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Serum sex hormone binding globulin profile and its association with insulin resistance in Chinese peri-menopausal women

Profil stężeń globuliny wiążącej hormony płciowe w surowicy i jego związek z insulinoopornością u Chinek w okresie okołomenopauzalnym

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Abstract

Introduction: The aim of this study was to measure serum sex hormone binding globulin (SHBG) profile in Chinese peri-menopausal women, and assess its correlation with insulin resistance (IR)-related parameter, namely HOMA-IR, in this special population.

Material and methods: A cross-sectional study by the method of cluster sampling was performed in 1,827 women, who were in hospital for routine check-up. Serum SHBG profile and anthropometric indices of hormonal, adiposity, and metabolic variables were measured. According to their age and menstruation status, the subjects were divided into three groups: pre-menopause group, peri-menopause group, and post-menopause group.

Results: Serum SHBG level was found to be negatively correlated with BMI in all groups and to increase in parallel with age in women of reproductive age. However, independently of age, it significantly increased from the onset of menopause transition, and slightly declined after menopause. After adjustment for age and BMI, HOMA-IR in peri-menopausal women was closely related only to SHBG. SHBG level was found to be the only independent significant determinant of HOMA-IR. On the basis of ROC curve analysis for the prediction of insulin resistance using HOMA-IR value, AUC for SHBG reached a value of 0.816 (0.636–0.996, 95% confidence interval). The best cut-off value that discriminates peri-menopausal women with or without insulin resistance is 41.73 nmol/L, with a sensitivity of 81.4% and a specificity of 87.5%.

Conclusions: Low SHBG level may be an independent risk factor of insulin resistance in Chinese peri-menopausal women. **(Endokrynol Pol 2013; 64 (3): 197–202)**

Key words: *sex hormone binding globulin (SHBG), peri-menopause, insulin resistance, predictive value*

Streszczenie

Wstęp: Celem badania było oznaczenie profilu stężeń globuliny wiążącej hormony płciowe (SHBG) w surowicy u Chinek będących w okresie okołomenopauzalnym oraz ocena korelacji tego profilu z parametrem insulinooporności HOMA-IR w tej szczególnej populacji.

Materiał i metody: Przeprowadzono badanie przekrojowe metodą doboru grupowego z udziałem 1827 kobiet przebywających w szpitalu na rutynowych badaniach kontrolnych. Oznaczono profil stężeń SHBG i parametry statusu hormonalnego, parametry otyłości i parametry metaboliczne. Uczestniczki badania podzielono ze względu na wiek i status menstruacyjny na trzy grupy: grupę w okresie przedmenopauzalnym, grupę w okresie okołomenopauzalnym i grupę w okresie pomenopauzalnym.

Wyniki: Stwierdzono, że stężenie SHBG w surowicy wykazuje ujemną korelację z BMI we wszystkich grupach i wzrasta z wiekiem kobiet w wieku reprodukcyjnym. Stężenie SHBG ulegało też, niezależnie od wieku, znamiennemu wzrostowi od początku zmian menopauzalnych, a następnie, po menopauzie, ulegało nieznacznemu zmniejszeniu. Po wzięciu poprawek na wiek i BMI, stwierdzono, że HOMA-IR u kobiet w okresie okołomenopauzalnym wykazuje ścisły związek wyłącznie z SHBG. Stwierdzono, że stężenie SHBG jest jedynym niezależnym istotnym determinantem HOMA-IR. Na podstawie analizy krzywej ROC dla predykcji insulinooporności na podstawie wartości HOMA-IR stwierdzono, że AUC dla SHBG osiąga wartość 0,816 (95% przedział ufności: 0,636–0,996). W przypadku kobiet w okresie okołomenopauzalnym najlepszą wartość odcięcia odróżniającą kobiety z insulinoopornością od kobiet bez insulinooporności jest 41,73 nmol/l przy czułości wynoszącej 81,4% i swoistości wynoszącej 87,5%.

