. J Clin Endocrinol Metab. 2004;89:3313–3318.

Manni A,Pardridge WM, CefaluW, Nisula BC, Bardin CW, Santner SJ, Santen RJ (1985) Bioavailability of albumin-bound testosterone. J Clin Endocrinol Metab 61:705–710

Matsumoto AM. 2002. Andropause: clinical implications of the decline in serum testosterone levels with aging in men. Journals of Gerontology. Series A, Biological Sciences & Medical Sciences 57(2):M76–M99.

Mazur, A., & Booth, A. (1998). Testosterone and dominance in men. Behavioral & Brain Sciences, 21, 353-397.

Mealey BL and Ocampo GL. Diabetes mellitus and periodontal disease. Periodontology 2000 2007; 44: 127–153

Mendel CM (1992) The free hormone hypothesis. Distinction from the free hormone transport hypothesis. J Androl 13:107–116

Mendel CM, Murai JT, Siiteri PK, Monroe SE, Inoue M (1989) Conservation of free but not total or non-sex-hormone-binding-globulin-bound testosterone in serum from Nagase analbuminemic rats. Endocrinology 124:3128–3130

Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva A, Hod M, Kitzmiler JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010; 33:676 – 682

Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002

Mooradian A. D., Morley J. E., Korenman S. G. Biological actions of androgens. Endocr Rev. 1987;8:1–28

Morimoto S, Mendoza-Rodrı´guez CA, Hiriart M, Larrieta ME, Vital P, Cerbo´n MA. Protective effect of testosterone on early apoptotic damage induced by streptozotocin in rat pancreas. J Endocrinol. 2005;187:217–224.
Morley JE, Patrick P, Perry HM3rd (2002) Evaluation of assays available to measure free testosterone. Metabolism 51:554–559

Muller M, Grobbee DE, den Tonkelaar I, Lamberts SW, van der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men. J Clin Endocrinol Metab. 2005;90:2618–2623.

Makhsida N, Shah J, Yan G, Fisch H, Shabsingh R. Hypogonadism and metabolic syndrome implications for testosterone therapy. Urol 2005; 174:827-34. Marin P, et al. Androgen treatment of abdominally obese men. Obes Res 1993; 1:245-51.

Maternal and Child Health needs Assessment viewed online 2-23-07 http://perfdata.hrsa.gov/mchb/mchreports/documents/needsassessments/2006/MT-needsassessment.pdf

Matsumoto AM, Sandblom RE, Schoene RB, Lee KA, Gibilin EC, Pierson DJ, Bremner WJ. Testosterone replacement in hypogonadal men: effects on obstructive sleep apnoea, respiratory drives and sleep. Clin Endocrinol (Oxf) 1985; 22:713-21.

Medlin, B. & Whitten, D. (2001) A comparison of internet and mail survey Methodologies, Quirks Marketing Research Review July/August 2001.

Miedema AMD, Lopez FL, Blaha MJ. Eligibility for statin therapy according to new cholesterol guidelines and prevalent use of medication to lower lipid levels in an older US cohort: The atherosclerosis risk in communities study cohort. JAMA Intern Med 2015;175(1):138-140.

Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012; 380(9841): 581‑590.

Mihos CG, Pineda AM, Santana O. Cardiovascular effects of statins, beyond lipid-lowering properties. Pharmacol Res 2014;88:12e19.

Miller WL, Bose HS. Early steps in steroidogenesis: intracellular cholesterol trafficking. J Lipid Res 2011;52(12): 2111-2135.
Ministry of Health-Libya. Tripoli: Ministry of Health-Libya; 2008. Pan Arab project for family health. National Survey of Family Health.

Ministry of Health-Libya. Tripoli: Ministry of Health-Libya; 2009. National Survey of Non-Communicable Disease Risk Factors.

Mlalkin CJ, Pugh PJ, Kapoor, Jones RD,Channer KS, Jones TH. The effect of testosterone replacement in endogenous inflammatory cytokines and lipid profiles in hypogonadal men. Journal of Clinical Endocrinology and Metabolism 2004; 3313-18.

Mohr BA, Guay AT, O'Donnell AB, McKinlay JB. Normal, bound and nonbound testosterone levels in normally ageing men: results from the Massachusetts Male Ageing Study. Clin Endocrinol. 2005;62(1):64-7

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002 Jul 6;360(9326):7-22.Heart Protection Study Collaborative Group.

Muhamad Jawad Sethi , MD and William P.Newmann, MD. Effect of statins on total testosterone levels in male veterans. Federal Practitioner; Sept 2012:35-38.

Mulligan T, Frick MF, Zuraw QC, Stemhangen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: The HIM study. Int J Clin Prac. 2006; 60(7):762-69.

Murray, C. L, Kulkarni, S., & Ezzati, M. (2005) Eight Americas: new perspectives on US health disparities. American Journal of Preventative Medicine, 25(581)
Najah A. 1995. Effect of nutritional and other factor on heart disease. Master Degree, Faculty of Agriculture, AL-Fateh University, Libya

Mooradian A. D., Morley J. E., Korenman S. G. Biological actions of androgens. Endocr Rev. 1987;8:1–28.

