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Determination of testosterone level in male patients with insulin resistance at Tikrit city

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ABSTRACT:

Background The low levels of testosterone in men have been shown to be associated with type 2 diabetes, visceral adiposity, dyslipid-aemia and metabolic syndrome. The effect of testosterone treatment had been investigated on insulin resistance and glycemic control in men with type 2 diabetes.**Aim** : To investigate the relationship between insulin sensitivity and testosterone level.

Patients & Methods: This was study include 50 diabetic men treated with age (35-65years) with type 2 diabetes attended the out-patients clinic/medicine department in Tikrit Teaching Hospital. This study was carried out from November 2012 up to May 2013. Patients history were taken and their concomitant medications, Physical examination and laboratory investigations done before and after testosterone therapy (injection/oral root) for 3 months.

Results : The present study revealed that (68%) were obese and increase waist circumference in (96%)with significant increase in Glycated hemoglobin in obese groups, hyperinsulinaemia in (28%) and low testosterone level in (60%). Although, hyper cholesterolemia present more than half but not reach to statistical significant level while significant increase triglyceride level especially in obese patients .About lipoprotein types showed significant reduction in HDL and increase In LDL but not for VLDL. Regarding electrolytes level, we found that (Ca),(P) levels appeared within the normal levels, while other electrolytes (Mg,K,Na), the majority of cases are within the normal levels. Patients were treated with i.m. testosterone 200 mg every 3 weeks or oral root for 3 months. Follow up study with testosterone therapy, the primary outcomes was significant decrease in glycated hemoglobin with no corresponding reduction in insulin level, while significant increase in testosterone level.However, a significant reduction in visceral adiposity as assessed by waist circumference, with significant reduction in weight and BMI . With respect to total cholesterol, was reduced in(76%),after testosterone therapy, but statistical analysis not significant. According to triglyceride level, after testosterone therapy,there was significant reduction as compare with it before treatment.There was no significant change in HDL and LDL, while significant reduction present in VLDL.With respect to electrolytes there was significant change except Ca.

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Introduction

Many studies reveled that testosterone plays an important role in blood glucose and lipid metabolism. With evidence that low serum testosterone was associated with metabolic syndrome and even the development diabetes mellitus(1). The metabolic syndrome is a predisposing to T2DM,morbidity and mortality of cardiovascular. The features of metabolic syndrome includ, insulin resistance, central obesity ,glucose intolerance, raised BP and hyperlipidemia (2).

Testosterone is conceder as one of insulin fat represent an overall decrease the risk of cardiovascular events sensitivity modulator. They find impaired Leydig cell secretion of testosterone in hypogonadism .(3). TRT decrease insulin resistance with good glycemic control in men of hypo gonadal withT2DM., IR, cholesterol and visceral fatty tissues.(4)

Patients and methods

A total of 50 patients are participated in the study was carried out from November 2012 to May 2013,with age ranged(35-65)years were suffering from DMT 2.These patients attended the out-patients clinic/medicine department in Tikrit Teaching Hospital. Prior to beginning testosterone replacement therapy, contraindications must be excluded, such as existing prostate cancer, or male breast cancer. The trial was 3 months in duration in which patients had testosterone supplement oral (proveron tablet 25 mg three times per day) or injection (sustanon 100 mg/ml, Organon Laboratories, Cambridge, UK, a depot preparation of testosterone given by deep i.m. injection, once injection given every 3weeks) was given for 3 months and reassessment includes Physical examination and laboratory investigation, with statistical analysis using ANOVA test.

Assessments (laboratory investigation) were always made between 8:00 and 10:00 h after an overnight fast. All concomitant oral hypoglycemic, anti-hypertensive and lipid-lowering medications were permitted and continued throughout the study without dose adjustment. However, those patients who were on insulin were permitted to make insulin dose adjustments to avoid hypoglycemia. Subjects' height and weight were recorded. The anthropometric indices of height and weight were measured while subjects were bare foot and wearing light clothing , waist circumference (WC) in cm., was measured at point between the costal margin and iliac crest, body mass index(BMI) was taken by BMI calculator .We classified them into three groups: First group: normal (18-24.9) Kg./m2.

