Determination of Testosterone level as predictor for insulin resistance in young men with family history of type2 diabetes and hypertension.

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Received 7, November, 2012
Accepted 9, December, 2012

Abstract:

Background: Insulin resistance is associated with metabolic syndrome , type 2 diabetes and representing a risk factor for cardiovascular disease . This relationship may be modulated to some extent by age related changes in sex hormone status.. In particular, reduced total testosterone (TT) levels have been associated with insulin resistance and subsequent risk for developing type 2 diabetes.

Aim of study: we examined whether low total testosterone level were associated with insulin resistance in young adult men.

Methods: a total of 83 men (young adult men) divided into 2 group : (group1) 49 men with a risk factor for insulin resistance(with a family history of type2 diabetes and hypertension) and (group2) 34 men without any risk factor aged (20-40) years. Age, body mass index (BMI) and waist circumference were measured. Early morning, they were assayed for total testosterone, and insulin levels. Insulin resistance was assessed using a homeostatic model (HOMA-IR).

Results: Total testosterone, declined progressively across increasing quintiles of HOMA-IR as a mean of(4.49±1.87) ng/ml in group1 compared mean (7.82±2.21) ng/ml in group 2 and correlated inversely with HOMA-IR(r = -0.424 , p = 002) also with insulin (r= -0.541) (p< 0.0001) in group1 . Total testosterone correlated inversely with BMI (r=-0.471 **,** p=0.001) in group1. There is a significant positive correlation between HOMA- IR of group1 and BMI (r= 0.472) (p<0.001), insulin levels (r=0.698) (p<0.0001) .

Conclusions: In young adult men, lower total testosterone is associated with insulin resistance.

key word : testosterone , insulin resistance.

Introduction:

Insulin resistance is a decreased ability in cells, tissues (especially skeletal muscle, adipose tissue ,liver, or the whole body) response to normal levels of exogenous or endogenous insulin . Thus insulin resistance has been implicated in the pathogenesis of the metabolic syndrome[1]**.**

Insulin resistance predisposes to metabolic syndrome and type 2 diabetes and may represent a risk factor for cardiovascular disease independently of these conditions[2,3].

In men, low testosterone concentrations are associated with insulin resistance [4, 5] and the development of metabolic syndrome and type 2 diabetes [6,7] , Testosterone is one of steroid hormone of the androgen group. It is the main male sex hormone and anabolic steroid. Testosterone the most important hormone that men need , and small quantities of testosterone precursors can provide a very important role for women too. In men

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testosterone plays a key role in the development of male reproductive tissues such as the testis and prostate as well as proming secondary sexual characteristic such as increased muscle ,bone mass, and the growth of body hair[8].The testes represented the primary source for Testosterone .

In the circulation, testosterone is bound with high affinity to sex hormone-binding globulin (SHBG) and weakly to albumin, with a small fraction of unbound or free testosterone [9]. During ageing, total and free testosterone levels decline, while SHBG levels increase [10]. Serum testosterone level is greater in the morning upon waking and decrease throughout the day.

Materials and Methods

Subjects (Selection):-

The study was conducted at National diabetes Center (NDC) /AL-Mustansiryia University between (Nov.2011– April 2012). Eighty three (young adult) Iraqi men were enrolled in the study. Group 1 Forty nine young adults, with age range (20-40) years were expected to have insulin resistance (have the risk factor for IR with a family history of type2 diabetes and hypertension) with BMI (31.57±4.94) . Group 2 Thirty four young adults age, range (20-40) years without any risk factor , with BMI (29.39±4.34), enrolled in the study, excluded from this study men taking testosterone replacement, non-fasting men, those with prostate cancer and those reporting diabetes. The following detailed informations were obtained : Age, the family histary of type 2 diabetes and Hypertension. All patients underwent physical examination .

Body mass index (BMI) was calculated according to the formula , weight (kg) / height^2 (m^2).

Collection of Blood Samples

Ten ml of blood were obtained by vene puncture using 10 ml disposable syringes between 8.00 and 11.00 a.m. after (12-14) hours fasting. The blood sample was divided into two aliquots;

- One ml of blood was put in a plain tube used before clotting for estimation of plasma glucose level.
- Nine ml of blood was dispensed in a plain tube and left for around an hour to clot at room temperature (25 ^{0}C), and then separated by centrifugation at (3000 rpm) for (10 min) to collect serum. The separated serum was divided into aliquots (250µl) in Eppendroff tubes and stored in the freezer (–20) ^{0}C until used for assays of hormones.

