Some Hormonal Changes in Women with Primary Hypothyroidism under the Effect of Thyroid Hormone Replacement Therapy

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Abstract

Hypothyroidism has been associated with disorders of glucose and insulin metabolism..The present study was designed to evaluate the possible change in some hormones (free testosterone, estradiol, prolactin, insulin), glucose and homeostasis model assessment of insulin resistance (HOMA-IR) in women with primary hypothyroidism under thyroid hormone replacement therapy .This cross-sectional study was carried on 62 hypothyroid patients′ women and 22 healthy women as control group at the specialized center for endocrinology and diabetes, AL-Rasafa Directorate of Health Baghdad, with age range(15-60 years), diagnosed as having primary hypothyroidism on thyroxine replacement therapy with duration not less than four months. Each of the selected patients women and the healthy control were distributed into two groups, normal cyclic and postmenopausal. Blood samples were collected to measure thyroid stimulating hormone(TSH), total thyroxine (TT4) , total triiodothyronine (TT3), free thyroxine(fT4), free testosterone (FT), estradiol(E2) ,prolactin(PRL), insulin , fasting blood glucose(FBG), homeostasis model assessment-insulin resistance(HOMA-IR). The results showed that the majority of hypothyroid women (older than 40 years and obese) had high levels of TSH in normal cyclic and postmenopausal patients women. A significant increase in f T4 and TT4 in postmenopausal patients women when compared with postmenopausal control group f T4 and TT4. A significant increase in free testosterone and FBG and significant decrease in TT3 and E2 levels in normal cyclic patients women when compared with normal cycle control group. High prolactin levels were found in the normal cyclic patients women in comparism with control group. Higher levels of insulin were found in normal cyclic and postmenopausal patients women as compared with control groups, however insulin was not statistically different. Significant increase in HOMA-IR of normal cyclic patients women compared with control group.

In conclusion, elevation of TSH levels in postmenopausal patients women were less than in normal cyclic patients women this explain the increase levels of thyroxine hormone(T4)in this group of patients as compared with both control group and normal cyclic patients women. Some hormonal changes were found in normal cyclic hypothyroid patients women as compared with control group.The alteration of these hormones disappear when euthyroid state restored, so adjustment of thyroxine therapy is required in these patients.

Key words: Hypothyroidism , Thyrid replacement therapy.

بعض التغيرات الهرمونة في النساء المصابات بقصور الغدة الدرقية الابتدائي تحت تأثير علاج الهرمون الدرقي البديل

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الخلاصة

ارتبط قصورالغدة الدرقية مع اضطرابات في التمثيل الغذائي للجلوكوز والأنسولين . صممت هذه الدراسة لتقييم التغير المحتمل في بعض الهرمونات (التستوستيرون الحر، الاستروجين استرادايول، البرولاكتين، الانسولين) ،جلوكوزالدم للصائم و مقاومة الانسولين (HOMA-IR) لدى النساءالمصابات بمرض قصورالغدة الدرقية الابتدائي تحت تأثيرعلاج الهرمون الدرقي البديل . هذه الدراسة العرضية اجريت على 62 أمرأة مصابة بقصور الغدة الدرقية و 22 أمرأة سليمة لمجموعة السيطرة في المركز التخصصي للغدد الصم والسكري،دائرة صحة بغداد الرصافة، باعمار تتراوح بين 15-60 سنة، تم تشخيصهم بالاصابة بمرض قصور الغدة الدرقية بناءا على التقييم التاريخي والسريري والمختبري. إن زيادة تركيزالهرمون المحفز للغدة الدرقية (TSH) هوعادة مشخص للاصابة بالمرض . جميع النساء المصابات عولجوا بالثايروكسين لمدة لا تقل عن اربعة اشه ر.إن النساء المصابات اللاتي تم اختيارهن والنساء السليمات تم توزيعهم الى مجموعتين ،ذوات الدورة الطبيعية وما بعد سن اليأس.

