RESEARCH
O&G Forum 2024; 34 – 3s: 1954-1961

EVALUATION OF INSULIN RESISTANCE IN POSTMENOPAUSAL WOMEN

Batool Adel Adai (1), **Aseel Jassim Al-Bdairi** (2)
Authors' Affiliations:
(1) M.B.Ch.B , Collage of medicine, University of Karbala'a, Iraq.
(2) Prof., Department of Physiology, College of Medicine, University of Kufa, Iraq.

Corresponding Author: batoola.alsudani@student.uokufa.edu.iq

Abstract
Background: menopause is a physiological process that carries with it many challenges. One of these is increased risk for development of cardiovascular and metabolic diseases. Some suggest that the reason behind this is the decline in ovarian hormones especially estrogen.
Population and method: 40 menopausal women aged 51 years and older were included in the study. All participant women given instructions to fast for at least eight hours prior blood sample collection. Three blood test were done: fasting blood sugar, fasting insulin level, serum estrogen level. HOMA-IR method was used to assess insulin resistance.
Results: the study showed that BMI had significant positive correlation with insulin resistance. There was non-significant negative correlation between estrogen level and insulin resistance in postmenopausal women.
Conclusion: BMI might be considered the main factor affecting insulin resistance in menopausal females.

Introduction

Menopause is the time that menstrual cycle stops for at least 12 consecutive months. It can occur from 45 to 55 with an average of 51 years. This means that women will spend about one- third of their life in menopause. The changes that occur during this period attributed to loss of ovarian follicles and consequently the loss of ovarian hormones. This result in menopausal symptoms, which can start years before menopause, and include:

- Vasomotor symptoms that include hot flushes and night sweats are the commonest affecting about 80% of females,
- Changes in sleep leading to insomnia,
- Fatigue,
- Mood changes accompanied by increased anxiety,
- Urinary symptoms varying from frequency to incontinence.

This period is associated with increased risks of cardiovascular diseases, osteoporosis rising risk of fractures, and due to weakened supportive structures of pelvis, consequently increased chances of pelvic organ prolapse (Talaulikar, 2022, Lobo and Gompel, 2022)

During menopause, estrogen level decrease dramatically. Synthesis of E2 and E1 changes from 400 µg/24h and 180 µg/24h in premenopausal women to 6 µg/24h and 40 µg/24h respectively in postmenopausal women. These changes might be explained by changing the main site for estrogen manufacture from the ovaries to the peripheral adipose tissue. Enzymes required for estrogen synthesis present throughout the body but mainly in the adipose tissue. In addition, levels of inhibin B decreases and FSH increases. This increase in FSH trying to elevate estrogen level (Purohit and Reed, 2002, Xiang et al., 2021).

Insulin is the hormone responsible for glucose homeostasis. It is a polypeptide manufactured in the beta cells of the pancreas. Insulin is known of its short life span of about 6 minutes. This life span can be elongated if insulin binds to its tyrosine kinase receptor. In the other hand, insulinase enzyme function to destruct insulin in liver, to lesser amount kidney muscles and only few in other tissues (Khalilov and Abdullayeva, 2023).

Insulin has various effect on various cell types. For example, liver cells it will cause storage of glucose as glycogen, increases lipogenesis and inhibit gluconeogenesis. As well as in skeletal muscles, it will enhance usage of glucose for cell machinery and storing glucose as muscle glycogen. In fatty tissue, it will increase lipogenesis and uptake of glucose while inhibiting lipolysis (Petersen, 2018).

Insulin resistance is a growing problem worldwide. It is defined as inability of cells to respond properly to the presence of insulin. This will require larger amount of insulin to produces the required physiological function. There are several suggested

mechanisms for such problem: defect in insulin receptors of the target tissue, antibodies against insulin, faster insulin destruction and certain mitochondrial malfunction can also lead to insulin resistance (Sathya Bhama C.V., 2012, Petersen, 2018, Olatunbosun ST, 2020).

Insulin resistance may precede and actually predict the development of type 2 D.M. The impaired insulin signaling, gene expression, ability of muscle to synthesize glycogen as well as accumulation of triglyceride inside the cells in people of high susptability considered as risk factors for development of insulin resistance. Some studies showed that about half of insulin resistance persons might develop diabetes in about 10- 20 years (Patti et al., 2003, Reaven, 2005, Sundström-Poromaa et al., 2020).

Menopause may be considered a risk factor for the development of insulin resistance. It is manifested that insulin resistance greatly increase after menopause. This may be attributed to the fact that estrogen decline plays significant role in development of central adiposity, insulin resistance, accumulation of fat in liver and type 2 D.M. Protective effect of estrogen can be suggested by the facts that insulin resistance is lowered in premenopausal females compared to postmenopausal females. Another fact that premenopausal females are more likely to be insulin sensitive than compared- age males. This protection seems to be lost after menopause. In addition, females taking estrogen replacement therapy are more likely to be more insulin sensitive than those who do not (Jelenik and Roden, 2013, Oya et al., 2014, Galmés-Pascual et al., 2020, De Paoli et al., 2021, A.M. Cybulska, 2023).