Laboratorytests*:*

Serum for total testosterone was analyzed by Elisa method (competitive Elisa method) , serum insulin was analyzed by (sandwich Elisa method) , Fasting serum glucose, total and high-density lipoprotein (HDL) cholesterol and triglycerides (TG) were assayed using enzymatic oxidation method Insulin resistance was estimated from fasting glucose and insulin results by homeostasis model assessment, according to the formula [11]:

serum glucose (mg/dL) x insulin (µU/mL) / 22.5 .

Results

The mean age for group1were (38.88±3.08) years and which was comparable to that of group2 mean (35.56.±6.06) years which was statically not significant (P =0.208). Group1 showed a slightly increased mean of BMI in comparison with group2 (31.57 *vs.* 29.39) and the differences were not significant in BMI between group1 and group2, (p=0.112 using Pearson chi-square statistic test). WHR value was significant difference between group1 and group2

(p=0.002) using person chi-square test at level 0.05 significance . There was significant elevation in the baseline value of FPG in group1 as compared with group2 (p=0.013). The mean serum total testosterone for group1 (4.49±1.87 ng/ml) was significantly (p=0.0001) lower than that of group2 mean (7.82±2.21 ng/ml) (using t-test). The mean Insulin levels for group1 was (18.35±8.48) significantly higher (P =0.0001) than that of group2 mean (12.30±4.45) using t-test. A significant increase in Insulin resistance (HOMA-IR) for group1mean (8.08±1.94) when compared with group2 (3.10±0.65).

Table (1) : the mean of parameter in group1 and group2.

Mean of parameter	Group1	Group2	p-valu
Age	38.88±3.08	35.65±6.06	0.208
BMI	31.57±4.94	29.39±4.34	0.112
WHR	1.00±0.05	0.96±0.16	0.002*
Glucose mmol	6.62±1.94	5.18±0.37	0.013*
Total testosterone ng/ml	4.49±1.87	7.82±2.21	0.0001*
Insulin μU/mL	18.35±8.48	12.30±4.45	0.0001*
HOMA-IR	8.08±4.69	3.10±1.12	0.0001*
Totalcholesterol (mg/dl)	200.69±54.71	160.24±43.00	0.001*
Triglycerides (mg/dl)	196.94±87.71	123.53±45.17	0.0001*
HDL (mg/dl)	34.51±5.19	44.53±4.49	<0.001*
LDL (mg/dl)	113.49±47.76	93.47±38.98	0.047*
VLDL (mg/dl)	39.14±17.35	25.47±10.28	0.0001*

significant at the 0.05 level

Correlation of the results

Correlation of group1 and group2 with total testosterone:-

There is a negative significant correlation between total testosterone levels of group1subjects and total cholesterol (r=-0.330) (p>0.021) as shown in Table (2). There is a negative significant correlation between total testosterone levels of group1 subjects and BMI (r=-0.471) (p< 0.001) as shown in Table (2). There is a negative significant correlation of total testosterone levels of group1with HOMA-IR % (r= -0.424), (p< 0.002), also with insulin (r= -0.541) (p< 0.0001), respectively as shown in Table (2).

There is a negative significant correlation between total testosterone levels of group2 subjects and total cholesterol (r= -0.382) (p< 0.026) and LDL (r= -0.391) (p< 0.022). Also there is a significant positive correlation between total testosterone levels and free testosterone in group2 subjects (r=0.469) (p< 0.005) as shown in Table (2).

Table (2):-Correlations of Total Testosterone with different parameter in group1 and group2.

		Total testosterone(ng/ml)	
		Group1with risk factor	Group2without risk factor
Age (years)	r	-0.276	-0.240
	P	0.605	0.171
BMI (Kg/m2)	r	-0.471**	-0.169
	P	0.001	0.341
WHR	r	-0.114	-0.212
	P	0.436	0.229
Fasting Glucose (mmol /L)	r	-0.042	-0.122
	P	0.773	0.490
Total cholesterol (mg/dl)	r	-0.330*	-0.382*
	P	0.021	0.026
Triglycerides (mg/dl)	r	-0.272	-0.189
	P	0.059	0.284
HDL (mg/dl)	r	0.095	0.087
	P	0.515	0.626
LDL (mg/dl)	r	-0.276	-0.391*
	P	0.055	0.022
VLDL (mg/dl)	r	-0.244	-0.106
	P	0.091	0.551
insulin (µU/mL)	r	-0.541**	-0.198
	P	0.0001	0.262
HOMA-IR	r	-0.424**	-0.217
	P	0.002	0.217

* Correlation is significant at the 0.05 level
** Correlation is significant at the 0.01 level