Najem FI, Elmehdawi RR, Swalem AM. Clinical and biochemical characteristics of polycystic ovary syndrome in Benghazi-Libya: a retrospective study. Libyan J Med. AOP: 071018.

National Heart, Lungs & Blood Institute (2006) The Clinical Guidelines on the Identification, Education and Treatment of Overweight and Obesity In Adults: The Evidence Report. Retrieved September 18, 2006 from http://www.nhlbi.nih.gov/guidelines/obesity/ob-guidelines

National Initiative for Children's Healthcare Quality (2007) Expert Committee Recommendations on the Assessment, Prevention and Treatment of Child and Adolescent Overweight and Obesity. Viewed online 11/10/2007 at www.ama-assn.org/ama/pub/category/11749.html

National Institute of Health Strategic Plan for Obesity Research (2004) viewed online @ http://obesityresearch.nih.gov

Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am J Hum Genet. 1962;14:353–62

Nelson, M. C., Gordon-Larson, P., Song, Y., & Popkin, B. M. (2006) Built and social environments: associations with adolescents overweight and activity. American Journal of Preventative Medicine 31(2):109-117. Viewed online 8-12-07 at www.ajpm_online.net

Neumark-Sztainer, D. & Hannan, P. J. (2000) Weight related behavior among adolescent girls and boys. Archive of Pediatric Adolescent Medicine: 154,569-577.

Neumark-Sztainer, D., Faulkner, N., Story, M., Perry, C., Hannan, P.J., & Mulert, S. (2002) Weight, teasing among adolescents: correlations with weight status & disordered early behaviors. International Journal of Obesity:26,123-131.

Nieschlag E, Behre H, Nieschalg S. Testosterone: action, deficiency, substitution, Cambridge: Cambrige University Press,2004.

Nieschlag E, Behre HM (eds). Andrology: male reproductive health and dysfunction. 3rd edn.Heidelberg,Springer,2010

Nishio E, Tomiyama K, Nakata H, Watanabe Y. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitor impairs cell differentiation in cultured adipogenic cells (3T3-L1). Eur J Pharmacol 1996;301:203e206.

Nissen SE, Nicholls SJ, Sipahi I, et al. (2006). Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 295(13):1556–65.

Naharci MI, Pinar M, Bolu E, Olgun A. Effect of testosterone on insulin sensitivity in men with idiopathic hypogonadotropic hypogonadism. Endocr Pract. 2007;13:629–635.

Nielsen TL, Hagen C, Wraae K, Brixen K, Petersen PH, Haug E, Larsen R, Andersen M. Visceral and subcutaneous adipose tissue assessed by magnetic resonance imaging in relation to circulating androgens, sex hormone-binding globulin, and luteinizing hormone in young men. J Clin Endocrinol Metab. 2007;92: 2696–2705.

Nishiyama T, Ishizaki F, Anraku T, Shimura H, Takahashi K. The influence of androgen deprivation therapy on metabolism in patients with prostate cancer. J Clin Endocrinol Metab. 2005;90: 657–660.

Norata GD, Tibolla G, Seccomandi PM, Poletti A, Catapano AL. Dihydrotestosterone decreases tumor necrosis factor-alpha and lipopolysaccharide-induced inflammatory response in human endothelial cells. J Clin Endocrinol Metab. 2006;91:546–554.

Oltmanns KM, Fruehwald-Schultes B, Kern W, Born J, Fehm HL, Peters A. Hypoglycemia, but not insulin, acutely decreases LH and T secretion in men. J Clin Endocrinol Metab. 2001;86:4913–4919.

Osuna JA, Gomez-Perez R, Arata-Bellabarba G, Villaroel V. Relationship between BMI, total testosterone, sex hormonebinding- globulin, leptin, insulin and insulin resistance in obese men. Arch Androl. 2006;52:355–361.

Ogden, C. L., Carroll, M. D., Curtin, L. R., McDowell, M. A., Tabak, C. J., & Flegal, K. M. (2006) Prevalence of overweight and obesity in the United States, 1999-2004,

Ogden, C.L., Flegal, K. M., Carroll, M.D. & Johnson C. L, (2002) Prevalence and trends in overweight among US children and adolescents 1999-2000. JAMA 288: 1728-1732.

Oliver, J., & Lee, T.,, (2005) Public opinion and the politics of obesity in America, Journal of Health Politics Policy and Law, 30(5).

Omran Bakoush and Targ Elmran Bakoush Do we have a diabetes epidemic in Libya Libyan J Med. 2006; 1(2): 123–1

Ormiston T, Wolkowitz OM, Reus VI, Johnson R,Manfredi F. Hormonal changes with cholesterol reduction: A double-blind pilot study. J Clin Pharm Ther.2004;29(1):71-73.

