

Indices of Free Testosterone And Hyperandrogenemia in Relation To Hirsutism in Middle Aged Egyptian females***Kandil H.T., * Hassan Z.A., * Abaza D.M. ** Abd. El Fattah . A.M.*** Endocrinology and ** clinical pathology
Departments- Al- Azhar university (Girls)**Abstract**

Hirsutism is an androgen excess related disorder that commonly affects women causing a variety of negative metabolic disturbances. Early and accurate diagnoses of androgen over-production or hypersensitivity to normal circulating androgen have an important implication for treatment and follow up of patients.

The aim of this work is to study the validity of hyperandrogenemic index (HAI) and index of free testosterone (IFT) in, diagnosis of hirsute Egyptian women, and its correlation to hair score as a clinical marker for hirsutism.

Twenty-four hirsute women aged 19-32 y's, median (24.25 ± 4.3) were studied. Ten age matched nonhirsute females, were studied as controls. Patients and control were subjected to the following, full history and clinical examination. Biochemical and hormonal parameters were measured, fasting blood sugar (FBS), 2 hours post prandial blood sugar (2h pp BL. S), serum total testosterone (TT), free testosterone (FT), dihydroepiandrosterone (DHEA), Dihydroepiandrosterone sulphate (DHEAS) androstenedion (ADION), prolactin (PL) and sex hormone binding globulin (SHBG). Index of free testosterone (IFT) and index of hyperandrogenemia (IHA) were calculated. Results showed significant higher BMI ($P < 0.009$), 2hrs PPBL.S. ($P < 0.001$), TT ($P < 0.005$), FT ($P < 0.000$), SHBG ($P < 0.02$) and (ADION) ($P < 0.000$) in hirsute females compared to controls. Hair score was positively correlated with IFT only while it was not correlated with all of the measured hormones.

FT was positively correlated with BMI ($P < 0.004$), FBS ($P < 0.001$) and 2hrs PPBL.S ($P < 0.000$). While TT was positively correlated with BMI ($P < 0.001$). Androstenedion was positively correlated with systolic BL.P ($P < 0.000$), diastolic BL.P ($P < 0.02$), FBS ($P < 0.001$) and 2hrs PPBL.S ($P < 0.000$). IFT was positively correlated with hair score ($P < 0.05$), BMI ($P < 0.01$), systolic BL.P ($P < 0.004$), FBS ($P < 0.001$) and 2hrs PPBL.S ($P < 0.01$).

SHBG was negatively correlated with systolic BL.P ($P < 0.04$), FBS ($P < 0.05$) and 2hrs PPBL.S ($P < 0.03$).

Conclusion

Hirsutism is a clinical symptom associated with hyperandrogenism. It must be diagnosed accurately, and as early as possible. The most accurate diagnostic measurement is IFT rather than IHA or other hormones individually.

Hirsutism must be studied in depth not as a simple complaint, as it may be the entrance to the more complex metabolic syndrome.

IFT is beneficial in diagnosis of borderline hirsute women.

Introduction

Hirsutism is one of the most common endocrine disorders in women of fertile age. In these women, the hairiness implies the presence of abnormal androgen level / or action, which may represent a serious or,

more likely, a nonserious medical problem; (*George et al 2003*).

Increased androgen production causes well-documented negative metabolic changes, (*Conway et al 1992*). Those women are at

substantially higher risk of hypertension, coronary artery disease and non-insulin dependent diabetes mellitus, (*Dahlgren et al 1992 and Cibula et al 2000*).

Proper diagnosis of hirsutism and / or hyperandrogenism is very important from the clinical point of view and has implications for future treatment and follow up of patients. Abdominal and pelvic examination is important in patients with hirsutism because more than half of them are due to ovarian or adrenal cause, while idiopathic hirsutism is common also, it is diagnosed by exclusion of other causes (*Gold Zieher + Young., 1992*).

Examination of the skin for acanthosis nigricans and body mass index are of importance, as a manifestation of insulin resistance which may be associated with increasing risks of hypertension and coronary heart disease (*Wild, 1995*).