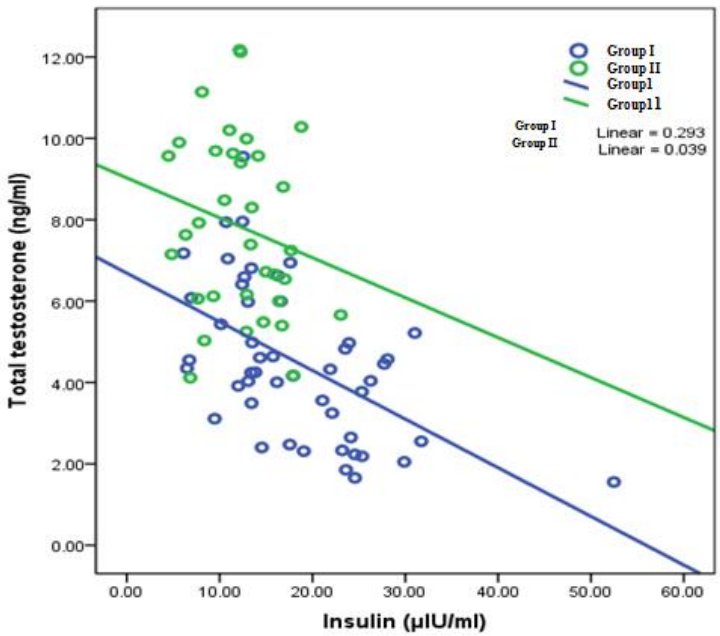
Correlations of HOMA-IR in group1and group2:

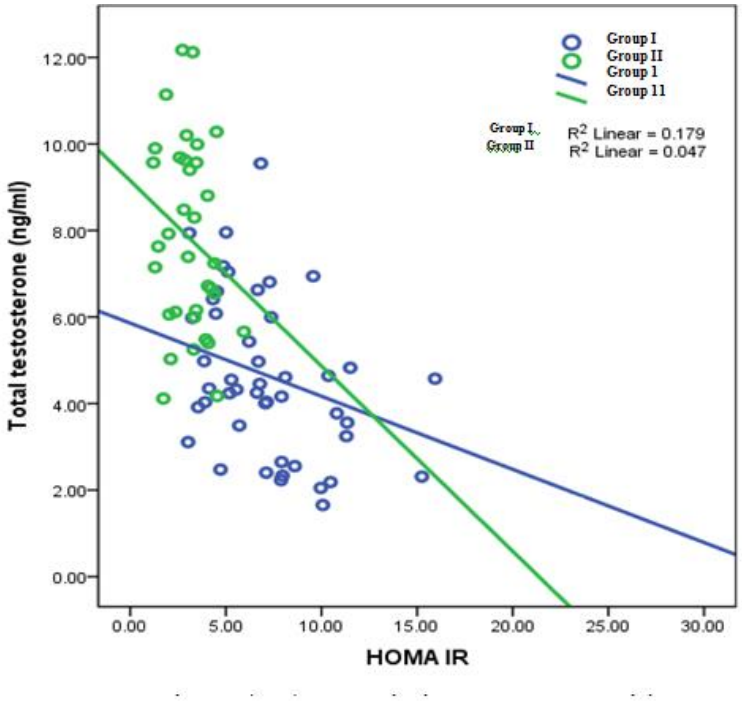
There is a significant positive correlation between HOMA- IR % of group1 and BMI (r= 0.472) (p<0.001), Fasting plasma glucose (r= 0.512) (p<0.000) , insulin levels (r=0.698) (p<0.000) .There is a negative significant correlation between HOMA-IR of group1 and total testosterone (r= -0.424) (p< 0.002).There is a positive significant correlation between HOMA- IR% of group2 and insulin level (r= 0.982) (p< 0.000) as shown in Table (3).

Table (3):Correlations of HOMA-IR with different parameter group1 and group2 .

		HOMA IR	
		Group1with risk factor	Group2without risk factor
Age (years)	r	-0.236	-0.325
	P	0.805	0.061
BMI (Kg/m2)	r	0.472**	0.115
	P	0.001	0.516
WHR	r	0.124	0.013
	P	0.398	0.944
Fasting plasma glucose (mmol/L)	r	0.512**	0.071
	P	0.0001	0.691
Total cholesterol (mg/dl	r	0.237	0.221
	P	0.101	0.208
Triglycerides (mg/dl)	r	0.240	0.060
	P	0.097	0.737
HDL (mg/dl)	r	-0.224	-0.108
	P	0.121	0.545
LDL (mg/dl)	r	-0.064	0.261
	P	0.663	0.135
VLDL (mg/dl)	r	0.233	-0.063
	P	0.107	0.725
insulin µU/mL	r	0.698**	0.982**
	P	0.0001	0.0001
Total testosterone(ng/ml)	r	-0.424**	-0.217
	P	0.002	0.217

* Correlation is significant at the 0.05 level
**Correlation is significant at the 0.01 level.