Wnioski: U Chinek w okresie okołomenopauzalnym niskie stężenie SHBG może stanowić niezależny czynnik ryzyka insulinooporności. **(Endokrynol Pol 2013; 64 (3): 197–202)**

Słowa kluczowe: *globulina wiążąca hormony płciowe (SHBG), okres okołomenopauzalny, insulinooporność, wartość predykcyjna*

Introduction

Peri-menopause and early post-menopause represent a critical period characterised by altered ovarian function, presenting as gradual and fluctuating decline of sex steroids, mostly oestradiol, synthesised and secreted by the ovaries [1]. Loss of ovarian oestrogen production is the key pathophysiological event responsible for

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the consequences of menopause, including oestrogen deficiency symptoms such as hot flushes, insomnia, depression and dyspareunia. Actually, the negative alterations of metabolic processes, latent inside the body, are not as provoking and prominent as the common complaints mentioned above, while the subsequent sequelae predispose this special population at high risk of developing long-term consequences, such as cardiovascular disease (CVD) and osteoporosis [2, 3]. Despite limited understanding of the exact mechanism by which oestrogen deficiency leads to increased CVD risks, several reports have revealed the effects of oestrogen deficiency on body fat distribution and excess body fat, and consequently insulin resistance (IR), which then increases the risk of dyslipidemia, inflammation, altered coagulation, and atherosclerosis [4–6]. Although IR can possibly be a result of physiological change directly due to ageing, it has been more noted as the central aetiological factor of all CVD-correlated metabolic disorders, whether in relation to menopause or not [7].

Sex hormone-binding globulin (SHBG) is a circulating glycoprotein involved in transporting testosterone and oestradiol, modulating their serum concentrations in biological active format and influencing their bioavailability. It is mainly synthesised in the liver and binds testosterone with high affinity and oestrogens with lower affinity. Previous studies have demonstrated oestrogens as a promoting factor, and testosterone as an inhibiting factor, of the synthesis and blood levels of SHBG [8, 9]. Moreover, insulin has been shown to be an important inhibiting regulator of SHBG synthesis *in vivo* and *in vitro*, and to block the stimulatory effect of 17β-oestradiol and T_4 on SHBG [9]. Considering its close relationship with sex steroids, SHBG has been studied in the population of both pre-menopausal and post-menopausal women [2, 10], showing the association between SHBG and IR. In addition, SHBG may have biological actions beyond simply binding circulating sex hormones, which may impact on IR [11].

Given the paucity of relevant literature reported in mainland China, in the present study SHBG concentrations were determined in Chinese peri-menopausal women defined by the criteria of the Stages of Reproductive Ageing Workshop (STRAW), and as well those within pre-menopause and post-menopause who were recruited as controls. Also, the relationship between SHBG levels and an IR-related parameter, namely HOMA-IR, was evaluated.

Material and methods

Subjects

This cross-sectional study was carried out by the method of cluster sampling on 1,827 adult women aged 18 to 89 years referred to our hospital for routine check-up in 2009 and 2010. None of the women studied had known cardiovascular disease, thyroid disease, neoplasms, chronic renal failure, chronic hepatopathy or a history of ovarectomy. Furthermore, no women had been on any medications within the previous three months, including oral contraceptives; glucocorticoids; ovulation induction agents; antidiabetic and antiobesity drugs; or oestrogenic, antiandrogenic, or antihypertensive medication; or drugs known to interfere with carbohydrate metabolism. The presence of medical conditions was assessed through self-report. Thyroid status was evaluated by free T3 (fT3), free T4 (fT4) and thyrotrophin (TSH) levels.

The menopausal status of each subject was defined according to the criteria of the Stages of Reproductive Ageing Workshop (STRAW) based on the retrospective menstrual calendars [12]. Women reporting a regular menstrual cycle were classified as pre-menopausal; peri-menopause was defined as regular menstrual cycles but with duration changes of seven days or more, and as amenorrhoea for less than 12 months once during a year; having 12 consecutive amenorrhoea with no other causes was defined as post-menopause. In addition, we determined follicle stimulating hormone (FSH) and oestradiol (E_2) blood levels as supplementary indicators of menopausal status, as previously suggested [13]. After providing written informed consent, all participants had blood taken in the fasted state, and essential anthropometric parameters (height, weight, waist and hip circumference) were measured.

Anthropometric measurements

All study participants underwent classic anthropometric parameters measurements (height, weight, waist and hip circumference), carried out three times by a single tester. The average of two measurements of blood pressure (BP) with the subject in the sitting position was taken at 5 min intervals after resting for at least 15 min.