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تم جمع عينات الدم من النساء المريضات والسليمات لقياس التغيرات المحتملة للمؤشرات المدروسة والتي تتضمن :الهرمون المحفز للغدة TSH، الثايروكسين الكلي TT4، TT3، الثايروكسين الحر (f T4)، التستوستيرون الحر، الاستروجين (استرادايول)، البرولاكتين، الانسولين ، جلوكوزالدم للصائم و مقاومة الانسولين (HOMA-IR). اظهرت النتائج ان اغلبية النساء المصابات بقصورالغدة الدرقية هن ممن تزيد اعمارهن عن 40 سنة وبدينات. استنتجت الدراسة وجود ارتفاع في مستويات قياس TSH في النساء المريضات ذوات الدورة الطبيعية، وفي النساء المريضات بعد سن اليأس . كذلك وجدت زيادة معنوية في الثايروكسين الكلي والثايروكسين الحر في النساء المريضات بعد سن اليأس بالمقارنة مع النساء السليمات بعد سن اليأس للثايروكسين الكلي والثايروكسين الحر . بينت النتائج وجود زيادة معنوية بالتستوستيرون الحر وجلوكوز الدم للصائم و نقصان معنوي بهرمون الغدة الدرقية TT3 و هرمون الاستروجين (الاسترادايول) في النساء المريضات ذوات الدورة الطبيعية بالمقارنة مع النساء السليمات ذوات الدورةالطبيعية . ارتفاع مستوى هرمون البرولاكتين في النساء المريضات ذوات الدورة الطبيعية بالمقارنة مع مجموعةالسيطرة . ارتفاع مستويات هرمون الانسولين في النساء المريضات ذوات الدورة الطبيعية و النساء المريضات بعد سن اليأس بالمقارنة مع مجموعات السيطرة ،احصائيا لايوجد فرق معنوي في مستوى الانسولين . زيادة معنوية بمقاومة الانسولين في النساء المريضات ذوات الدورة الطبيعية بالمقارنة مع مجموعة السيطرة .وبذلك يمكن الاستنتاج إن أغلبية النساء المصابات بقصور الغدة الدرقية هن ممن تزيد اعمارهن عن 40 سنة وبدينات . وجد ان ارتفاع مستوى هرمون TSH في النساء المريضات بعد سن اليأس اقل من ارتفاعه في النساء المريضات ذوات الدورة الطبيعية وهذا يوضح الزيادة الحاصلة في هرمون الثايروكسين في هذه المجموعة من المريضات بالمقارنة مع مجموعة السيطرة و النساء المريضات ذوات الدورة الطبيعية . وجدت بعض التغيرات الهرمونية في النساء المريضات ذوات الدورة الطبيعية بالمقارنة مع مجموعة السيطرة . ان تغير هذه الهرمونات يختفي عند اعادة الوظيفة الطبيعية للدرقية ،لذلك يتطلب تنظيم علاج الثايروكسين لتلك المريضات.

الكلمات المفتاحية :قصور الغدة الدرقية ، الهرمون الدرقي البديل .

Introduction

Hypothyroidism has been associated with disorders of glucose and insulin metabolism, involving defective insulin secretion in response to glucose, hyperinsulinemia, altered peripheral glucose disposal, and IR[1].

The mechanisms linking hypothyroidism with IR in general and in skeletal muscles (SM) in particular are still under investigation. Insulin resistance in hypothyroidism is associated with a negative regulation of one or more intracellular enzymes involved in glucose catabolism[2]. An impaired translocation of Glucose Transporter 4 (GLUT4) on the plasma membrane has been also observed in the monocytes of subjects with clinical and subclinical hypothyroidism, in relation to a decreased Insulin-mediated glucose uptake (IMGU)[3]. An effect of thyroid hormones on insulin receptors has been suggested, but the existing data are rather conflicting, supporting either no relationship between thyroid status and the affinity of insulin receptors or diminished high affinity insulin receptors (HAIRs) in hypothyroidism[4].

In patients with primary hypothyroidism, increased levels of thyroid releasing hormone(TRH) can cause elevation of prolactin levels[5]. Many studies supported the existence of interplay between prolactin and insulin along with the influence of dopamine in the regulation of insulin secretion[6].