Obesity Reviews, 7, 271-293. Retrieved October 1, 2006 from: http://www.lib.montan.edu/epubs/indexes/health.html

Paresh Dandona, Sandeep Dhindsa, Anil Chandl, Shehzad Topiwala-Low testosterone in men with T2DM- a growing public health concern; Diabetic voice. June 2009; 54(2):27-29.

Pasquali R , et al. Insulin regulates testosterone and sex hormone-binding globulin concentrations in adult normal weight and obese men. J Clin Endocrinol Metab 1995; 80:654-835.

Patterson, P.D., Moore, C., Probst, J., & Shinogle, J.A.(2004). Obesity and physical inactivity in rural America. The Journal of Rural Health, 20(2), p. 151-159. Retrieved October 1, 2006 from: http://www.lib.montan.edu/epubs/indexes/health.html

Paxson, C. Donahue, E., Orleans, C. T., & Grisso, J. A. (2006) Childhood obesity: The future of children 16(1). Retrieved online 3/20/07 at www.futureofchildren.org

Plymate SR, Matej LA, Jones RE, Fried KE. Inhibition of sex hormone binding globulin production in the human heptamo (Hep G2) cell line by insulin and Prolactin. J Clin Endocrinol Metab 1988; 67: 460-64.

Polit, D. F. & Beck, C. T., (2004) Nursing research: Principals and methods, (7th ed.) Philadelphia: Lippincott Williams & Wilkins

Polley, D. C., Spicer, M. T., & Knight, A. P. Hartley, B. L. (2005) Interfamilial correlates of overweight and obesity in African American and Native American grandparents, parents and children in rural Oklahoma. Journal of American Dietetic Association 105:262-265.

Popkin, B.M., Kim, D., Rusev, E.R., Du, S. & Zizza, C., (2006) Measuring the full Economic costs of diet, physical activity and obesity-related chronic diseases.

Pagotto U, Gambineri A, Pelusi C, Genghini S, Cacciari M, Otto B, Castaneda T, Tschop M, Pasquali R. Testosterone replacement therapy restores normal ghrelin in hypogonadal men. J Clin Endocrinol Metab. 2003;88:4139–4143.

Pan CY, So WY, Khalid BA ; ASDIAB Study Group. Metabolic, immunological and clinical characteristics in newly diagnosed Asian diabetes patients aged 12–40 years. Diabet Med 2004; 21: 1007–13.

Parazzini F, Menchini Fabris F, Bortolotti A, Calabro A, Chatenoud L, Colli E, Landoni M, Lavezzari M, Turchi P, Sessa A, Mirone V. Frequency and determinants of erectile dysfunction in Italy. Eur Urol. 2000;37:43–49.

Parikh NI, Pencine MJ, Wang TJ, Lanier KJ, Fox CS, d'Agostino RB, Ramachandran SV. Increasing trends in incidence of overweight and obesity over 5 decades. Amer J Med. 2007;120:242–250.

Park K, Ku JH, Kim SW, Paick JS. Risk factors in predicting a poor response to sildenafil citrate in elderly men with erectile dysfunction. BJU Int. 2005;95:366–370.

Pasquali R, Casimirri F, Cantobelli S, Melchionda N, Morselli Labate AM, Fabbri R, Capelli M, Bortoluzzi L. Effect of obesity and body fat distribution on sex hormones and insulin in men. Metabolism. 1991;40:101–104.

Pasquali R, Casimirri F, De Iasio R, Mesini P, Boschi S, Chierici R, Flamia R, Biscotti M, Vicennata V. Insulin regulates testosterone and sex hormone-binding globulin concentrations in adult normal weight and obese men. J Clin Endocrinol Metab. 1995;80:654–658.

Pasquali R, Macor C, Vicennati V, Novo F, De Lasio R, Mesini P, Boschi S, Casimirri F, Vettor R. Effects of acute hyperinsulinemia on testosterone serum concentrations in adult obese and normalweight men. Metabolism. 1997;46:526–529.0.

Pereira MA, Jacobs DR Jr, Van Horn L, Slattery ML, Kartashov AI, Ludwig DS: Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA Study. JAMA 287:2081–2099, 2002.
Perry R, Baron A: Impaired glucose tolerance. Why is it not a disease? Diabetes Care, 1999; 22: 883–84

Pick A, Clark J, Kubstrup C et al: Role of apoptosis in failure of b-cell mass compensation for insulin resistance and b-cell defects in the male Zucker diabetes fatty rat. Diabetes, 1998; 47: 358–64

Pitteloud N, Dwyer AA, DeCruz S, Lee H, Boepple PA, Crowley WF Jr, Hayes FJ. Inhibition of luteinizing hormone secretion by testosterone in men requires aromatization for its pituitary but not its hypothalamic effects: evidence from the tandem study of normal and gonadotropin-releasing hormone-deficient men. J Clin Endocrinol Metab. 2008;93:784–791.

Pitteloud N, Hardin M, Dwyer AA, Valassi E, Yialamas M, Elahi D, Hayes FJ. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. J Clin Endocrinol Metab. 2005a;90:2636–2641.

