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EVALUATION OF INSULIN RESISTANCE IN PERIMENOPAUSAL WOMEN

Batool Adel Adai
M.B.Ch.B Collage of medicine, University of Karbala'a, Iraq

Aseel Jassim Al-Bdairi
Prof., Department of Physiology, College of Medicine, University of Kufa, Iraq

Abstract: Background: Estrogen is an important female hormone that affect many metabolic process and it's deficiency can lead to many problems not only regarding reproductive function but also other organs and systems in the body.

Insulin is the major anabolic hormone responsible for glucose and energy homeostasis. Any defect in insulin function will result in insulin resistance that will lead to diabetes mellitus eventually.

Aim of the study: To detect insulin resistance in perimenopausal women and investigate the effect of estrogen hormone and BMI on insulin resistance.

Material and method: This cross-sectional study involved 38 women aged 30 – 51 years. All participants were in their second to fifth day of the menstrual cycle. They were instructed to fast for at least 8 hours before blood sample collection. The selected sample were carefully assessed to eliminate any possible factors that could affect the results of the study. Insulin resistance was measured using HOMA-IR method and values of more than two were considered insulin resistance. SPSS version 26 was used to statistically analyze the data.

Results: The study yield non-significant negative correlation between estrogen level and insulin resistance. Significant positive correlation between BMI and insulin resistance.

Conclusion: insulin resistance is higher in women with lower estrogen levels could suggest estrogen as protective factor against insulin resistance.

Introduction

Estrogen is one of the two sex hormones. It is a fat- soluble steroid compound synthesized from cholesterol. It has 18 carbon atoms. There are four types of estrogen identified: 17β-estradiol (E2), the most powerful, estrone (E1) main estrogen during menopause, estriol (E3) found during pregnancy synthesized by the placenta and estetrol (E4) produced by fetal liver. E2 is the wide spread type of estrogen and it binds with estrogen receptors with high affinity compared to the other types (1-3).

Estrogen effect on insulin and glucose homeostasis not clearly understood yet. Some studies suggest that estrogen receptor has a role in glucose metabolism. This function through regulating glucose transporter GLUT-4 in skeletal muscle and altering hepatic insulin sensitivity. ERα specifically present in β-cells of the pancreas that might be responsible for increasing insulin level. It act via promoting insulin gene

expression, increasing insulin content in β-cells as well as release of insulin. On the other hand, ERβ is thought to have unfavorable effect on glucose metabolism by decreasing GLUT-4 expression (4, 5).

The time precedes menses cessation called perimenopause or sometimes called menopausal transition. It usually starts in the 40s but can begin as early as the 30s. It may last for 4 years typically but can last only several months or may extend for about 10 years. This period can start gradually or abruptly. It usually begins with fluctuation in menstrual cycle due to decreased hypothalamic-pituitary axis to negative and positive feedback from the ovarian hormones. All these affect physical, emotional and social life of females leading to clinical symptoms very similar to that of menopause (6-8)

Insulin is a polypeptide hormone synthesized from beta cells of the pancreas. It contains 51 amino acids arranged in two chains joined by two disulfide bonds it has a molecular weight of 5808. Insulin has short half-life of about 6 minutes. When insulin combine with its receptor in the target cell it escape rapid destruction and half-life becomes elongated. Insulinase enzyme is responsible for destruction of insulin mainly in the liver, to lesser amount in kidneys and muscles, while slight amount in remaining other tissues (9).

Insulin resistance defined as elevated insulin levels required for achieving desired physiological effect. This occur when cells no longer respond to the usual amount of insulin. The possible mechanisms responsible for development of insulin resistance are defective receptor of target cell, autoantibodies to insulin, rapid insulin degradation. As mitochondria is the main regulator of energy in cells any mitochondrial malfunction can lead to insulin resistance (10-12).

Prevalence of insulin resistance might reach more than one third of the population. It can occur in healthy and obese individuals. However not all obese and overweight personnel are insulin resistant. Insulin resistance in young women carries a risk for future development of gestational diabetes and type 2 diabetes mellitus. In addition, insulin resistance in pregnant women carries adverse impact on the developing fetus with higher risk of miscarriage (13, 14).