The spectrum of clinical presentations of hirsute women ranges from normal menses and mild hirsutism to amenorrhea and signs of virilization. Testosterone ranges from normal to frank elevation (*Smith et al 1979*). In idiopathic hirsutism the most often reported parameter is the level of testosterone or index of free testosterone (IFT), but increased levels of androstenedione (representing the 5 α -reductase enzyme activity) and/or other androgen precursors is the only finding in many patients. More over the androgen levels may be found close to the upper or lower reference value and may be not accurate in diagnosis of hirsute case (*Hatch et al 1981*).

Aim of the work

To study the validity of Index of hyperandrogenemia (IHA) and Index of free Testosterone (IFT) in diagnosis of hirsute Egyptian women, and its correlation to hair score as a clinical marker for hirsutism.

Subjects and methods

The present study included 24 hirsute young women aged (19-32 years), median (24.25 \pm 4.3). They were selected from the outpatient clinic of Endocrinology

Department Al-Zahraa university hospital from 2001 through 2002 year. Exclusion criteria included history of medication that may affect hair growth, ovarian dysfunction that may cause hormonal disturbances in the preceding three months. Endocrinal disorders including thyroid dysfunction Cushing's syndrome and diabetes mellitus. Other cardiac, chest or abdominal illnesses were also excluded. Ten age matched non hirsute women without clinical or hormonal evidence of endocrine disease served as controls. All women participating in the study gave their informed consent.

Methods

All women included in the study were subjected to the following : full history taking included onset of hirsutism, menstrual history and family history of similar condition. Clinical examination included, pulse, arterial blood pressure measurements. Anthropometric measurements, included body height and weight. Body mass index (BMI) was calculated as weight in kilogram divided by the square of height in meter (*flier and faster 1997*). Acne, acanthosis nigricance were also examined.

Increased body hair was graded using *Ferriman and Galway* methods (F-G score). Hirsutism was defined as (F-G score) greater than 6 (*Ferriman and Gallaway 1961, Knochemhaver et al 1998*). Fasting and 2hrs postprandial blood sugar were measured.

Hormonal assays: blood samples were collected from all women in the early follicular phase "between day 3 and 6 of the menstrual cycle" then allowed to clot at room temperature, and centrifuged. Separated serum was collected and frozen at- 20 c^o until estimation. The following parameters were evaluated; total, free testosterone and androstenedione were assessed by radioimmunoassay method (*Judd and Yen., 1973*). DHEA, DHEA-S and SHBG were measured by using radioimmunoassay method (Immunotech-IOT, Marseille, France). Kit from Gamatrade company (*Abraham 1979*).

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The index of free testosterone (IFT) was calculated based on the levels of total testosterone and SHBG according to the formula:

$$\text{IFT} = 100 \times \text{XT} \text{ (nm/L)} / \text{SHBG} \text{ (nmol/L)}$$

The index of hyperandrogenemia (IHA) was calculated according to the following formula

$$\text{IHA} = 5 \sqrt{\text{IFT} \times \text{ADTON} \times \text{DHEA} \times \text{DHEAS}}$$

The fifth root in the formula was chosen for the best approximation to gaussian data distribution enabling the utilization of simple statistical methods (Cibula et al., 2000).

The reference values for normal hormonal levels were as follow: T.T (0.5-2.63 mg/l), FT (0.8 – 1.9mg/l), androstenedione (1.57-5.4 nmol) DHEA (0.8-10.5 mg/l), DHEA-S (2.4-14.5 M mol/l) and SHBG (43.2-96.0 nmol/L).

Table (1): Mean ± SD of Demographic, Clinical Parameters, in Hirsute and Control Groups:

Parameters	Hirsute	Control	T	P
Age in years	24.25 ± 4.33	25.1 ± 5.13	- 0.495	> 0.05
BMI Kg/m ²	30.37 ± 3.21	27.0 ± 3.23	0.278	0.009*
Age of menarche	12.83 ± 0.82	12.9 ± 1.1	- 0.196	> 0.05
Systolic B1/P	121.25 ± 12.87	118.5 ± 12.48	0.572	> 0.05
Diast B1/P	79.38 ± 8.08	77.0 ± 7.89	0.75	> 0.05

*Significant higher BMI in hirsute compared to control group

Table (2): Mean ± SD of Biochemical and Hormonal Parameters in Both Hirsute and Control Groups.