Hyperinsulinemia increases the production of androgens in the ovaries and of insulin-like growth factor(IGFs) in the liver[7].The direct effect of insulin and IGF-1 is increased 17-hydroxylase activity in the ovaries, causing an excessive production of androgens, particularly androstenedione and testosterone and its precursor, 17-hydroxyprogesterone(17-OHP)[8]. Free testosterone had been found to be positively correlated with insulin resistance[9] ,as well as with components of the metabolic syndrome, including fasting plasma glucose, adiposity[10], fasting and post challenge insulin levels[11], insulin-to-glucose ratio[12], and blood pressure[13]. High levels of free testosterone [11] have been shown to predict incident type 2 diabetes in women, giving the relation between androgens and insulin sensitivity.

The aim of the study was to determine whether there is any change in serum levels of free testosterone, estradiol, prolactin, insulin, glucose and homeostasis model assessment of insulin resistance (HOMA-IR) in women with primary hypothyroidism under thyroid hormone replacement therapy.

Materials and methods

This study was performed on 62 hypothyroid patient women at the specialized center for Endocrinology and diabetes, AL-Rasafa Directrate of health-Baghdad with age range(15-60 years) with mean duration of hypothyroidism of 4 months.The patients women were distributed into two groups: normal cyclic and postmenopausal. These were compared with 22 healthy women as control group with the same age range of patients, and also distributed as normal cyclic and postmenopausal.The hypothyroid women were diagnosed as hypothyroid by a senior physician through historical, clinical, and laboratory assessment. The demonsetration of an elevated TSH concentration is usually diagnostic[14].

Table 1: Characteristics of control women and hypothyroid patients women.

variable	Hypothyroid patients women(mean ±S.D)	Healthy control women(mean ±S.D)
Number (total)	62	22
Normal Cyclic women Age(years) BMI(kg/m²)	42 **37± 9.04** **31.7 ± 5.39**	12 **36 ± 6.68** **29.9 ± 2.73**
Postmenopausal women Age(years) BMI(kg/m²)	20 **52 ± 5.40** **32.3 ± 5.33**	10 **50 ± 4.27** **30.5 ± 3.03**

The data are expressed as mean ± SD.

Exclusion criteria

The study exclude any patient women with: secondary hypothyroidism, PCOS, inherited TBG disease, heart disease , renal disease , liver disease ,pregnancy, lactation, diabetic disease, smoking and any drugs effect thyroid function except thyroxine.

Blood specimen collection and preparation

Blood was taken after 12 hr fasting and at the early follicular phase (in women with normal cycle) for measurement of thyroid function tests (TSH,TT4,TT3,fT4),fasting blood glucose(FBG)levels, fasting insulin levels, free testosterone levels, estradiol levels and prolactin levels.TSH,TT4 and TT3 were measured, radioimmunoassay(RIA kits) while f T4,insulin, free testosterone, estradiol and prolactin immunoassay readymade-kits(ELISA) were had been used.

Statistical analysis

The following statistical data analysis approaches were done through the Statistical Package of Social Sciences (SPSS) program(version-10) and Excel application and used in order to analyze and assess the results of the study:

I . Descriptive data analysis:

Statistical tables (Frequencies, percents), mean value, standard deviation, standard error, (95%) confidence interval or population mean values, two extreme values (min. and max.) respondents.

***II- Inferential data analysis*:**

Student t-test for equality of means coincidence testing in two independent samples.