There are multiple methods for measuring insulin resistance such as Hyperinsulinemic euglycemic glucose clamp described as the gold standard method to assess insulin resistance. But since this technique is hard in research setting another method was used. Homeostasis model assessment of insulin resistance (HOMA-IR) is much easier and sufficiently accurate method for assessing insulin resistance. It only requires blood withdrawal from fasting subject to measure fasting blood sugar and fasting insulin level. The disadvantage of this method is that it gives information about the fasting state only but no clue about the stimulated state. This reflect insulin functioning on the hepatic glucose but not on the peripheral glucose. (Patarrão et al., 2014, Sánchez-García et al., 2020, Minh et al., 2021, Amisi, 2022, Ruyatkina et al., 2023, A.M. Cybulska, 2023)

Aim of the study

To detect insulin resistance in a group of postmenopausal women and evaluate the effect of estrogen level on insulin resistance in this age group.

Material and method

Forty postmenopausal volunteer women recruited from health care center and hospitals in Karbala 'a directorate. Women aged 51 to 70 years were enrolled in this study, non-menstruating for at least 12 successive months. Women who were hypertensive, diabetic, taking medication that might affect any of the hormones measured in the research were excluded. Eligible women were told to fast for at least 8 hours. All participants interviewed using a preformed questioner and fully examined. Blood withdrawn from antecubital fossa and placed in gel tubes for analysis. Chemiluminescence immunoassay analyzer used to analyze blood samples. Three tests (fasting blood sugar, fasting insulin level, serum estrogen level).

Using HOMA-IR (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 26.

Results

Mean age for the collected sample was 56.8±4.9, while mean BMI was 29.01±5.1 with only one participant having underweight (below 18.5), 8 normal weight (18.5 to 24.9 kg/m^2), 16 overweight (25 to 29.9 kg/m^2) and 15 obese (more than or equal to 30 kg/m^2). 52.5% of the recruited sample had insulin resistance.

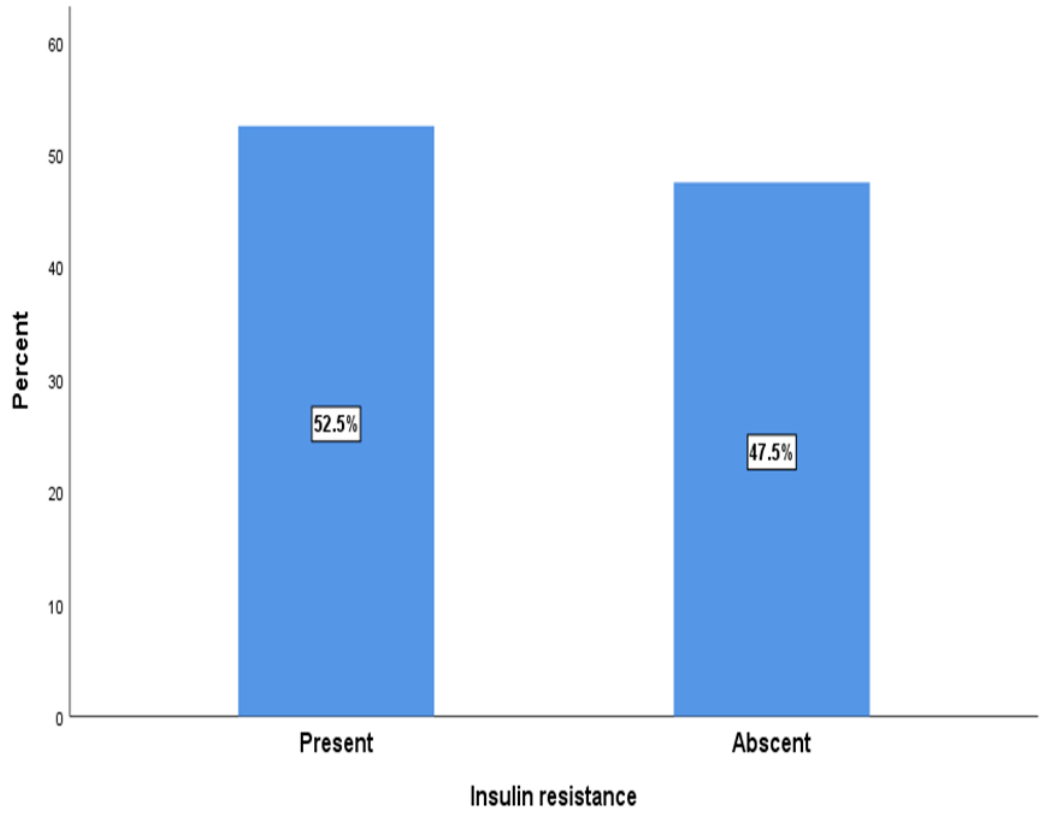

Figure (1) shows insulin resistance percentage in the collected sample.