Some studies suggest that estrogen may plays an important role in the metabolism of glucose. Estrogen receptors present in different type of cells specifically alpha type (ERα). Activation of this receptor in pancreatic cells improves fasting insulin levels and insulin production in response to glucose. In addition, it protect beta- cells from damages induced by oxidative stress. Furthermore, ERα activation in hepatic cells alters gluconeogenesis, improves insulin sensitivity and decrease insulin destruction in hepatocyte. For this reason, insulin resistance and estrogen deficiency are causes for many metabolic and hormonal disturbances. Insulin resistance along with increased levels of insulin might enhance androgen production at the expense of lowering estrogen synthesis (15-17).

Homeostasis model assessment of insulin resistance (HOMA-IR) first described in 1985 by Matthews *et al*. It uses fasting insulin and glucose levels then certain equation applied to reflect insulin sensitivity and β cell function. Advantages of this method is simple, non-invasive requiring single blood withdrawal, much lower cost compared to other techniques. Major disadvantage of this method is it provide information about fasting state only and not stimulated circumstances. That is to say, it reflect the effect of insulin on hepatic glucose and not on the peripheral glucose. Also, individuals with impaired or absent β cell function might have incorrect results. (18-23)

Materials and methods

A cross –sectional study design. Women of reproductive age group from 30 years to 51 years old were requited from hospitals and health care centers in karbala'a directorate. Thirty-eight women fit the criteria for research. All women were menstruating and not taking any medication that could interfere with neither insulin nor estrogen. Participating female were free from diabetes, hypertension polycystic ovarian

syndrome and other diseases that could cause insulin resistance. Any pregnant and breast feeding women were excluded from the study.

After identifying a women as eligible for participating in the study she was given an appointment during period from 2nd to 5th day of her cycle. They were told to fast at least for 8 hours prior to blood withdrawal. They were interviewed for medical history and fully examined before blood collection. Blood withdrawn from antecubital fossa and sent to the laboratory for analysis.

Fasting blood glucose, fasting insulin, and estrogen levels were measured in all females. Insulin resistance was measured using HOMA-IR (homeostasis model assessment of insulin resistance) equation: (Fasting blood sugar (mg\dl) × fasting insulin level (uIU\ml)) ÷ 405 , any value that exceeded 2 was considered to have insulin resistance. After that, data were statistically analyzed using SPSS program version 27.

Ethical approval

Ethical approval was obtained from medical ethical committee in Kufa university \ faculty of medicine and from Iraqi health ministry Karbala health department. Each participant was informed of her right to quit the research after full explanation of study aim and importance. Verbal consent from all participants was obtained as well.

Results

Mean age of the collected sample was 37.6±5.8. Mean BMI was 28.5±4.9 with 10 subject having normal BMI (18.5 to 24.9 kg/m^2), 13 subjects were overweight (25 to 29.9 kg/m^2) and 15 subjects considered obese (more than or equal to 30 kg/m^2). Prevalence of insulin resistance in this sample was 65.8%.