	Hirsute	Control	T	P
FBL.S mg/ dl	92.04 ± 13.2	82.8 ± 9.64	1.86	> 0.05
2hrs PPBL.S mg/dl	110.58 ± 12.42	94.2 ± 9.5	3.73	< 0.001*
TT	1.06 ± 0.43	0.63 ± 0.2	3.01	0.005*
FT	2.16 ± 0.8	0.88 ± 0.4	4.75	<0.000*
DHEA	9.32 ± 7.95	5.1 ± 2.05	1.64	>0.05
DHEAS	6.56 ± 4.54	3.71 ± 1.59	1.92	>0.05
Prolactin	12.22 ± 3.25	9.13 ± 4.1	2.1	0.044*
SHBG	67.5 ± 22.59	88.0 ± 14.07	-2.39	0.02*
ADION	15.87 ± 5.98	7.67 ± 1.9	4.27	0.000*

*Significant difference in 2h.P.P.Bl.s, TT, FT, prolactin, SHBG and ADION in hirsute compared to control group.

Table (3) Correlation Between Hair Score, Clinical Data and Blood Sugar with Different Hormonal Values in Hirsute Group

Parameters	Hair score	BMI kg/m ²	Blood pressure mm/hg		Bl. Sugar mg/dl	
			Systolic	Diastolic	Fasting	PP Bl.s
TT	Ns	ro.677 P<0.001**	Ns	Ns	Ns	Ns
FT	NS	Ro.4/5 P< 0.04*	Ns	Ns	ro.643 P <0.001**	r 0.654 P<0.001**
SHBG	NS	NS	r-0.406 P< 0.04*	Ns	r-0.400 P<0.05*	r-0.433 P< 0.03*
ADION	Ns	Ns	r-0.669 p<0.000**	r-0.456 p<0.02*	r-0.644 p<0.001**	r-0.710 p<0.000**
IFT	0.508 P<0.05*	r-0.517 p<0.01**	r-0.569 p<0.004**	NS	r-0.642 p<0.001**	r-0.508 p<0.01**
IHA.	NS	NS	NS	NS	NS	NS

* Significant correlation at p value < 0.05

** Significant correlation at p value <0.01

Table 3 showed

Positive correlation between hair score and IFT only

- BMI positively correlated with TT, FT and IFT
- Systolic Bl. P positively correlated with ADION & IFT
- Diastolic Bl p positively correlated with ADION
- Fasting & 2hs PP Bl-s was positively correlated with FT, ADION & IFT while negative correlation was found between SHBG and systolic Blood pressure fasting and 2h PP Bl. sugar

Discussion

Hirsutism is one of the most common endocrinal disorders. About 8% of racially mixed, non hospital- based female

population showed evidence of mild hirsutism (ferryman Gallwey scor> 6) (Konchenhaver *et al.*, 1998). Others rely on biochemical evaluation as opposed to clinical criteria to document hyperandrogenism. Most commonly, this is done with serum assay to document elevation in circulating androgen levels, (Ayala *et al.*, 1999 and Penttila *et al.*, 1999).

While 60 to 80% of women with hirsutism have increased levels of circulating androgens, degree of hirsutism correlates poorly with androgen levels, (Carmina and lobo 1991).

In the present study we compared the significance of clinical findings as well as the laboratory and hormonal levels in both hirsute and non-hirsute group. Also we correlated hair score (F-G score) with all studied hormones, IFT and IHA as a trial to

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find the most accurate and reliable method for diagnosis of hyperandrogenemia.

As regard the clinical findings we found significant higher BMI in hirsute compared to control group. The same result was found by *Nike et al., (2003)* and *Dunaif et al., (1989)*. They found that BMI was significantly higher in hirsute compared to controls.