Second group: over weight (25-29.9)Kg./m2 and third group: obese(>30) Kg./m2.

Blood pressure measurement was taken by using a mercury sphygno-manometer while the subject was in a sitting position, with the arm at the level of the heart and after 5 min rest. Hypertension was defined as elevated systolic (≥140 mmHg) or diastolic (≥90 mmHg) blood pressure. A venous blood sample (20 ml) was drawn between 8:00 and 10:00 am after an overnight fast. Blood was withdrawn from the cubital fossa from each participant, using a disposable syringe. It was injected into the plain complete blood count tube; the specimen. There is biochemical investigation involved HbA1c, serum testosterone and insulin by (Elisa), lipid profile, serum electrolyte include calcium , potassium, sodium, phosphorus and magnesium (without tornica in respect to calcium level measurement) by chemical procedure.

Result:

A cross section study of 50 male patients attending medical department of Teaching Tikrit Hospital, were diagnosed of diabetes mellitus type 2 (DMT2).

Figure(1).shows that out of 50 cases, normal BMI2(4%),over weight14 (28%)and obese 34 (68%).

Figure (2): shows high HbA1c groups had direct correlation with BMI, and distributed as follows 18(36%) with BMI (30 & above), and the rest10 (20%) within BMI (25-29.9)group.According to the normal HbA1C group was distributed as follow 9 (18%) with BMI(25-29.9), then group of BMI (30 & above) was 7(14%)then last 6(12%)within BMI (18-24.9) group, on the other hand, statistical analysis showed significant increase HBA1C ($P<0.05$) within BMI (30 & above)as compared with normal HbAIC while not significant in other groups.

Figure (3) :Distribution of Cases According to Insulin and Testosterone With respect to serum insulin hormone level, show that the majority of the cases reported 68% are normal level, followed by 28% are increase level, then the lower level was represent4%.As for serum testosterone level, we observe that most of cases 58% within normal level, then 42%was lower level.There is sharing area20% of both increase serum insulin hormone level and decrease serum testosterone hormone level which represent as area of metabolic syndrome.

Table(1): Distribution of Cases According to BMI Before &After Testosterone Replacement Therapy(TRT).we found that decrease BMI after(TRT) 36 (72%),with no

change in BMI 14=(28%).Statistical analysis of the data found to be significant decrease BMI after3 motnths of testosterone treatment.

Table(2):Distribution of Cases According to HbA1c Before&After (TRT). We revealed the group before (TRT) had highest prevalence of increase HbAIc level 28 (56%) followed by normal HbAIc level 22 (44%) while group after (TRT) reveals that the highest prevalence with decrease in HbA1c is 46 (92%).On the other hand with no change in HbA1c 4 (8%).However, the statistical analysis showed significant decrease after therapy.

Table 3: Distribution of Cases According Patient Insulin Level Before &After(TRT).As it appears in this table , the group before(TRT), with the majority number of cases had normal insulin level were 34 (68%) giving the rate of cases more than among those with increase level of insulin14(28%) and the lowest with Decrease 2(4%) as compared after(TRT) the most cases with increase insulin level 26(52%) followed with decrease level of insulin 18(36%) and the lowest with out change 6(12%), statistical analysis showed no significant difference.

Table 4:Distribution of Cases According to Testosterone Level Before & After (TRT).According to testosterone level before(TRT) we had the highest group among patients with decrease level 30 (60%)which more than normal level 20=(40%) .In respect to same group after (TRT)with the most of cases were among who had increase testosterone level 28(56%), followed by group who had decrease testosterone level 14(28%) then group had no change 8(16 %). Statistical analysis of the data indicates significant increase testosterone level.

Table 5: Change in Patient Lipid Profile Level After (TRT).