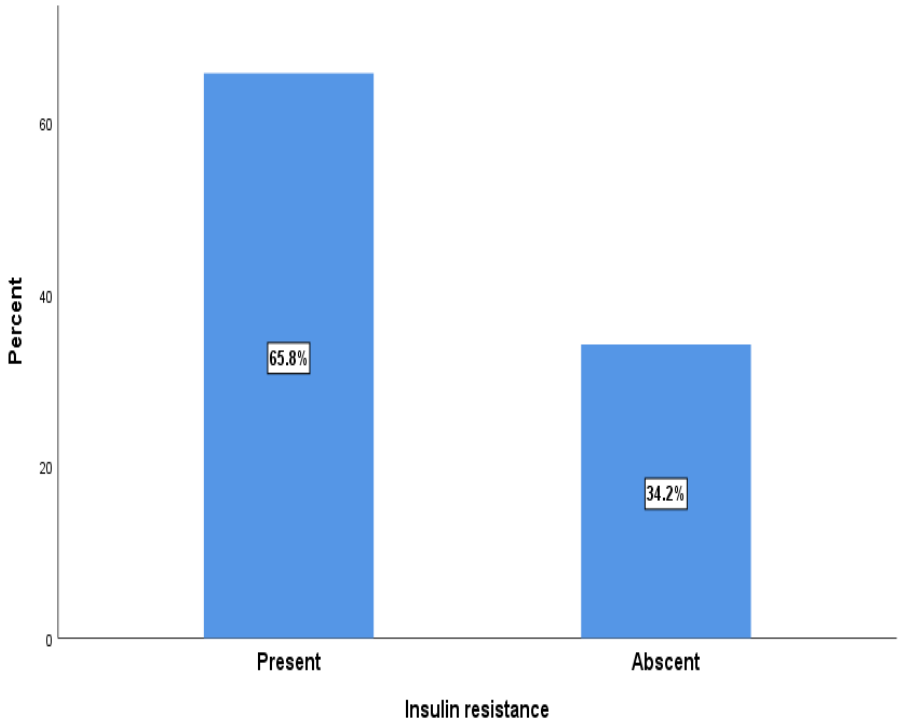

Figure (1) shows percentage of insulin resistance in the collected sample.

Table 1: mean and standard deviation of blood tests and insulin resistance for menstruating female participating in the study.

Tests	Mean±SD
Estrogen level (pg\mL)	57.9±24.1
Fasting blood sugar (mg\mL)	93.4±8.9
Fasting insulin level	11±4.4
Insulin resistance	2.5±1.1

Table 2: show correlations between body mass index (BMI), estrogen level (E2), fasting blood sugar (FBS), fasting insulin level and insulin resistance for perimenopausal women.

Correlations						
		BMI	E2	FBS	Fasting insulin	Insulin resistance
BMI	r		0.042	0.352*	0.429**	0.479**
	P value		0.804	0.030	0.007	0.002
E2	r			-0.056	-0.095	-0.128
	P value			0.739	0.572	0.443
FSB	r				0.307	0.508**
	P value				0.060	0.001
Fasting insulin	r					0.966**
	P value					0.0001
*. Correlation is significant at the 0.05 level						
**. Correlation is significant at the 0.01 level						

Table 2 show that estrogen has non-significant negative correlations with fasting blood sugar, fasting insulin and insulin resistance (P-value > 0.05). While fasting blood sugar has significant positive correlation with insulin resistance (P-value < 0.01). However, fasting blood sugar has non-significant positive correlation with fasting insulin (P-value > 0.05). In the other hand, fasting insulin level has significant positive correlation with insulin resistance (P-value < 0.01). In terms of body mass index, there is a significant positive correlation with fasting blood sugar (P-value < 0.05), fasting insulin and insulin resistance (P-value < 0.01). While there is no significant correlation with estrogen level (P-value > 0.05).