Height and weight were measured in light clothing without shoes. Body height was measured by a statometer and body weight by a digital electronic weighing scale. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres. Waist circumferences were measured using a flexible measuring tape, midway between the xiphoid and the umbilicus during the mid-inspiratory phase. Hip circumference was obtained as the widest circumference at the level of the buttocks.

Biochemical and hormonal analysis

After an overnight fast, blood samples were collected between 08:00 and 10:00 a.m. Samples were stored at −80°C and measured, as previously described [14], within six months.

Table I. *Comparisons of clinical and biochemical characteristics in three study groups*
Tabela I. *Porównanie trzech badanych grup pod względem parametrów klinicznych i biochemicznych*

	Pre-menopause group	Peri-menopause group	Post-menopause group
	n = 1249	n = 239	n = 339
Age (years)	30.09 ± 8.16	48.88 ± 3.42*	56.80 ± 5.01*, **
BMI [kg/m^2]	21.49 ± 7.21	23.33 ± 3.15*	23.26 ± 3.34*
WC [cm]	73.08 ± 8.31	82.28 ± 8.44*	82.53 ± 8.15*
WHR	0.81 ± 0.06	0.85 ± 0.05*	0.86 ± 0.06*, **
SBP [mm Hg]	111.77 ± 12.75	118.94 ± 15.56*	123.12 ± 17.75*, **
DBP [mm Hg]	72.30 ± 9.08	78.00 ± 9.80*	78.90 ± 10.20*
FPG [mmol/L]	5.25 ± 0.70	5.14 ± 0.82	5.38 ± 0.99*, **
FIN [μU/mL]	6.08 ± 23.13	7.01 ± 7.57	7.09 ± 4.63
HOMA-IR	1.43 ± 5.37	1.66 ± 2.20	1.75 ± 1.40
T [nmol/L]	1.79 ± 1.14	0.96 ± 0.52*	0.91 ± 0.88*
SHBG [nmol/L]	61.72 ± 30.09	70.03 ± 39.27*	66.15 ± 37.56
Log FAI	0.61 ± 0.24	0.40 ± 0.22*	0.39 ± 0.25*
TG [mmol/L]	1.11 ± 0.86	1.63 ± 1.54*	1.78 ± 1.17*, **
HDL-C [mmol/L]	1.49 ± 0.37	1.58 ± 0.38*	1.56 ± 0.38*
LDL-C [mmol/L]	2.63 ± 2.14	3.27 ± 0.85	3.43 ± 0.90
TC [mmol/L]	5.49 ± 18.19	5.40 ± 1.09	5.77 ± 0.98

Data is presented as mean ± SD. WC — waist circumference; WHR — waist to hip circumference ratio; SBP — systolic blood pressure; DBP — diastolic blood pressure; FPG — fasting plasma glucose; FIN — fasting plasma insulin; HOMA-IR — homeostasis model assessment-insulin resistance; T — total testosterone; SHBG — sex hormone binding globulin; FAI — free androgen index; TG — triglycerides; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; TC — total cholesterol. *$p < 0.05$, compared to pre-menopause group; **$p < 0.05$, compared to peri-menopause group

Sex hormone binding globulin (SHBG) was measured by enzyme-linked immunosorbent assay (ELISA). Intra- and inter-assay coefficients of variation of SHBG were < 6% and < 12% respectively. Testosterone, FSH, and E_2 were measured by chemiluminescence (ACS180 SE, Bayer, Germany). Fasting venous blood samples were also used to measure the levels of glucose, insulin, TC, TG, and HDL-C. Plasma glucose was measured by the glucose oxidase method (Hitachi 7600) and plasma insulin was measured using a chemiluminescence immunometric assay and commercial kit (Immulite 2000 Analyser; CPC). TC, HDL-C, and TG were measured using an enzymatic calorimetric method with the 7600 autoanalyser (Hitachi 7600). The LDL cholesterol level was calculated using Friedewald's equation. Homeostasis model assessment (HOMA) was applied to estimate the degree of IR. The equation used to obtain this value was as follows: HOMA-IR = [fasting plasma glucose (mmol/L)*insulin (μU/mL)]/22.5. Subjects were defined as having IR if their HOMA-IR values were higher than the 95th percentile of HOMA-IR in all participants as a whole.