Table (5) revealed that the HDL Lipoprotein were the higher in cases with decrease level after testosterone treatment 30(60%), followed by increase HDL Lipoprotein 16(32%) and the least group with no change 4(8%). Statistical analysis of data found to be insignificant. In respect to LDL Lipoprotein found that the highest frequency among decrease level 38(76%), followed by increase level 12(24%), The deference among them was found to be statistically not significant. About VLDL Lipoprotein groups, the distribution of cases were more common with increase level 22(44%), followed by decrease level 18(36%), while no change in level 10(20%).The deference among them was found to be statistically significant change .In respect toT.C we found that a high frequency exist among cases with decrease total

cholesterol and this represented as 38 (76%) and without change 12(24%).Statistical analysis of data found to be insignificant. About TG level, where the higher in cases with decrease Level 38(76%) foll0wed by 11(22%) without change and just1(2%)go with increased level.

Table (6):Change in Patient Serum Electrolyte After(TRT). with respect to sodium level, the majority of cases were reported within group of increase level 30(60%), followed by low level 14(28%), and the last 6(12%) had no change. About Potassium level, table shows same values in groups increase and decrease levels 24(48%), and just 2 (4%) of cases without changes. While Calcium level, appears that the most cases were belong to low level 28(56%), followed by increase level 20(40%), then in no change level 6(12%).According to(Mg), we observed that cases was distributed gradually as 22(44%) in increase level group, 14(28%) in decrease level group and finally 14 cases (28%) in no change group. About (P). also our table shows obvious changes in cases and most cases within increase group 36(72%), followed by decrease group 12(24%) and only 2 cases within no change group which represent 4%.Statistical analysis of the data was revealed that significant increase in(Na), (K)and(P),while decrease in (Mg)with no significant change in (Ca).

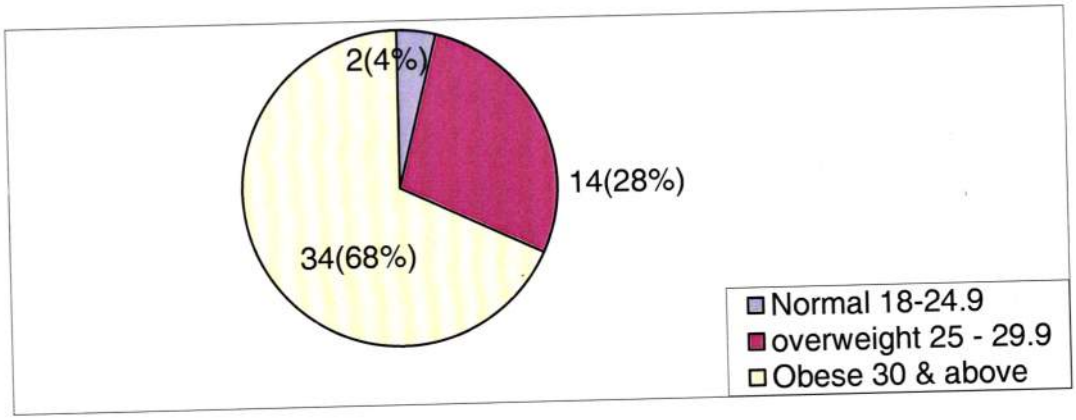

Figure (1) Distribution of Cases According to BMI.