Results

The results showed that an increase incidence of hypothyroidism in women with age older than 40 years old, while frequency of patients as the following : between (15-19)years old were 2(3.2%),between(20-29)years old were 7(11.3%),between (30-39)years old were 12(19.4%) , between (40-49)years old were25(40.3%) and between (50-60)years old were 16 (25.8%). The majority of hypothyroid patients were obese, in the normal cyclic patients women group were 22 (52.4%) as well as in the postmenopausal patients women were 14 (70%). The results in table(1,2,3) showed high levels of TSH were found in normal cyclic patients women (10.37±3.03, 95% C.I=4.24-16.49 µIU/ml) and in postmenopausal patients women(4.23±1.12, 1.89-6.57 µIU/ml)were observed. A significant increase in f T4 (14.51±0.85 , 12.72-16.30 pmol/l),and TT4 (117.8±8.34,100.31-135.23 nmol/ml) in postmenopausal patients women when compared with postmenopausal control group f T4 (10.58±0.41, 9.64-11.52 pmol/l) and TT4 (89.71±4.19, 80.24-99.1 nmol/ml). A significant increase in the plasma free testosterone(1.65±0.26, 1.11-2.18 pg/ml) and FBG (5.36±0.13, 5.09-5.64 mmol/l)and significant decrease in TT3(1.57±0.07, 1.42-1.71 nmol/ml) and E2(50.63±4.20, 42.15-59.11 pg/ml) levels in normal cyclic patients women when compared with normal cycle control group ,free testosterone (0.76±0.16,0.41-1.11 pg/ml), FBG(4.78±0.19, 4.36-5.20mmol/l) ,TT3 (1.90±0.06, 1.77-2.03nmol/ml)and E2(76.80±9.79, 55.25-98.35pg/ml). High prolactin levels were found in normal cyclic patients women (22.57±4.43, 13.63-31.52 ng/ml) as compared with control group(17.51±1.68, 13.82-21.20 ng/ml). Higher levels of insulin were found in normal cyclic and postmenopausal patients women as compared with control groups ((15.86±1.47 , 12.89-18.84 versus 11.34 ±1.28, 8.52-14.16) , (15.47±1.92, 11.46-19.49 versus 9.90±1.41, 6.71-13.1)µIU/ml) repectively, however insulin was not statistically different. Significant increase in HOMA-IR of normal cyclic patients women (3.83±0.39,3.05-4.62) when compared with control group (2.41±0.29,1.79-3.04).

Table 2: Distribution of thyroid hormones levels in patients and control groups

Parameters	Groups	N	Mean ± Std.E.	95% C. I. for Mean		Min.	Max.	C.S p-value
				L.b.	U.b.			
TSH (µIU/ml)	Control (normal cycle) a	12	1.48 ± 0.18	1.09	1.87	0.30	2.3	a×c p=0.061 NS
	Control (postmenopause) b	10	1.75 ± 0.20	1.31	2.19	0.80	2.7	b×d p=0.655 NS
	Patients (normal cycle) c	42	10.37 ± 3.03	4.24	16.49	0.05	78.0	c×d p= 0.118 NS
	Patients (postmenopause) d	20	4.23 ± 1.12	1.89	6.57	0.04	17.9	
fT4 (pmol/l)	Control (normal cycle) a	12	11.26 ± 0.40	10.38	12.15	9.0	13.9	a×c p=0.299 NS
	Control (postmenopause) b	10	10.58 ±0.41	9.64	11.52	8.9	12.0	b×d p=0.001 HS
	Patients (normal cycle) c	42	12.31 ± 0.50	11.29	13.33	7.2	24.6	c×d p= 0.010 HS
	Patients (postmenopause) d	20	14.51 ± 0.85	12.72	16.30	8.2	24.9	
TT4 (nmol/ml)	Control (normal cycle) a	12	88.53 ± 2.07	83.98	93.08	75.9	99.8	a×c p=0.161 NS
	Control (postmenopause) b	10	89.71 ± 4.19	80.24	99.19	71.7	113.7	b×d p=0.017 HS
	Patients (normal cycle) c	42	102.3 ± 4.92	92.32	112.20	52.3	183.5	c×d p= 0.05 S
	Patients (postmenopause) d	20	117.8 ± 8.34	100.31	135.23	58.3	206.9	
TT3 (nmol/ml)	Control (normal cycle) a	12	1.90 ± 0.06	1.77	2.03	1.6	2.2	a×c p=0.017 HS
	Control (postmenopause) b	10	1.62 ± 0.10	1.39	1.85	1.1	2.0	b×d p=0.314 NS
	Patients (normal cycle) c	42	1.57 ± 0.07	1.42	1.71	0.7	2.7	c×d p= 0.355 NS
	Patients (postmenopause) d	20	1.46 ± 0.10	1.25	1.66	0.8	2.4	

a: control(normal cycle)group, b:control(postmenopause)group, c:patients(normal cycle)group, d:patients(postmenopause)group.
S: significant, NS: non-significant, HS: high significant.
L.b: lower bound, u.b: upper bound.
C.I: confidence interval.