Pitteloud N, Mootha VK, Dwyer AA, Hardin M, Lee H, Eriksson KF, Tripathy D, Yialamas M, Groop L, Elahi D, Hayes FJ. Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. Diabetes Care. 2005b;28: 1636–1642.

Ponholzer A, Temml C, Mock K, Marszalek M, Obermayr R, Madersbacher S. Prevalence and risk factors for erectile dysfunction in 2869 men using a validated questionnaire. Eur Urol. 2005;47:80–86.

Pugeat MM, Dunn JF, Nisula BC (1981) Transport of steroid hormones: interaction of 70 drugs with testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metab 53: 69–75

Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344(8934): 1383-1389.

Rao GM, Morghom LO. Prevalence of obesity in Libyan diabetic patients. Garyounis Med J.1985;8:115–21.

Ray KK, Kastelein JJ, Matthijs Boekholdt S, Nicholls SJ, Khaw KT, Ballantyne CM, et al. The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the

uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011. Eur Heart J 2014; 35(15): 960‑968.

Redmond GP. Androgens and women's health. Int J fertility women's Med 1998; 43(2): 91‑97.

Reilly J. J., Armstrong, J., Dorosty, A. R., Emmett, P.R., Ness, A., Rodgers, I, Steer, C., & Stewart, A., (2005). Early life risk factors for obesity in childhood: a cohort study. BMJ 330:1357. Viewed online at http://www.bmj.com/cgi/content/full/330/7504/1357?ehom

Robinson, T. N. (1999) Reducing children's television viewing to prevent obesity: randomized controlled trial. JAMA 282:1561-1567.

Rural Assistance Center (2007) What is rural. Viewed online 3/24/07 at www.raconline.org/info_guides/ruraldef

Rural Assistance Center (2008) Rural Health Disparities, viewed online 2/21/08 At www.raconline.org/info_guides/disparities

Rural Healthy People 2010 reviewed online 10-12-06 at http://www.srph./hsc.edu/centers/rhp2010/publications.htm

Rader DJ. Effect of insulin resistance, dyslipidemia, and the intraabdominal adiposity on the development of cardiovascular disease and diabetes mellitus. Amer J Med. 2007;120:512–518.

Raivio T, Palvimo JJ, Dunkel L, Wickman S, Janne OA (2001) Novel assay for determination of androgen bioactivity in human serum. J Clin Endocrinol Metab 86: 1539–1544

Rao RM, Jo Y, Leers-Sucheta S, Bose HS, Miller W, Azhar S, Stocco DM (2003) Differential regulation of steroid hormonebiosynthesis in R2C and MA-10 Leydig tumor cells: Role of SR-B1- mediated selective cholesteryl ester transport. Biol Reprod 68:114–121

Rhoden EL, Ribeiro EP, Riedner CE, Teloken C, Souto CA. Glycosylated haemoglobin levels and the severity of erectile function in diabetic men. BJU Int. 2005;95:615–617.

Roger D. Stanworth, Bmedsci. Dheeraj Kapoor,MD. Kevin S. Channer,MD. DIABETES CARE, VOLUME 32, NUMBER 4, APRIL 2009

Robert ER; Type 2 Diabetes Mellitus: The Grand Overview. Diabet. Med. 1998:15 (Suppl. 4): S4–S7

Romeo JH, Seftel AD, Madhun ZT, Aron DC. Sexual function in men with diabetes type 2: association with glycemic control. J Urol. 2000;163:788–791.
Rosenbloom A, Jol J, Young R, Winter W: Emerging epidemic of Type- 2 diabetes in youth. Diabetes Care, 2001; 22: 867–71

Rosner W, Hryb DJ, Khan MS, Nakhla AM, Romas NA (1999) Sex hormone-binding globulin mediates steroid hormone signal transduction at the plasma membrane. J Steroid Biochem Mol Biol 69:481–485

Rosner W. 1972. A simplified method for the quantitative determination of testosteroneestradiol binding globulin activity in human plasma. Journal of Clinical Endocrinology and Metabolism 34(6):983–988.

Rosner W. 2001. An extraordinarily inaccurate assay for free testosterone is still with us. Journal of Clinical Endocrinology and Metabolism 86(6):2903.

Raivio T, Palvimo JJ, Dunkel L, Wickman S, Janne OA (2001) Novel assay for determination of androgen bioactivity in human serum. J Clin Endocrinol Metab 86: 1539–1544

Rao RM, Jo Y, Leers-Sucheta S, Bose HS, Miller W, Azhar S, Stocco DM (2003) Differential regulation of steroid hormonebiosynthesis in R2C and MA-10 Leydig tumor cells: Role of SR-B1- mediated selective cholesteryl ester transport. Biol Reprod 68:114–121

Rhoden EL, Ribeiro EP, Riedner CE, Teloken C, Souto CA. Glycosylated haemoglobin levels and the severity of erectile function in diabetic men. BJU Int. 2005;95:615–617.