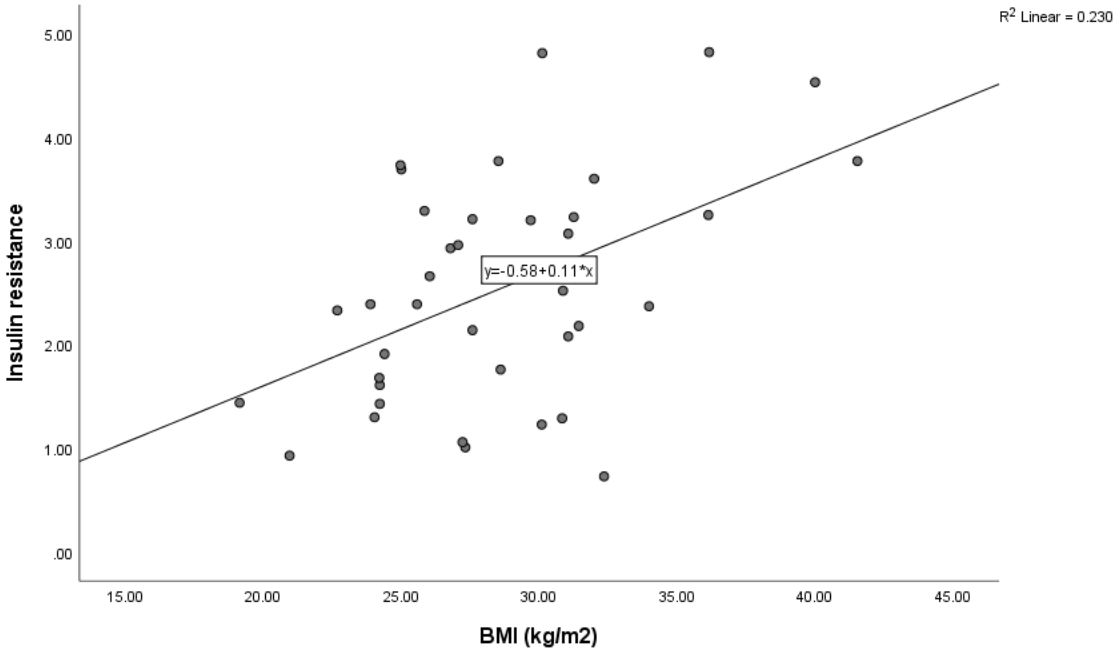

Figure 1: correlation between body mass index (BMI) and insulin resistance among perimenopausal women (P- value < 0.01)

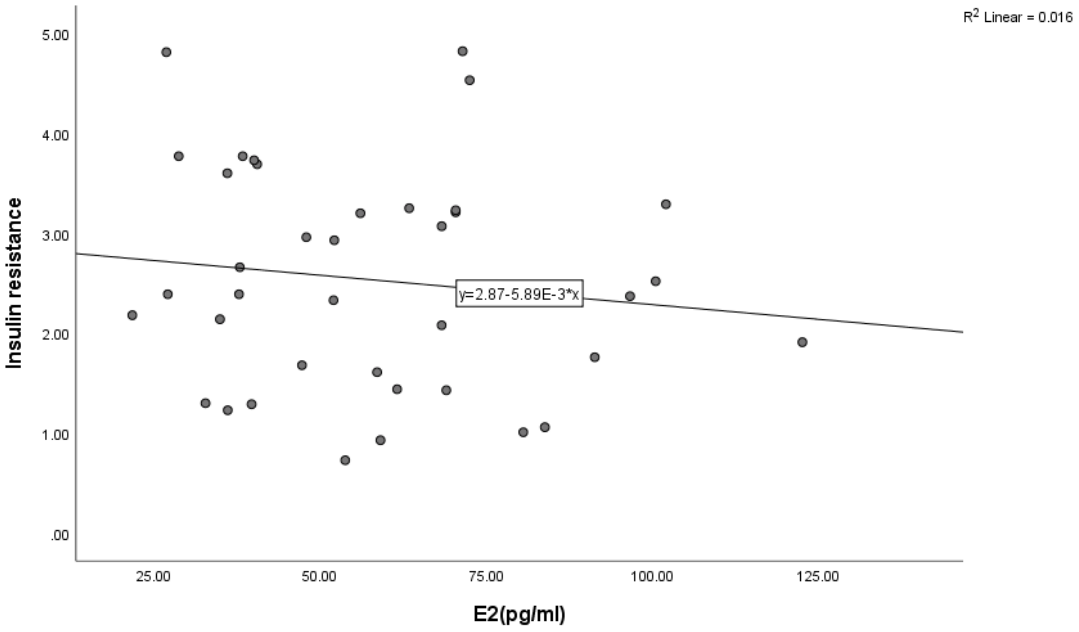

Figure 2: correlation between estrogen level (E2) and insulin resistance among perimenopausal women (P- value > 0.05).