Statistical analyses

Statistical analysis was carried out with SPSS 11.0 (SPSS, Chicago, IL, USA). The normal distribution of all studied parameters was checked with histograms and the Kolmogorov- Smirnoff test. After testing, all serum values showed normal distribution. Comparisons between groups were made with Student's t-test. Pearson correlation coefficients were calculated to determine the correlations between various parameters. SHBG was used as diagnostic parameter. Multiple regression analyses were performed in the peri-menopausal women, including HOMA-IR as the dependent variable and the other clinical, hormonal and metabolic parameters as independent variables. ROC analysis was performed to examine its diagnostic test performance, i.e. the ability to distinguish women with and without IR. Sensitivity against (1 – specificity) was plotted at each level, and the area under the curve (AUC) — which reflects the probability of correctly identifying women with normal or abnormal insulin sensitivity. The Youden index (sensitivity + specificity – 1) was calculated to determine the best compromise between sensitivity and specificity; the closer the value is to 1, the greater the diagnostic power. Two-tailed $p < 0.05$ was considered statistically significant.

Results

According to the STRAW criteria described above, our cohort consisted of 1,249 pre-menopausal, 239 peri-menopausal, and 339 post-menopausal women. Clinical and biochemical data is set out in Table I.

Table II. *Pearson's correlation between SHBG and HOMA-IR and other relevant parameters after adjustment for age and BMI in three study groups*

Tabela II. *Korelacja Pearsona między SHBG i HOMA-IR oraz innymi istotnymi parametrami po wzięciu poprawki na wiek i BMI w trzech badanych grupach*

Parameters	SHBG [nmol/L]						HOMA-IR					
	PRM-group	P	PEM-group	P	POM-group	P	PRM-group	P	PEM-group	P	POM-group	P
WC	–0.234	0.000	–0.115	NS	–0.011	NS	0.032	NS	0.109	NS	0.146	0.008
WHR	–0.185	0.000	–0.096	NS	–0.043	NS	0.018	NS	0.054	NS	0.032	NS
SBP	–0.110	0.000	–0.022	NS	–0.043	NS	0.011	NS	0.047	NS	0.119	0.030
DBP	–0.062	0.035	–0.006	NS	–0.007	NS	0.034	NS	0.122	NS	0.088	NS
FPG	–0.009	NS	–0.109	NS	–0.120	0.029	—	—	—	—	—	—
FIN	0.002	NS	–0.178	0.007	–0.162	0.003	—	—	—	—	—	—
HOMA-IR	0.001	NS	–0.164	0.013	–0.157	0.004	—	—	—	—	—	—
SHBG	—	—	—	—	—	—	0.001	NS	–0.164	0.013	–0.157	0.004
T	–0.027	NS	0.062	NS	–0.004	NS	–0.008	NS	–0.055	NS	0.140	0.011
FAI	–0.335	0.000	–0.482	0.000	–0.338	0.000	–0.010	NS	–0.063	NS	0.173	0.001
TG	–0.140	0.000	–0.195	0.003	–0.181	0.001	0.020	NS	0.096	NS	0.296	0.000
HDL	0.041	NS	0.185	0.005	0.168	0.002	–0.045	NS	–0.116	NS	–0.175	0.001
LDL	–0.082	0.005	–0.021	NS	0.056	NS	–0.008	NS	0.046	NS	0.100	NS
TC	–0.026	NS	–0.005	NS	0.054	NS	–0.005	NS	0.019	NS	0.113	0.039

P values < 0.05 are in bold; PRM-group — pre-menopause group; PEM-group — peri-menopause group; POM-group — post-menopause group; NS: not statistically significant

As disclosed by ANOVA analysis, most anthropometric parameters, including WC, WHR, SBP, DBP, FPG, FIN, HOMA-IR and TG, were different among groups, with a trend toward an increase passing from pre- to peri- and post-menopause, though some of the differences did not reach statistically significant levels between two groups. With regard to SHBG, independently of age, it significantly increased from onset of menopause transition, and slightly declined after menopause.

HOMA-IR showed no correlation with age or BMI in pre-menopausal women, a positive correlation (r = = 0.260, P = 0.043) with BMI, and no correlation with age in peri-menopausal women, and positive correlations with both age (r = 0.154, P = 0.040) and BMI (r = 0.435, P = 0.037) in post-menopausal women.