Robert ER; Type 2 Diabetes Mellitus: The Grand Overview. Diabet. Med. 1998:15 (Suppl. 4): S4–S7

Romeo JH, Seftel AD, Madhun ZT, Aron DC. Sexual function in men with diabetes type 2: association with glycemic control. J Urol. 2000;163:788–791.

Rosenbloom A, Jol J, Young R, Winter W: Emerging epidemic of Type- 2 diabetes in youth. Diabetes Care, 2001; 22: 867–71

Rosner W, Hryb DJ, Khan MS, Nakhla AM, Romas NA (1999) Sex hormone-binding globulin mediates steroid hormone signal transduction at the plasma membrane. J Steroid Biochem Mol Biol 69:481–485

Rosner W. 1972. A simplified method for the quantitative determination of testosteroneestradiol binding globulin activity in human plasma. Journal of Clinical Endocrinology and Metabolism 34(6):983–988.

Rosner W. 2001. An extraordinarily inaccurate assay for free testosterone is still with us. Journal of Clinical Endocrinology and Metabolism 86(6):2903.

Sallis, J. F. & Glanz, K. (2006) The Role of built environments in physical activity, eating and obesity in childhood. The future of our Children, vol. 16:1 @ http://www.aecf.org

Sarkar NN. Hormonal profiles behind the heart of a man. Cardiol J.2009; 16(4):300-306.

Scandanavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Study (4S). Lancet. 1994; 344:1383-89.

Scharff, J. E. (2006) The distinctive nature and scope of rural nursing practice: philosophical bases as taken from Rural Nursing: Concepts, Theory, and Practice, p. 179-204. New York: Springer Publishing Company.

Scott, J. G., Cohen, D., DiCicco-Bloom, B., Orzano, A. J., Gregory, P., Flocke, S. A., Maxwell, C., & Crabtree, B., (2004) Speaking of weight: how patients and primary care clinicians initiate weight loss counseling. Preventative Medicine 38: 819-827. Viewed online at www.elsevier.com/locate/ypmed.

Seldon, T. M. (2006) Compliance with well child visit recommendations: evidence from The medical expenditure panel survey, 2000-2002. Pediatrics 118:1766-1778. Retrieved online 8/13/07 at http://www.pediatrics.org/cgi/content/full/118/6/e1766

SelvinE, Feinbib M, Zhang Lei, Rohrmenr S, Rifal N, Nelson WG, et al. Androgen and diabetes in men. Diabetes care 2007; 30:234-38.

Shalet SM. Normal testicular function and spermatogenesis. Pediatr Blood Cancer 2009; 53(2): 285‑288.

Sheriff DS Statin Therapy - Is Hypogonadism a Cause for Concern?. Endocrinol Metab Syndr 2015; 4: 208. doi:10.4172/2161-1017.1000208

Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. Arch Intern Med.2006; 166(15):1660-65.

Simoni M, Baraldi E, Baraghini GF, Boraldi V, Roli L, Seghedoni S, Verlardo A, Montanini V (1988) Twenty-four-hour pattern of plasma SHBG, total proteins and testosterone in young and elderly men. Steroids 52:381–382

Simoni M, Montanini V, Fustini MF, Del Rio G, Cioni K, Marrama P (1992) Circadian rhythm of plasma testosterone in men with idiopathic hypogonadotrophic hypogonadism beforeand during pulsatile administration of gonadotropin-releasing hormone. Clin Endocrinol 36: 29–34

Smals AG, Weusten JJ, Benraad TJ, Kloppenborg PW. The HMG-CoA reductase inhibitor simvastatin suppresses human testicular testosterone synthesis in vitro by a selective inhibitory effect on 17-ketosteroidoxidoreductase enzyme activity. J Steroid Biochem Mol Biol 1991; 38(4): 465‑468.

Stanworth RD, Channer KS, Kapoor D, Jones TH. Statin therapy is associated with lower total but not bioavailable or free testosterone in men with type 2 diabetes. Diabetes Care. 2009; 32(4):541-546.

Stern MP, Fatehi P, Williams K, Haffner SM. Predicting Future Cardiovascular Disease:Do we need the oral glucose tolerance test? Diabetes Care. 2002, 25:1851-1856.

Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013.

Strauss, R. S., & Pollack, H. A. (2003) Social Marginalization of overweight children Archives of Pediatric and Adolescent Medicine 157:746-752 Viewed online 10/2007 at www.archpedi.ama-assn.org/cgi/conten/full/157/8/746?chk=nck

Sung BH, Izzo JL Jr, Wilson MF. Effects of cholesterol reduction on BP response to mental stress in patients with high cholesterol. Am J Hypertens 1997; 10: 592–599.
Rader DJ. Effect of insulin resistance, dyslipidemia, and the intraabdominal adiposity on the development of cardiovascular disease and diabetes mellitus. Amer J Med. 2007;120:512–518.