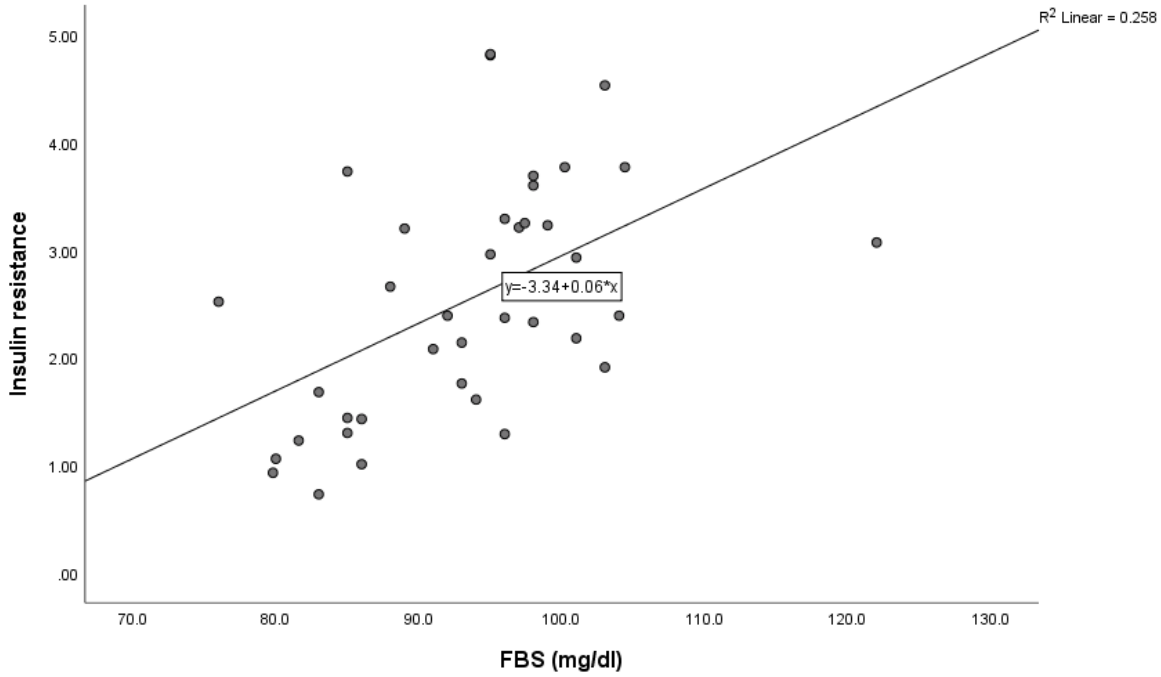

Figure 3: correlation between FBS and insulin resistance among perimenopausal women (P- value <0.01)