Table 3: Distribution of (free testosterone, estradiol and prolactin) hormones in patients and control groups

Parameters	Groups	N	Mean ± Std.E.	95% C. I. for Mean		Min.	Max.	C.S P-value
				L.b.	U.b.			
FT (pg/ml)	Control (normal cycle) a	12	0.76 ± 0.16	0.41	1.11	0.13	2.1	a×c p=0.047 S
	Control (postmenopause) b	10	1.26 ± 0.32	0.53	1.99	0.03	2.7	b×d p=0.491 NS
	Patients (normal cycle) c	42	1.65 ± 0.26	1.11	2.18	0.04	7.2	c×d p=0.044 S
	Patients (postmenopause) d	20	0.90 ± 0.16	0.57	1.23	0.01	2.6	
E2 (pg/ml)	Control (normal cycle) a	12	76.80 ± 9.79	55.25	98.35	32.48	137.8	a×c p=0.002 HS
	Control (postmenopause) b	10	30.76 ± 7.82	13.06	48.45	6.29	83.9	b×d p=0.623 NS
	Patients (normal cycle) c	42	50.63 ± 4.20	42.15	59.11	14.66	120.2	c×d p=0.001 HS
	Patients (postmenopause) d	20	25.88 ± 3.10	19.39	32.36	7.94	52.8	
PRL (ng/ml)	Control (normal cycle) a	12	17.51 ± 1.68	13.82	21.20	9.59	26.7	a×c p=0.464 NS
	Control (postmenopause) b	10	19.65 ± 2.55	13.88	25.42	9.93	32.4	b×d p=0.287 NS
	Patients (normal cycle) c	42	22.57 ± 4.43	13.63	31.52	3.59	163.0	c×d p=0.045 S
	Patients (postmenopause) d	20	10.91 ± 1.38	8.03	13.79	4.05	29.0	

a: control(normal cycle)group, b:control(postmenopause)group, c:patients(normal cycle)group, d:patients(postmenopause)group.
S: significant, NS: non-significant, HS: high significant.
L.b: lower bound, u.b: upper bound.
C.I: confidence interval.

Table 4: Distribution of of insulin, fasting blood glucose and HOMA-IR levels in patients and control groups.

Parameters	Groups	N	Mean ± Std.E.	95% C. I. for Mean		Min.	Max.	C.S P-value
				L.b.	U.b.			
Insulin (µIU/ml)	Control (Normal cycle) a	12	11.34 ± 1.28	8.52	14.16	4.54	17.87	a×c p=0.100 NS
	Control(Postmenopausal)b	10	9.90 ± 1.41	6.71	13.10	4.05	16.83	b×d p=0.088 NS
	(Normal cycle) patients c	42	15.86 ± 1.47	12.89	18.84	3.80	44.00	c×d p=0.863 NS
	Postmenopausal Patients d	20	15.47 ± 1.92	11.46	19.49	4.35	35.61	
FBG (mmol/l)	Control (Normal cycle) a	12	4.78 ± 0.19	4.36	5.20	3.83	5.68	a×c p=0.025 S
	Control (Postmenopausal)b	10	5.37 ± 0.21	4.90	5.83	4.45	6.52	b×d p=0.835 NS
	(Normal cycle) patients c	42	5.36 ± 0.13	5.09	5.64	4.10	8.20	c×d p=0.764 NS
	Postmenopausal Patients d	20	5.43 ± 0.15	5.10	5.75	3.60	6.96	
HOMA-IR	Control (Normal cycle) a	12	2.41 ± 0.29	1.79	3.04	0.77	3.90	a×c p=0.05 S
	Control (Postmenopausal)b	10	2.37 ± 0.37	1.55	3.20	0.80	3.90	b×d p=0.099 NS
	(Normal cycle) patients c	42	3.83 ± 0.39	3.05	4.62	0.70	11.40	c×d p=0.950 NS
	Postmenopausal Patients d	20	3.80 ± 0.52	2.70	4.89	0.89	8.60	

a: control(normal cycle)group, b:control(postmenopause)group, c:patients(normal cycle)group, d:patients(postmenopause)group.
S: significant, NS: non-significant, HS: high significant.
L.b: lower bound, u.b: upper bound.
C.I: confidence interval.