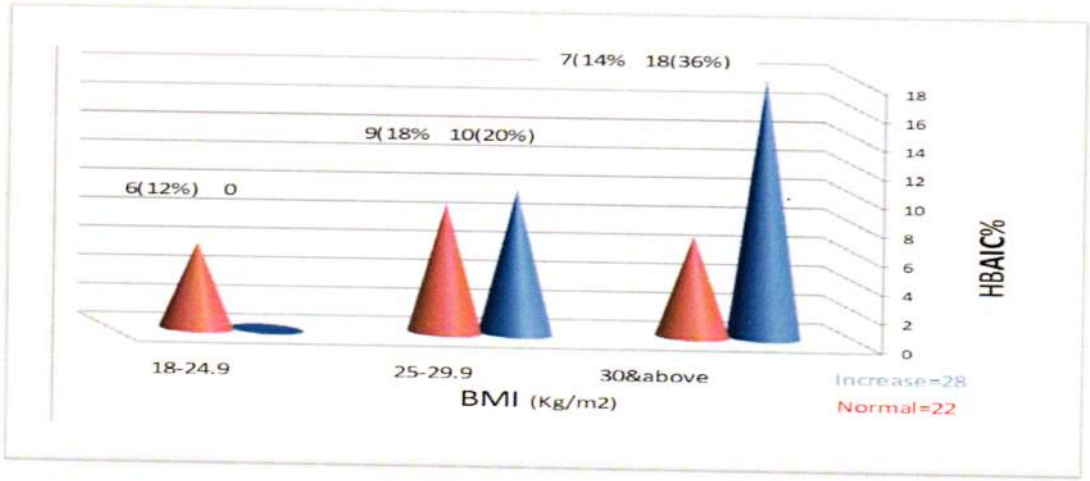

Figure (2)Distribution of Cases According to HbA1C Level

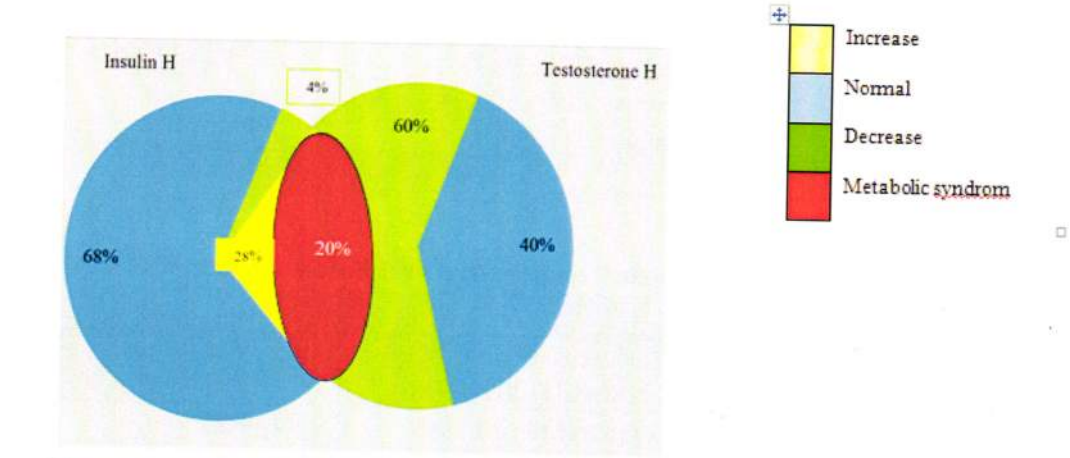

Figure (3)Insulin H. and testosterone H.levels distribution in the study sample

Table(1):Distribution of Cases According to BMI Before &After (TRT).

BMI(%)	Total number	Mean+SD
Before Testosterone Replacement Therapy (TRT)	Normal((2=(4%)) Over weight((14=(28%)) Obes((34=(68%))	30.5± 4.62
After Testosterone Replacement Therapy(TRT)	Decrease((36=(72%)) No change ((14=(28%))	27.4±4.25
P. value	0.01	

Table(2):Distribution of Cases According to HbA1c Before &After (TRT).

HbAlc(%)	Total number	Mean±SD
Before(TRT)	Increase((28=(56%)) Normal ((22=(44%))	6.9±1.38
After (TRT)	Decrease((46=(92%)) No change ((4=(8%))	5.5±0.9
P.value	0.05	

Table(3):Distribution of Cases According to Insulin Level Before& After (TRT).

Insulin Level(mlU/ml	Total number	Mean±SD
Before testosterone therapy	Normal((34=(68%)) Increase((14=(28%)) Decrease((2=(4%))	17.3±14.55
After testosterone therapy	Increase((26=52%)) Decrease((18=(36%)) No change((6=(12%))	17.3±12.0
P.value	NS	

Table(4):Distribution of Cases According to Testosterone Level Before & After(TRT).