SHBG was found to be significantly negatively correlated with BMI in all three groups [r = –0.074 (P = = 0.047), r = –0.364 (P = 0.032) and r = –0.204 (P = 0.038) respectively], and to be significantly positively correlated with age only in the pre-menopausal group (r = 0.105, P = 0.042). After adjusting for age and BMI, HOMA-IR in peri-menopausal women was closely related only to SHBG (Table II). Multiple regression analyses were performed in the peri-menopausal women, including HOMA-IR as the dependent variable and the other clinical, hormonal and metabolic parameters as independent variables. As a result, SHBG level was found to be the only independent significant determinant of HOMA-IR.

The diagnostic value of SHBG for predicting IR was tested by the ROC curve. As displayed in Table III and Figure 1, AUC for SHBG only in the peri-menopausal group reached a value of 0.816 (0.636–0.996, 95% confidence interval) and the difference reached a statistically significant level. Several threshold values of serum SHBG level were analysed in terms of specificity and sensitivity from the ROC curve data. The best cut-off value that discriminates peri-menopausal women with or without insulin resistance is 41.73nmol/L, with a sensitivity of 81.4% and a specificity of 87.5%.

Discussion

The lower incidence of ischaemic heart diseases and thromboembolic diseases in women before menopause compared to men of the same age is well established [15, 16], while the gender advantage disappears after menopause, which over recent decades has been interpreted primarily as reflecting oestrogen-mediated protection against atherosclerosis, indicating that female hormones participate in their modulation [17, 18]. Thus, previous studies have paid more attention to the impact of oestrogen deficiency from the onset of menopause on the pathogenesis of cardiovascular

Table III. *ROC analysis of SHBG profile for diagnosis of IR in three groups*
Tabela III. *Analiza ROC profilu stężeń SHBG w diagnostyce insulinooporności w trzech badanych grupach*

Groups	ROC	Standard error	P	95% confidence interval	
				Lower limit	Upper limit
Pre-menopause	0.509	0.053	0.878	0.405	0.613
Peri-menopause	0.816	0.092	0.002	0.636	0.996
Post-menopause	0.654	0.071	0.059	0.516	0.793

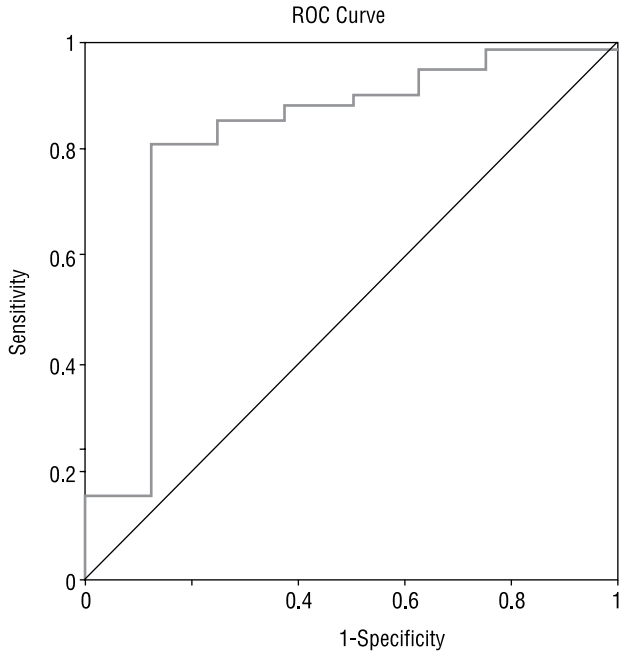

Figure 1. *Receiver operating characteristic (ROC) curves giving the diagnostic value of SHBG for predicting IR in peri-menopausal women*

Rycina 1. *Krzywe ROC przedstawiające wartość diagnostyczną SHBG w predykcji insulinooporności u kobiet w okresie okołomenopauzalnym*

and cerebrovascular diseases, while the pathogenic effect of abnormal androgen metabolism or oestrogen to androgen ratio imbalance has been little studied.