Traish AM, Guay AT, Feeley R, Saad F. The dark side of testosterone deficiency: I. Metabolic syndrome and erectile dysfunction. J Androl. 2009;30(1):10–22.
Traish AM, Saad F, and Guay A.The Dark Side of Testosterone Review Deficiency: II. Type 2 Diabetes and Insulin Resistance. J Androl 2009;30:23–32

Tuomilehto J, Lindstr◌m J, Eriksson JG et al: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Eng J Med, 2001; 344: 1343–50

Takemoto M,Liao JK. Pleiotropic effects of 3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors. Arterioscler Thromb Vasc Biol 2001:21; 1712-19.

Tan RS, Pu SJ. Impact of obesity on hypogonadism in the andropause. Int J Androl 2002; 25:195-201.

Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013; 1: CD004816.

Tenover JS, Matsumoto AM, Plymate SR, Brenner WJ. The effects of aging in normal men on bioavailable testosterone and luteinizing hormone secretion: response to clomiphene citrate. J Clin Endocrinol Metb 1987; 65:1118-26.

The long –term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with prevastatin in patients with coronary heart disease and a broad range of intial cholesterol levels. NEngl J Med. 1998; 339:1349-57.

Terzolli L, Mircoli L, Raco R, Ferrari AU. Lowering of elevated ambulatory blood pressure by HMG-CoA reductase inhibitors. J Cardiovasc Pharmacol 2005; 46: 310–315

Tietz, N.W. ed., Clinical Guide to Laboratory Tests, 3rd Edition, W.B. Saunders, Co., Philadelphia, 1995: 578-580.

Tomar R, Dhindsa S, Chaudhuri A, et al. Contrasting testosterone concentrations in type 1 and type 2 diabetes. Diabetes Care. 2006; 29:1120-2.

Tomar R, Dhindsa S, Chaudhuri A, Mohanty P, Garg R, Dandona P. Contrasting testosterone concentration in type 1 and type 2 diabetes: Diabetes Care, 29,5. May 2006:1120-22.

Tomiyama K, Nishio E, Watanabe Y. Both wortmannin and simvastatin inhibit the adipogenesis in 3T3-L1 cells during the late phase of differentiation. Jpn J Pharmacol 1999;80:375e378.

Torzewski M et al. C-reactive protein in the Arterial Intima: role of C-reactive protein receptor-dependent monocyte recruitment in atherogenesis. Atheroscler Thromb Vasc Biol 2000; 20:2094-99.

Turner, M. A. & Kaye, D. R. (2006) Does well-being vary across different types of neighborhoods? The Urban Institute: Washington DC. Viewed online 4-19-07 @ www.aecf.org

VanHaren L, Cailleau J, Rommerts FFG (1989)Measurement of steroidogenesis in rodent Leydig cells: a comparison between pregnenolone and testosterone production. Mol Cell Endocr 65:157–164

VanNoortM, Rommerts FFG, van Amerongen A,Wirtz KWA (1988) Intracellular redistribution of SCP2 in Leydig cells after hormonal stimulation may contribute to increased pregnenolone production. Biochem Biophys Res Commun 154:60–65

Vermeulen A, Verdonck L, Kaufman JM. 1999. A critical evaluation of simple methods for the estimation of free testosterone in serum. Journal of Clinical Endocrinology and Metabolism 84(10):3666–3672.

Vermeulen A. Androgen replacement therapy in the aging male—a critical evaluation. J Clin Endocrinol Metab. 2001;86:2380–2390.

Verma S et al. A self –fulfilling prophency: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. Circulation 2002; 106:913-919.

Vermeulen A, Kaufman JM, Giagulli VA. Influence of some biological indexes on sex hormone-binding globulin and androgen levels in aging or obese males. J Clin Endocrinol Metab 1996; 81(5): 1821-1826.

VanHaren L, Cailleau J, Rommerts FFG (1989)Measurement of steroidogenesis in rodent Leydig cells: a comparison between pregnenolone and testosterone production. Mol Cell Endocr 65:157–164

VanNoortM, Rommerts FFG, van Amerongen A,Wirtz KWA (1988) Intracellular redistribution of SCP2 in Leydig cells after hormonal stimulation may contribute to increased pregnenolone production. Biochem Biophys Res Commun 154:60–65

Vermeulen A, Verdonck L, Kaufman JM. 1999. A critical evaluation of simple methods for the estimation of free testosterone in serum. Journal of Clinical Endocrinology and Metabolism 84(10):3666–3672.

Vermeulen A. Androgen replacement therapy in the aging male—a critical evaluation. J Clin Endocrinol Metab. 2001;86:2380–2390.

Winter WE. Molecular and Biochemical Analysis of the MODY Syndromes. Pediatric Diabetes 2000: 1: 88–117

Winters SJ, Kelley DE, Goodpastor B. 1998. The analog free testosterone assay: are the results in men clinically useful? Clinical Chemistry 44(10):2178–2182.

Winter WE. Molecular and Biochemical Analysis of the MODY Syndromes.
Pediatric Diabetes 2000: 1: 88–117

Winters SJ, Kelley DE, Goodpastor B. 1998. The analog free testosterone assay: are the results in men clinically useful? Clinical Chemistry 44(10):2178–2182.