Testosterone Level	Total number	Mean±SD
before testosterone therapy	Decrease((30=(60%)) Normal ((20=(40%))	30.5± 4.62
after testosterone therapy	Increase((28=(56%)) Decrease((14=(28%)) No change((8=(16%))	27.4±4.25
P.value	0.01	

Table(5):Distribution of Cases According to Lipid Profile Level After(TRT).

Lipid profile	Increase		Decrease		No change		Testosterone Treatment (Mean±SD)		P. value
	No.	%	No.	%	No.	%	Before	After	
HDL	16	32	30	60	4	8	51.0±4.7	47.6±5.9	NS
LDL	12	24	38	76	0	0	11.3±17.3	106±12.9	NS
VLDL	22	44	18	36	10	20	40.4±7.9	36.21±7.0	0.01
T.C	0	0	38	76	12	24	199±27.24	191.1±16.24	NS
T.G	1	2	38	76	11	22	233.8±43.9	210.8±50.12	0.05

Table (6):Distribution of Cases According Serum Electrolytes After (TRT).

Serum electrolyte	Increase		Decrease		No change		Testesterone Treatment (Mean±SD)		P. value
	No.	%	No.	%	No.	%	Before	After	
Sodium(Na)	30	60	14	28	6	12	138.4±14.4	144.8±8.5	0.01
Potassium(K)	24	48	24	48	2	4	4.0±0.44	4.23±0.33	0.01
Calcium(Ca)	20	40	28	56	6	12	9.5±0.39	9.3±0.37	NS
Magnesium(Mg)	22	44	14	28	14	28	0.8±0.14	0.7±0.19.0	0.01
Phosphorus(P)	36	72	12	24	2	4	3.62+0.4	3.9±0.3	0.05

Discussion:

1-Distribution of Cases According to BMI. In the present study,BMI was noticed in (68%)of cases were obese (BMI30 & above),which was more than study done in Amman byAyman Al Hayek, where BMI was (43.8%)of diabetics were obese, and(39.3%) overweight[5] which more than the present study(28%).Obesity and T2DM are associated with insulin resistance. When a person is overweight, the cells in the body become less sensitive to the insulin specially fat cells[6]. The present study go with other studies [7].

2- **Distribution of Cases According to HbA1c Level.**The present study reveals that the most frequent cases are among high HBA1C level (56%)compared to the cases that belong to normal HbA1c(44%). There is highly significant increase HbAIc as compared to normal level in obese group withdirect relationship with BMI,due to increase level in obese group withdirect relationship with BMI,due to body weight associated hyperinsulinemia[8].

3-Distribution of Cases According to Insulin and Testosterone. The present study revealed that diabetic patients who had high Insulin level and low serum testosterone level represent 20% of cases which can conceder as metabolic syndrome(MS)that different from other studies with different criteria were applied. . Prevalence of this syndrome is 19% in Mongolia[9],21% in Jordon[10],17% in Palestine[11],The incidence of MS among the Asian ethnic groups is not well defined whereas Asia is probably prone to the highest prevalence of diabetes and cardiovascular diseases in near future and 35.9%in Iran, 24.2% in Malaysia ,21.17% in Taiwan[12],12.2% in Singapore,12% in Japan,14.8% in China, 28.8% in India, and 28.6% and 27.8%, respectively, in male Koreans while

,in U.S 25% of the adults are affected by the metabolic syndrome[13].Variation in prevalence due to differences in population characteristics and criteria uses of MS may be considered as the main sources of this variation.

4- Change in Patient BMI after TRT. There was significant decrease in BMI after TRT, in (72%),due to testosterone supplementation in obese individuals has been shown to reducing body weight, body fat[14].A dramatic reduction in adipose content, with the greatest effects seen in the subcutaneous and skeletal muscle areas. Testosterone enhances lipolysis in adiposities by increasing the expression of beta adrenergic receptors, adenylatecyclase, proteinkinase A and hormosensitive lipase[15].Androgen therapy also leads to a significant increase in lean skeletal muscle mass and strength.The rest of cases that without loss in weight and BMI after TRT (20%), (28%) respectively, due to some patients poor compliance with TRT specially oral type.