In this study, correlating BMI with all studied hormones, revealed positive correlation with TT, FT and IFT. Insignificant correlation was found with the other studied androgenic hormones.

In the current study we found significant elevated 2hs. Postprandial blood sugar in hirsute group compared to control and non significant difference between F.B.I.s among both groups. These results are in agreement with *Wild (1995)* and *Dunaif, (1995)*, who found strong relationship between hyperandrogenism and insulin resistance type 2 diabetes, hypertension and PCOS.

In the current study, we correlated fasting and 2hs post prandial blood sugar with different studied hormones. Significant positive correlation was found with free testosterone and androstenedione only. In agreement with our results (*Conway et al., 1992*), found that impaired glucose tolerance and type 2 diabetes were found in 40 to 45% of patients with PCOS and hyperandrogenism. Also *Legro et al., (1999)* and *Ehrmann et al (1999)*, reported the presence of hyperinsulinemia and insulin resistance with glucose intolerance in women with hyperandrogenemia associated with PCOS. Hyperglycemia found in our cases could be explained by hyperinsulinemia and insulin resistance, which may be induced by obesity or hyperandrogenemia. SHBG was negatively significant with both fasting and 2 hrs postprandial Blood sugar. This negative correlation may be due to associated low total testosterone with increased SHBG.

Ehrmann et al., (1995) reported that undiagnosed type 2 diabetes mellitus is very prevalent, and the rate of conversion to frank type 2 diabetes is at least five folds in obese hyperandrogenemic PCOS women compared to normal.

In the present study correlation of blood pressure changes with different hormonal levels revealed positive correlation between androstenedione with systolic and diastolic blood pressure. These results are mostly due to increased 5 α -reductase enzyme activity, which leads to increased response to the circulating androgen, which may leads to hirsutism, insulin resistance and PCOS which is strongly related to dyslipidemia and coronary heart disease. Negative correlation was found between SHBG and systolic blood pressure. This result may be due to decreased level of free testosterone associated with increased SHBG. Similar results were found by (*Conway 1992 and Garg, 1998*).

Kieren et al., (2000) and *Conway et al (1992)* reported that hyperandrogenemia associated with PCOS is usually accompanied by hyperinsulinemia, insulin resistance, hyperlipidemia, hypertension and associated risk of coronary heart disease.

In the present study we correlated hair score (FG- Score) with different hormonal parameters, IFT and IHA. Significant positive correlation was found with IFT and not with IHA or other hormones.

Haseltine et al., (1994) demonstrated a highly significant correlation between F-G score and IFT as well as DHEA. *Cibula et al (2000)*, studied the F-G score with all androgenic hormones as well as IFT and IHA and found that the strongest relationship was between F-G score and IHA, correlation was significant also with androstenedione and DHEA, while it was insignificant with IFT.

The difference between our results and the other may be due to small number of studied group, low mean value of FG-score of these patients (9.3 ± 2.1). The studied hormones were mildly elevated and most of them were closely near to high normal values.

Diagnosis of hirsutism is usually not dependent on single hormone measurement because free testosterone level may increase in case of decreased sex hormone binding globulin, also the other androgenic hormones may be mildly elevated, so accurate

diagnosis of hyperandrogenemia is multi hormonal dependent formula which may diagnose the presence of hyperandrogenism but not diagnostic to the cause of hyperandrogenism, that needs another investigations.

Conclusion

Hirsutism is a clinical symptom associated with hyperandrogenism. It must be diagnosed accurately and as early as possible. The most accurate diagnostic measurement is IFT rather than IHA or other hormones individually.

Hirsutism must be studied in depth not as a simple complaint as it may be the entrance to the more complex metabolic syndrome.

IFT is beneficial in diagnosis of borderline hirsute women.