Wang, G., & Dietz, W.H. (2002) Economic Burden of obesity in youths aged 6-17 Years: 1979-1999. Pediatrics 109:81-86. Viewed online 8/29/07 at http://pediatrics.aappublications.org/cgi/content/abstract/109/5/e81

Wang, Y. & Zhang, Q. (2006) Are American children and adolescents of low socioeconomic status at increased risk of obesity: changes in the association between overweight and family income between 1971-2002. American Society for Nutrition 84(4):707-716. Retrieved online 816/07 at http://www.ajcn.org/cgi/content/abstract/84/707

Wang, Y. (2001) Cross national comparison of childhood obesity the epidemic and the relationship between obesity and socio-economic status. International Journal Of Epidemiology 20:1129-1136 89

Wang, Y., Monteiro, C., & Popkin, B.M. (2002) Trends of obesity and underweight in older children in the US Brazil, China & Russia. American Journal of Clinical Nutrition 75:971-977. Viewed online at http://www.ajcn.org/cgi/content/abstract/75/6/971.

Wellman, N. S. & Friedberg, B. (2002) Causes and consequences of adult obesity: health, social and economic impacts in the United States. Asia Pacific Journal of Clinical Nutrition, 2002, 11(supplement): S705-S709.

Wells JC. Ethnic variability in adiposity and cardiovascular risk: the variable disease selection hypothesis. Int J Epidemiol. 2009;38:63–71

Whitlock, E. P., Williams, S. B., Gold, R., Smith, P. R. & Shipman, S.A. (2005) Screening and interventions for childhood overweight: a summary of evidence for the US Preventive Services Task Force.Pediatrics:116. 124-144.Viewed online at http://www.pediatrics.org/cgi/content/full/116/1/e125

WHO Collaborating Centre for Drugs Statistics Methodology. Complete ATC index 2014.

WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO expert consultation. Geneva, World Health Organization (WHO), 1995

Williams, J., Wake, M., Hesketh, K., Maher, E., and Waters, E., (2005) Health related Quality of life of overweight and obese children.JAMA293:1,70-76

World Health Organization. Global infobase. 2007. Available from:https://apps.who.int/infobase/Indicators.aspx [cited 30 June 2012]

Xu T, Wang X, HouS, Zhu J,Zhang X, Huang X. Effect of surgical castration on risk factors for atheriosclerosis of patients with prostate cancer. Chinese Medical Journal 2002; 1336-40.

United States Department of Agriculture, Economic Research Center.(2004) Measuring Rurality: rural urban commuting area codes. Viewed online at www.ers.usda.gov

United States Department of Health and Human Services National Center For Health Statistics (2000) Healthy People 2010, Focus Area 19; Nutrition and Weight. Viewed online at http://www.cdc.gov/nchs/about/otheract/hpdata2010/focusareas/fa19-nutrition.htm

United States Department of Health and Human Services, Office of Applied Studies (2004) National Survey on Drug Use and Health Viewed online 2-25-07 @ http://www.oas.samhsa.gov/nhsda.htm

United States Preventative Services Task Force (2005) Recommendation Statement: Screening and Intervention for Overweight in Children and Adolescents, Viewed 1-20-08 at http://www.ahrq.gov/clinic/uspstfo5/chovenwt/chovens.htm

United States Preventative Services Task Force Agency for Healthcare Research and Quality, (2005) Screening and interventions for overweight in children and adolescents: recommendation statement. AHRQ Publication No. 05-0574-A Viewed 9/1/07 online at http://www.ahrq.gov/clinic/uspstfo5/choverwt/choverrs.htm

Yang W, Kelly T, He J. Genetic epidemiology of obesity. Epidemiol Rev. 2007;29:49–61

Yamasaki H, Ogawa K, Sasaki H, Nakao T, Wakasaki H, Matsumoto E, Furuta H, Nishi M, Ueda K, Iwo K, Nanjo K. Prevalence and risk factors of erectile dysfunction in Japanese men with type 2 diabetes. Diabetes Res Clin Pract. 2004;66S:S173–S177.

Yannucci J, Manola J, Garnick MB, Bhat G, Bubley GJ. The effect of androgen deprivation therapy on fasting serum lipid and glucose parameters. J Urol. 2006;176:520–525.

Yialamas MA, Dwyer AA, Hanley E, Lee H, Pitteloud N, Hayes FJ. Acute sex steroid withdrawal reduces insulin sensitivity in healthy men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2007;92:4254–4259.

Zhang XH, Filippi S, Morelli A, Vignozzi L, Luconi M, Donati S, Forti G, Maggi M. Testosterone restores diabetes-induced erectile dysfunction and sildenafil responsiveness in two distinct animal models of chemical diabetes. J Sex Med. 2006;3:253–266.

Zirkin BR, Chen H. Regulation of Leydig cell steroidogenic function during aging. Biol Reprod. 2000;63:977–981.