5- Change in Patient HbA1c % after TRT. It was noticed that (92%) of cases had significant decrease HbA1c after TRT with and other (8%) without decrease HbA1c.The observed correlations of HbA1c with TRT found that testosterone plays a significant role in insulin sensitivity. Testosterone substitution in hypogonadal men improves insulin sensitivity. Furthermore, testosterone reduces insulin levels and insulin resistance in men with obesity[1],[16], [17]. By contrast, two studies replacing testosterone in men with type 2 diabetes and hypogonadism found little or no effect on glycemic control[30][31].The mechanism by which testosterone reduces insulin resistance are uncertain. There is considerable evidence linking abdominal obesity to insulin resistance and the excess visceral fat results in the liver being exposed to higher amounts of free fatty acids leading to hepatic and eventually systemic insulin resistance [18].

6- Change in Patient Insulin Level after TRT. Although there was decrease in insulin level after TRT 18(36%),but not reach to significant level.The possible explanation for this is that our patients received testosterone treatment for 3 months only and others studies have shown significant decreases in over a longer period of time[19],[32].

7- Change in Patient Testosterone Level after TRT. Testosterone therapy in hypogonadal men is indicated if bioavailable testosterone is below 30% or total testosterone is below 12 nmol/L, and clinical signs of androgen deficiency are evident[3].The aim of testosterone therapy is to

substitute the androgen within normal adult male ranges and keep levels as physiological as possible[3].The present study revealed that increase testosterone level(56%), followed by group who had decrease testosterone level(28%) then group had no change (16 %) with significant increase in testosterone level after TRT.

8-Change in Patient Lipid Profile Level After (TRT). Testosterone inhibits lipoprotein lipase activity, which reduces triglyceride uptake into adipocytes[19] and causes a more rapid turnover of triglycerides in the subcutaneous abdominal adipose tissue and femoral fat and, maybe, mobilizes lipids from the visceral fat depot[1]. The present study revealed that no significant difference of HDL after TRT like other study [20],[18],[2] . About LDL found without significant difference after TRT similar to study[18],[20].Michael Klentze found, that testosterone therapy results in a decline in serum levels of total cholesterol and (LDL) cholesterol, and no change in HDL cholesterol, although a few new studies show a decline in HDL cholesterol with treatment[5].A study revealed that reduction in total serum cholesterol was (76%) of cases, similar finding was reported by others[21],[22],[23], previously reported a significant reduction in total cholesterol with testosterone therapy in men with predominantly coronary heart disease or T2DM. Along with other authors[24],[25] recently reported that the use of cholesterol-lowering drugs (statins) was associated with low testosterone, other studies did not report any effect on HDL cholesterol, but demonstrated an improvement in total cholesterol[26]. In this study, although reduction in total serum cholesterol was observed after TRT but without significant value ,the short duration of trial therapy may cause no significant effect.

The pattern of triglyceride Level was found that reduction in(76%) cases with significant reduction level and this is in agreement with two other studies [1],[21], which reported a similar effect of androgen, other studies found no significant differences was observe for triglyceride Level[22].

9- Change in Patient Serum Electrolyte after TRT. With respect to electrolytes changes, (Na),(K) levels had the majority of cases were reported within group of increase level (60%),(58%), followed by decrease level (28%),(38%), and the last (12%),(4%) had no change respectively, this is agree with study [27] reveled that (Na) and (K) excretion were decreased by testosterone, Plasma aldosterone was decreased in the presence of testosterone, while other study revealed that serum sodium and magnesium levels were

decreased in Chinese subjects with diabetes, while the observed increase in calcium level correlated with increasing glucose level[28],other hyperglycemia-induced hypo-natremia–calculation of expected serum(Na)depression[29].In present study, found (Mg) with significant reduction, probably due to improve insulin sensitivity after testosterone therapy.