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معاملات التستوستيرون الحر وارتفاع هرمونات الذكورة في الدم وعلاقته بالشعر الذكوري الزائد في السيدات المصريات متوسطات العمر

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الشعر الذكوري الزائد في السيدات هو اضطراب يتعلق بزيادة هرمونات الذكورة، وهو اضطراب شائع يسبب سلبيات في عملية الايض. التشخيص المبكر والدقيق لاضطراب هرمونات الذكورة او زيادة حساسية الخلايا لهذه الهرمونات شى بالغ الاهمية فى علاج ومتابعة هؤلاء المرضى.

الهدف من البحث:

هو دراسة قيمة وفائدة معامل زيادة الاندروجين ومعامل التستوستيرون الحر فى تشخيص السيدات المصريات اللاتى يعانين من زيادة فى نمو الشعر الذكري بالجسم وعلاقة هذين المعاملين بمعدل زيادة الشعر والمشرات الاكلينيكية المصاحبة له فى السيدات اللاتى يعانين من هذه المشكلة.

طريقة البحث:

فى هذا البحث تم دراسة 24 سيدة تتراوح اعمارهن بين 19-32 سنة بمتوسط عمرى (24.25 ± 4.3) . يعانين من مشكلة نمو الشعر الذكوري. كما تم دراسة عشر سيدات فى نفس العمر ولا يعانين من هذه المشكلة كمجموعة ضابطة. مجموعة المريضات والمجموعة الضابطة خضعن للاتى:
دراسة تاريخ المرض وفحص اكلينيكي كامل، كما تم عمل التحاليل الكميائية والهرمونية الاتية:

- سكر صائم وبعد الاكل بساعتين.
- تستوستيرون كلى وحر، هرمونات الذكورة المفترزة من الغدة فوق الكلوية (داى هيدروابى اندروستيرون) و (داى هيدروابى اندروستيرون سلفات).
- اندروستيديون- برولاكتين- الجلوبيولين الحامل لهرمون الذكورة.
- كما تم حساب معامل التستوستيرون الحر ومعامل ارتفاع الاندروجين فى الدم.
- وكانت النتائج كالاتى:
- وجد ارتفاع ذو دلالة احصائية فى معامل الكتلة الجسمية، السكر بعد الاكل بساعتين والتستوستيرون الكلى الحر والجلوبيولين الحامل لهرمون الذكورة والاندروستيديون فى المجموعة المريضة مقارنة بالمجموعة الضابطة.
- معدل نمو الشعر الذكوري فى الجسم كان ذو دلالة احصائية ايجابية مع معامل التستوستيرون الحر فقط وليس له علاقة بمعامل زيادة الهرمونات الذكورية او الهرمونات الاخرى كلا على حدة.
- التستوستيرون الحر كان ذو علاقة احصائية ايجابية مع معامل كتلة الجسم والسكر الصائم والسكر بعد الاكل بساعتين بينما كان التستوستيرون الكلى ذو علاقة ايجابية مع معامل كتلة الجسم فقط.
- الاندروستيديون كان ذو علاقة احصائية ايجابية مع ارتفاع ضغط الدم والسكر فى الدم سواء كان صائما او بعد الاكل بساعتين.

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- معامل زيادة التستوستيرون الحر كان ذو علاقة احصائية ايجابية مع معدل نمو الشعر ومعامل الكتلة الجسمية وارتفاع ضغط الدم والسكر الصائم والفاطر بالدم.
- اما الجلوبيولين الحامل لهرمونات الذكورة كان ذو علاقة احصائية سالبة مع ضغط الدم والسكر الصائم وبعد الاكل بساعتين.

ويستنتج من هذا البحث:

ان الشعر الذكوري الزائد في السيدات هو عرض غالبا ما يصاحب زيادة هرمونات الذكورة وهذا لا بد له من التشخيص المبكر الدقيق كلما امكن.
اكثر القياسات دقة هو قياس عامل التستوستيرون الحر اكثر من عامل زيادة هرمونات الذكورة او كل هرمون على حده. الشعر الذكوري الزائد لا بد وان يدرس بعمق (وليس كشكوى بسيطة) لانه ربما يكون مدخلا لمتلازمة ايضيه اكثر تعقيدا.