Discussion:

The present study has shown an inverse correlation between serum testosterone (T) and fasting insulin levels in men [12 ,13,14]. Furthermore, men with insulin resistance states have significantly lower T levels than age-matched healthy men. The mechanism underlying the low T levels associated with insulin resistance in men has not been elucidated. This study has shown that there is significant increase in mean value of HOMA IR in group with risk factor than in healthy group without risk factor . In addition, the study shows that there is positive correlation between HOMA-IR and fasting plasma glucose in group with risk factor , and positive correlation between insulin level and HOMA IR in both groups. Silva et al. [15] found HOMA-IR, positive correlation with 2-h plasma glucose and serum insulin in a group of normal glucose tolerant Brazilian adolescents with family history of type 2 diabetes .

There is a negative significant correlation between total testosterone levels and HOMA-IR in group1 with risk factor . Hyperinsulinemia , as encountered in insulin resistance, might impair testosterone secretion by the Ledig cell, maybe directly since there are insulin receptors on the Ledig cell .

The current findings are consistent with previous studies that included middle-aged and older men . Osuna et al. [16] found a significant negative correlation of each waist circumference, body mass index (BMI), insulin ,and homeostatic model assessment of insulin resistance (HOMA-IR) to testosterone levels in obese men. Yeap et al.[17] have also reported that lower total and free testosterone were independently associated with higher insulin resistance in older men.

In particular , visceral adiposity is an important cause of insulin resistance and also decreases testosterone concentrations through conversion to estradiol by aromatase [18]. In the present study, as well as others [19, 20], testosterone levels in men with

insulin resistance were significantly inverse correlated with BMI. Although BMI and weight are suboptimal markers of visceral adiposity, previous studies have reported an association of loss of weight in obese insulin resistant men with increased testosterone levels [21].

The present study involves men younger than 40 years which is the main difference from other studies in middle and older ages. Also, the relationship between testosterone and insulin resistance at present will be more accurate because testosterone levels decline with aging and will be at a high levels in young adults ,so no other factor affects lower testosterone levels ,In fact this lower testosterone is related to insulin resistance.

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هرمون التيستوستيرون يتنبا بمقاومه الانسولين لدى الرجال الذين لديهم تاريخ عائلي لمرض السكري وارتفاع ضغط الدم

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الخلاصة:
ترتبط مقاومه الانسولين بالمتلازمه الايضيه وبمرض السكري وتمثل عامل خطوره للاصابه بامراض الاوعيه القلبيه. هذه العلاقه قد ترتبط الى حد ما بالعمر وبالتالي حدوث تغييرلهرمون الجنس خصوصا ان انخفاض مستوى هرمون التيستوستيرون ارتبط بمقاومه الانسولين وخطر الاصابه بالنوع الثاني لمرض السكري .ان الهدف من الدراسه هو ايجاد فيما لو كان انخفاض مستوى هرمون التيستوستيرون يرتبط بزياده مقاومه الانسولين لدى الرجال الشباب .
تمت دراسه 83 عينه للرجال الشباب انقسموا الى مجموعتين المجموعه الاولى 49 رجل لديهم عوامل خطوره للاصابه بمقاومه الانسولين(لديهم تاريخ عائلي لمرض السكري ,لديهم ارتفاع بضغط الدم) والمجموعه الثانيه 34 عينه للرجال الذين ليس لديهم عوامل الخطوره للاصابه بمقاومه الانسولين للاعمار من 20-40 سنه . وتم قياس هرمون التيستوستيرون ،هرمون الانسولين ، lipidprofile و تم حساب العمر، كتله الجسم(BMI) ، WHR ، مقاومه الانسولين تم حسابها بطريقه HOMA-IR (homeostatic model) . لقد اعطت المجموعه الاولى اعلى متوسط لمقاومه الانسولين (8.08±1.94) مقارنه بالمجموعه الثانيه (3.10±0.65) بينما اعطى هرمون التيستوستيرون اقل متوسط للمجموعه الاولى (4.49±1.87 ng/ml) مقارنه بالمجموعه الثانيه (7.82±2.21 ng/ml) وبالتالي اعطى التيستوستيرون هرمون علاقه عكسيه مع مقاومه الانسولين في المجموعه الاولى و (r =-0.424 , p= 002)علاقه عكسيه مع هرمون الانسولين (r= -0.541, p< 0.0001) وعلاقه عكسيه مع معدل كتله الجسم (BMI) (r=-0.471 ,p=0.001) بينما اعطت مقاومه الانسولين علاقه طرديه مع (BMI) (r= 0.472) (p<0.001) والانسولين هرمون (r=0.698) (p<0.0001) . ارتبط انحفاض مستوى هرمون التيستوستيرون بزياده مقاومه الانسولين لدى الرجال الشباب .
الكلمات المفتاحيه :التيستوستيرون مقاومه الانسولين .