Zhang, X. Christoffel, K. K., Mason, M. & Liu, L., (2006) Identification of contrasted and comparable school neighborhoods for childhood obesity and physical activity research. International Journal of Health Geographic 5:14. Retrieved online 8/11/07 at http://www.ij-healthgeographics.com/content/5/1/14/abstract

Appendix

(Questionnaire)

Patient Name: ..... **Patient number :** ☐

Age: ☐ **Weight:** ☐ . **Gender:** male

Do you have diabetic : **yes** ☐ **No** ☐

Type1DM ☐ **or** **Type2 DM** ☐

Are you fasting : **yes** ☐ **No** ☐

Do you have Hypertension : **yes** ☐ **No** ☐

Do you have Other diseases:

.....
.....
.....
.....
.....

Do you take Statins : **yes** ☐ **No** ☐

Do you take Other drugs:

.....
.....
.....

BENGHAZI UNIVERSITY
FACULTY OF MEDICINE

دراسة معدل مستوى هرمون التستوسترون ادي مرضي السكر النوع الثانى مع وبدون علاج الستاتين فى ليبيا

هذه الرسالة للحصول على درجة الماجستير فى علوم الكيمياء الحيوية

كلية الطب البشري –جامعة بنغازى

بنغازى - ليبيا

مقدمة من

وليـد محـمد الشريف

تحت اشراف

الأستاذ الدكتور : عبد الله محمد الجرارى

جامعة بنغازى -كلية الطب البشري –قسم الكيمياء الحيوية

2016

الملخص العربي

أجريت هذه الدراسة لتقييم اثر تناول دواء الستاتين على مستوى هرمون التستستيرون في الدم عند الرجال المصابين بداء السكري النوع 2 والرجال مصابين بداء السكري النوع 2 مع ارتفاع ضغط الدم في ليبيا.

يوصف الستاتين لمرضى السكري بهدف الحد من ارتفاع الكولسترول بمفرده أو بالاشتراك مع العقاقير المضادة لمرض السكري مما يسبب انخفاض في مستوى هرمون التستستيرون في الدم.

في هذه الدراسة تمت مقارنة مستوى هرمون التستستيرون ما بين مجموعة الأشخاص العير مصابين مع كل من المجموعات التالية:

1- مرضى لديهم ارتفاع في مستوى الكولوسترول في الدم (تحت العلاج).
2- مرضى السكري النوع 2.
3- مرضى السكري النوع 2 (مع المعالجة بعقار الستاتين).
4- مرضى السكري النوع 2 ومصابين بارتفاع في ضغط الدم.
5- مرضى السكري النوع 2 ومصابين بارتفاع في ضغط الدم (مع المعالجة بعقار الستاتين).

كذلك تم تقسيم المرضى الذين يعالجون بالستاتين إلى مجموعتين الأولى للمرضى الذين تناولوا العلاج لمدة تقل عن سنة والثانية للمرضى الذين تناولوا العلاج لمدة تزيد عن السنة.

لاجراء الدراسة تم تجميع 240 عينة وتم تقسيمها إلى 8 مجموعات بواقع 30 عينة للمجموعة الواحدة وذلك وفق التصنيف التالي:

1) الاشخاص الاصحاء.
2) مرضى لديهم ارتفاع في مستوى الكولوسترول في الدم.
3) مرضى داء السكري النوع 2.
4) مرضى داء السكري النوع 2 تناولوا العلاج لفترة زمنية تقل عن سنة.
5) مرضى داء السكري النوع 2 تناولوا العلاج لفترة زمنية تزيد عن سنة.

6) مرضى مصابين بداء السكري النوع 2 ومصابين بارتفاع في ضغط الدم.
7) مرضى مصابين بداء السكري النوع 2 ومصابين بارتفاع في ضغط الدم وتناولوا العلاج لفترة زمنية تقل عن سنة.
8) مرضى مصابين بداء السكري النوع 2 ومصابين بارتفاع في ضغط الدم وتناولوا العلاج لفترة زمنية تزيد عن سنة.

بعد إجراء التحاليل الاحصائية للعينات وبعد المقارنة مع العينات الاشخاص الاصحاء تبين الاتى :

كان هناك انخفاض كبير في مستويات هرمون تستوستيرون المصل في المرضى الذين استخداموا هذا الدواء.

أنخفضت مستويات هرمون التستوستيرون في الدم بشكل ملحوظ مقارنة مع عينات سليمة و كان هناك انخفاض ملحوظ في مستويات هرمون تستوستيرون عند مرضى السكري وهذا انخفاض يزداد عند استعمال علاج ستاتين.

وجود ارتفاع ضغط الدم لا يؤثر على انخفاض مستوى هرمون التستوستيرون في الدم وكذلك مرض سكر النوع 2 .

علاج ستاتين عند استخدامه كعلاج من قبل مرضى السكري من النوع2 يتسبب فى انخفاض ملحوظ فى مستويات هرمون تستوستيرون.

انخفاض مستوى هرمون التستوستيرون في الدم كان أكثر وضوحا عند المرضى الذين يتناول ستاتين كعلاج لأكثر من سنة مقارنة مع أولئك الذين يتناول ستاتين كعلاج أقل من سنة واحدة.