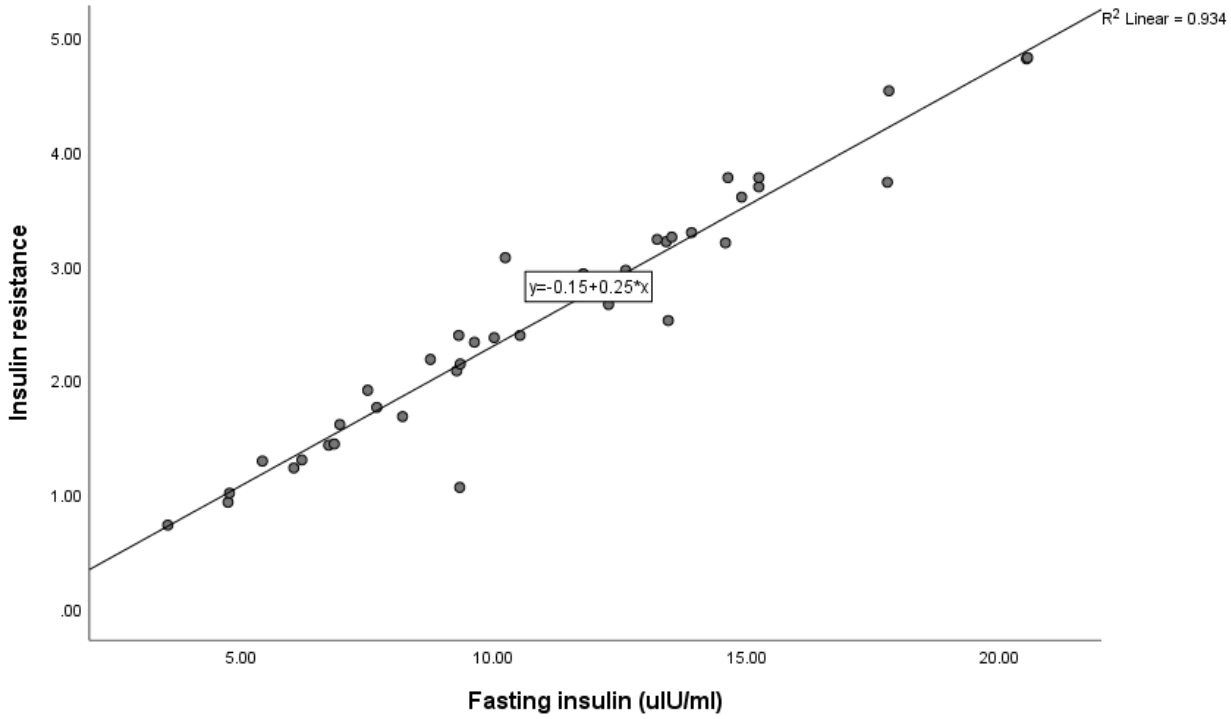

Figure 4: correlation between fasting insulin and insulin resistance among perimenopausal women (P- value < 0.01).

Discussion

Perimenapausal women participating in this study are menstruating so that the level of estrogen hormone is within normal level for their reproductive age. These results was almost similar to what Sowers *et. al.* (24) found. The later research also suggested that there was no significant difference in estrogen level between different ethnic groups of perimenopausal females. Although other study mentioned that different level of estrogen could be encountered between parous and nulliparous perimenopausal women caused by different number of ovulatory cycles (25).

The studied sample has normal fasting blood sugar and insulin levels since the participating feamles are not diabetic. This is similar to what Bahijri, Alissa (26) ,a Saudi study, but the sample has higher values than Phillips, Jing (27) and Yeung, Zhang (28) who found lower values in their studies. Sayın, Kutlu (29) had lower values regarding females with normal weight while comparable results regarding overweight and obese women. Yeung *et al*. suggested that levels of insulin varies throughout the menstrual cycle changing every few days (28)(25)(25)(25)(25)(19)(5).

Insulin resistance has dramatically increased nowadays. This increase can be attributed to the sedentary life style, unhealthy diet and eventually obesity. Previous studies has showed lower insulin resistance in perimenopausal women for example (28, 30).

Although the results in table 2 showed non-significant positive correlation between BMI and estrogen, possibly due to small sample size. Freeman, Sammel (31) found that obese perimenopausal women are more likely to have lower estrogen levels and vice versa. While Sowers, Derby (24) suggested negative correlation between BMI and estrogen level. On the other hand, Sayın, Kutlu (29) found no significant correlation between BMI and estrogen.

Significant correlation between BMI and insulin resistance was found in this study since BMI is the main contributor on increasing insulin resistance. This result was similar to many other studies such as (29, 32, 33).

Estrogen was found to have negative correlation with FBS and insulin although it was non-significant might be due to small sample size. Yeung, Zhang (28) found similar significant negative correlation between estrogen and glucose level but a positive correlation with insulin level.

Table 2 showed that there is a negative correlation between estrogen and insulin resistance. Even though this result was non-significant that could due to small recruited sample. Similarly, (24), Matsui, Yasui (34), found the same results. In contrast to Yeung, Zhang (28) who found significant positive correlation.

Conclusion

Effect of estrogen level on insulin resistance was and still unfinished debate. This study had found that the main effect on insulin resistance is BMI. Estrogen level although non-significant correlation found also has some protective effect against insulin resistance in premenopausal women.

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