Discussion

The results of an increase incident of hypothyroidism in women with age older than 40 years old were in agreement with the results of Yamada et al.(1984)[15], who referred this to increase in the level of production of antithyroglobulin antibodies , antiperoxidase antibodies and increase level of TSH hormone ,also the mean of TRH hormone increase with advance age specially in women. Subtle elevation of TSH is associated with measurable deficiency in resting energy expenditure and increased body weight. Fox et al.(2008) [16] noted that modest increases in serum TSH concentration within the reference range may be associated with weight gain , women gained more weight than men did , although both sexes gained.the result of this study confirmed previous results that hypothyroidism and obesity frequently co-exist in varying degree of severity.

Most patients in this study showed persistent elevation of TSH levels, despite they were under treatment for hypothyroidism. The elevation of TSH levels in postmenopausal patients women is less than in normal cyclic patients women**,** this may explained by the decreased clearance of thyroxine (T4) in postmenopausal patients women and this may confirmed by the significant higher level of thyroxin(fT4, TT4) in postmenopausal patients women when compared with both control group and normal cyclic patients women[17]. In most patients the circulating concentration of TSH serves as a reflection of thyroid hormone effect upon the pituitary and thereby as an effective marker of the adequacy of the replacement dose[18]. Triiodothyronine represented the active form of thyroid hormone for it easy separation from binding protein and easy binding to the receptors in the cells of target organ ;while T4 is the less active biologically than T3 ,and T4 represent the stored spare in the blood. This explain the presence of a significant difference in T3 level between patients women group and control group, because it is in continueous use[19]. This finding is confirmed in this study by the presence of significant decrease in T3 levels in the normal cyclic patients women in comparison with control group.

There is a significant elevation of free testosterone levels in normal cycle of patients women in comparism with control group. Estrogen deficiency leads to reduced sex hormone binding globulin(SHBG) production in the liver[20]. Testosterone has a high affinity for SHBG.With decreasing SHBG concentration, less testosterone is bound to SHBG and the free testosterone in the blood increases, resulting in a relative hyperandrogenemia. The present work demonstrated that estradiol level is decreased in both groups of patients women (normal cyclic and postmenopausal) when compared with their control groups. Estradiol is produced by both the interconversion of estrone[21] and the aromatization of testosterone. The main source of estrogen in postmenopausal women appears to be the aromatization of plasma androstenedione to estrone[22]. Women with hypothyroidism had decreased metabolic clearance rates of androstenedione and oestrone and an increase in peripheral aromatization [23] . The present study showed a high levels of prolactin hormone in normal cyclic patients women as compared with control group. Hyperprolactinaemia is not seen in all patients with hypothyroidism, but it has been reported to occur in 0-40% of hypothyroid patients[24]. Prolactin hormone levels return to normal with appropriate L-thyroxine treatment. There is a significant increase in FBG levels and HOMA-IR in the normal cyclic patients women when compared with control group. Obesity is a predictor of impaired fasting glucose(IFG), and pre-diabetic state. Insulin resistance is increased by abdominal obesity, and fasting hyperinsulinemia farming a risk factor for the development of impaired fasting glucose[25] . The loss of T3 within the cells leads to increase in the level of TSH and the reduction of the activity of GLUT-4 in the insulin sensitive tissue such as skeletal muscles and adipose tissues, thus contributing to the stimulation of insulin resistance , this was observed in high percentage among obese individuals[26].The results of the present study were in agreement with study by Singh et al.(2010)[27]. The study concluded that patients with hypothyroidism demonstrated insulin resistance as observed by the higher HOMA-IR level as compared to controls. Maratou et al.(2009)[3] ,had concluded that insulin resistance is associated with comparable HOMA-IR values in overt hypothyroidism and subclinical hypothyroidism. The study showed that insulin resistance in hypothyroidism is associated with a negative regulation of one or more intracellular enzymes involved in glucose catabolism.

Conclusions

The majority of hypothyroid patients women were older than 40 years old and obese. The elevation of TSH levels in postmenopausal

patients women were less than in normal cyclic patients women, this indicate good compliant with treatment in postmenopausal group and this explain the increase levels of thyroxine hormone(T4)in this group of patients. Some hormonal changes were found in normal cyclic hypothyroid patients women as compared with control group. The alteration of these hormones disappears when euthyroid state restored, so adjustment of thyroxine therapy is required in these patients. Further research, is needed to optimize thyroid disease monitoring therapy, adjust dosages and encourage compliance.

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