As the major carrier of sex steroids in human plasma, SHBG influences the bioactivity of testosterone and oestradiol, and is regulated by their feedback control at the same time, indicating its important role in the maintenance of relative balance of oestrogen and androgen after menopause. Found in patients with diverse metabolism-related disorders, IR was considered a common risk factor and could exist for several years prior to a confirmed diagnosis of these diseases. Insulin has been shown to be an important inhibiting regulator of SHBG synthesis *in vivo* and *in vitro*, and to block the stimulatory effect of 17β-oestradiol and T_4 on SHBG [9]. Low SHBG level appears to be a biologic marker for IR [19]. Therefore, we mainly aimed at investigating the relationship between SHBG, IR-related parameter, namely HOMA-IR, and other anthropometric measurements, and the value of SHBG profile in the prediction of IR in women of different ages, in order to provide supporting data for preventing and treating IR-related diseases among peri- and post-menopausal women.

In accordance with previous studies [4, 20], various degrees of parallel change in BMI, waist circumference and WHR with ageing were found in this study, and the physical shape of women gradually changed to central adiposity with the tendency of HOMA-IR increase. Adipose tissue in the intra-abdominal region tends to increasingly accrete, according to BMI and WHR, in peri- and post-menopausal women compared to those still pre-menopause, due to the decline of oestrogen and relative free testosterone excess after menopause. Reported recently to be an active endocrine organ, visceral adipose tissues closely correlate with the pathogenesis of IR by secreting diverse cytokines such as leptin, TNF-α and inhibin [21]. Despite being most commonly used for assessing IR, HOMA-IR, lacking variations due to a significantly greater biological variability in individuals, will not be likely to reflect the minor change of insulin sensitivity in healthy individuals [22, 23]. Considering its low biological variability during follicle phase, SHBG concentration was more reliable for evaluating IR change caused by treatment or body mass in a specific individual [22].

SHBG has been reported to increase along with ageing in the male population [24], while conflicting results have been revealed among women in terms of the relationship between SHBG and age. According to a recent study by Maggio [9], serum SHBG levels showed an age-related U-shaped trajectory, declining from the age of 20 to approximately 60 and then progressively increasing at older ages. Conversely, in a population of 1,423 Australian women aged 18–75 Davison et al. [25] found that SHBG increased slightly, though significantly, with age. In addition, other studies recruiting

small samples of peri-menopausal women showed either a decline or no substantial age-related changes in SHBG levels [26, 27].

In our study, SHBG was found to be significantly positively correlated with age only in pre-menopausal women, while, independent of age, SHBG significantly increased from onset of menopause transition, and slightly declined after menopause. SHBG has been demonstrated to vary in a single menstrual cycle, showing stable in follicular phase and highest in luteal phase [28]. Hence, the conflicting results shown above might be relevant to the cyclic fluctuation of female steroids and the time of investigation in different menstruation phases.

It is worth noting in this study that after adjustment for age and BMI, HOMA-IR in peri-menopausal women was closely related only to SHBG. Afterwards, in multiple linear regression analysis, SHBG level was found to be the only independent significant determinant of HOMA-IR. To the best of our knowledge, this would be the first study to investigate the possibility of SHBG as a predictor for insulin resistance. To define the best discriminating parameter between insulin tolerance and insulin resistance, ROC curves, a method often used to investigate such an issue, were calculated and analysed in our study. There was no difference regarding HOMA-IR in our cohort in different ages. Hence, subjects were defined as having IR if they were above the 95th percentile of HOMA-IR when all participants were considered as a whole. The AUC of SHBG reached a value of 0.816 (0.636~0.996, 95% confidence interval, $p = 0.002$). With the best cut-off value of 41.73 nmol/L, the serum SHBG level had a specificity of 81.4% and a sensitivity of 87.5%.

The strengths of our study lie in the large sample of participants and well-established criteria for identifying their menopausal status.

However, despite our findings, it is important to point out that the cross-sectional nature of our study limits conclusions about the temporal relation of SHBG and IR. In addition, though a simple and commonly used marker, HOMA-IR cannot be put on a par with the hyperglycaemic-euglycaemic clamp test, known as the golden criterion of IR.

Conclusions

The results of this study indicate that low SHBG level may be an independent risk factor of insulin resistance in women within the peri-menopause. SHBG is valuable in the prediction of insulin resistance during this particular period.

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