Conclusion:

The present research revealed that men with insulin resistance had the following findings:

1-Men with insulin resistance are common in obese BMI (30 & over) in (68%) with increase waist circumference in (68%)of cases.

2-HbA1c increased in (56%),with hyperinsulinemia in(28%).

3-Hypogonadisim represent in(44%),which are common in obese diabetic men.

4-Dyslipidemia present in the form of increase total serum cholesterol (52%) and triglyceride(68%).

5-Metabolic syndrome form in (20%) with both elevated insulin level and decrease testosterone level.

6-Testosterone administration for three months improvesglyce-metabolic control with significant reduction of fat mass,BMI, HBA1C and lipid profile.

Recommendation: 1-There is evidence that hypotestosteronemia should be an element in the definition of the metabolic syndrome since low levels of testosterone are associated with or predict the development of the metabolic syndrome and of diabetes mellitus.

2-Emerging evidence suggests that testosterone therapy may be able to reverse some aspects of metabolic syndrome testosterone levels were significantly lower in men with type 2 diabetes. Further, in men with low plasma testosterone the risk of diabetes mellitus is increased.

3-Physicians who treat diabetic patients should concentrate on the diagnosis and treatment of androgen deficiency.

4-Androgen replacement therapy in hypogonadal type 2 diabetic men could potentially improve glycemic control and reduce complication like micro vascular and cardiovascular events in these patients.

5-Request to Salah Al-deen DOH to establish a special diabetic center at Teaching Tikrit Hospital

References

1-Saad F. and Gooren L, "The role of testosterone in the metabolic syndrome: a review," Journal of Steroid Biochemistry and Molecular Biology, 2009;vol. 114, no. 1-2, pp. 40–43,.

2-K.George MM Alberti, PaulZimmte, Jonathan Shaw:The metabolic syndrome-anew world widedefinition.Lancet,24september 2005;366:1095.

3-Michael Klentze: The Male Hormone Connection: Treating Diabetes and Heart Disease. Munich:- Jeffrey Dach. Testosterone Health Benefits, Myths and Misconceptions.2007,page 66.

4-Kapoor D, Goodwin E, Channer KS, et al. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity, and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol , 2006;154:899e906.

5-A Al Hayek,Yousef S Khader, Sahar Jafal, Nahla Khawaja, Asirvaham A Robert and Kamel Ajwni.Journal of Family& Community mdicine, 2013:20: 179-186).

6-Michael Roden et al. "Mechanism of free fatty acid-induced insulin resistance in humans".Journal of Clinical Investigation.1996;97 (12): 2859–2865.

7-Hamid R Saberi, Ali R Moravveji, EsmaeilFakharian, Masoud Motalebikashani and Ali R Dehdashti: Prevalence of metabolic syndrome in bus and truck drivers in Kashan ,Iran.*Diabetology& Metabolic Syndrome.2011*;**3**:8

8-Ernani L. Rhoden, Eduardo P. Ribeiro, ClaudioTeloken and Carlos A.V. Souto: Diabetes mellitus is associated with subnormal serum levels of free testosterone in men.BJUI international, Oct. 2005; 96:867-870.

9-Shiwaku K, Nogi A, Kitajima K, Anuurad E, Enkhmaa B, Yamasaki M, et al:Prevalence of the metabolic syndrome using the modified ATP III ,definitions for workers in Japan, Korea and Mongolia. J Occup Health. 2005;47(2):126-35.

10-McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE,et al: The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study.Diabetes Care. 2005;28(2):385-90.

11-Jaber LA, Brown MB, Hammad A, Zhu Q, Herman WH: The prevalence of the metabolic syndrome among arabamericans. Diabetes Care .2004;27(1):234-8.

12-Kim MH, Kim MK, Choi BY, Shin YJ: Prevalence of metabolic syndrome and its association with cardiovascular disease in korea. J orean Med Sci.2004;19:195-201.

13-Tan CE, Ma S, Wai D, Chew SK,

Tai ES: Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? Diabetes Care. 2004; 27(5):1182-6.

14-Boyanov MA, Boneva Z, ChristovVG.Testosterone supplementation in men with type 2 diabetes, visceral obesity andpartial androgen deficiency. Aging Male .2003; 6: 1–7

15-Marin P, Oden B, BjorntorpP.Assimilation and mobilization of triglycerides in subcutaneous abdominaland femoral adipose tissue in vivo in men:effects of androgens. J ClinEndocrinol Metab.1995; 80: 239–43

16-Melis Conrad Stöppler, MD Insulin Resistance. Medicine. NET.com. 2013, 19: july.

17-D Kapoor ,E Goodwin,K S Channer and T H Jones. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. . Eur J Endocrinol. 2006;154(6):899-906.

18-Synder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen CJ & Strom BL. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. Journal of *Clinical Endocrinology and Metabolism*. 1999; 89: 2647–2653.

19-Kenny AM, Prestwood KM, Gruman CA, Marcello KM &Raisz LG. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. Journal of Gerontology. Series A, Biological Sciences and Medical Sciences, 2001; 56: M266–M272.

20-G. Corona,M. Monami,G. RastrelliA. Aversa, A. Sforza, A. Lenzi, G. Forti, E. Mannucci and M. Magg .Type 2 diabetes mellitus and testosterone: a meta-analysis study.2011;34:p528-38.

21-Saad F, Gooren L. The role of testosterone in the metabolic syndrome: a review. J Steroid BiochemMol Biol. 2009;114(1-2):40-3.

22-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 hypogonadalmen .JClinEndocrinolMetab.2004; 89: 3313–3318

23-. Kapoor D, Goodwin E, Channer KS & Jones TH., Testosterone replacement therapy improves insulin resistance, glycaemiccontrol,visceral adiposity

and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol,2006; 154: 899–906.

24-Stanworth RD, Kapoor D, Channer KS & 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: 541–546.

25-Corona G, Boddi V, Balercia G, Rastrelli G, De Vita G, Sforza A, Forti G, Mannucci E & Maggi M. The effect of statin therapy ontestosterone levels in subjects consulting for erectile dysfunction.J Sex Med,2010; 7: 1547–1556.

26-Isidori AM, Giannetta E, Greco EA, Gianfrilli D, BonifacioV,Isidori A, Lenzi A &Fabbri A.Effects of testosterone on body composition, bone metabolism and serum lipid profile in middleaged men: a meta-analysis. ClinEndocrinol (Oxf). (2005); 63: 280–293.

27-Jonathan Toot, Cathy Jenkins, Gail Dunphy, Shannon BoehMike Hart, Amy Milsted, Monte Turner[1] and Daniel Ely Testosterone influences renal electrolyte excretion in SHR/y and WKY males*BMC Physiology* 2008, **8**:

28-Shenqi Wang, XuhongHou, Yu Liu, Huijuan Lu, Li Wei, YuqianBao and WeipingJia level .Serum electrolyte levels in relation to macrovascular complications in Chinese patients with diabetes mellitus*cardiovascular Diabetology* 2013, **12**:146

29-Katz MA: Hyperglycemia-induced hyponatremia–calculation of expected 8-serum sodium depression. *N Engl J Med*.1973;289(16):843-844.

30-Corrales JJ, Almeida M, Burgo R, Mories MT, Miralles JM, OrfaoA.Androgen-replacement therapy depresses the ex vivo production of inflammatory cytokines by circulating antigen-presenting cells in aging type-2 diabetic men with partial androgen deficiency. J Endocrinol. 2006;189 (3): 595-604.

31-Lee CH, Kuo SW, Hung YJ, Hsieh CH, He CT, Yang TC, et al. The effect of testosterone supplement on insulin sensitivity, glucose effectiveness, and acute insulin response after glucose load in male type 2 diabetics. Endocr Res. 2005;31(2):139-48.

32-Synder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen CJ & Strom BL. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. Journal of Clinical Endocrinology and Metabolism. 1999; 89: 2647–53.