Table (1) showing results of the performed blood tests and calculated insulin resistance for postmenopausal women in this research.

Blood test	**Mean ±SD**
Estrogen level (pg\ml)	36.1±21.6
Fasting blood sugar (mg\dl)	95.2±8.7
Fasting insulin (uIU\ml)	10.1±4.7
Insulin resistance	2.4±1.3

Table (2) showing correlation between BMI, estrogen level (E2), fasting blood sugar (FBS), fasting insulin level, insulin resistance.

Correlations						
		BMI	**E2**	**FBS**	**Fasting insulin**	**Insulin resistance**
BMI	r		0.017	0.4*	0.411**	0.448**
	P value		0.916	0.011	0.008	0.004

E2	r			0.371*	-0.058	0.013
	P value			0.019	0.724	0.936
FSB	r				0.568**	0.687**
	P value				0.0001	0.0001
Fasting insulin	r					0.985**
	P value					0.0001
*. Correlation is significant at the 0.05 level.						
**. Correlation is significant at the 0.01 level.						

Table show that estrogen has significant positive correlation with fasting blood sugar (P- value < 0.05), non-significant negative correlation with fasting insulin (P-value >0.05), non-significant positive correlation with insulin resistance (P-value >0.05). Also, show that fasting blood sugar has significant positive correlations with both fasting insulin and insulin resistance (P-value <0.01). In contrast, fasting insulin level has significant positive correlation with insulin resistance (P-value <0.01). In terms of body mass index, has non-significant positive correlation with estrogen level (P-value > 0.05) and significant positive correlations with fasting blood sugar (P-value <0.05), fasting insulin level and insulin resistance (P-value <0.01).

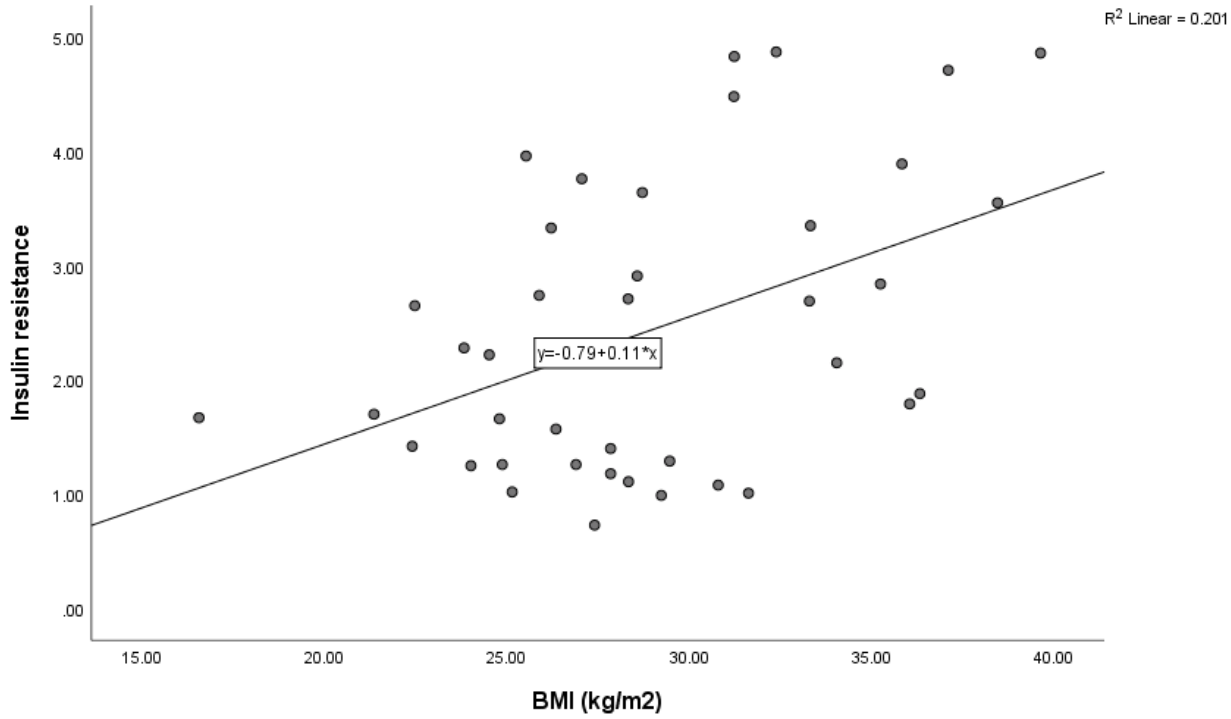

Figure (1): Correlation between BMI and insulin resistance among menopausal women (P-value <0.01)

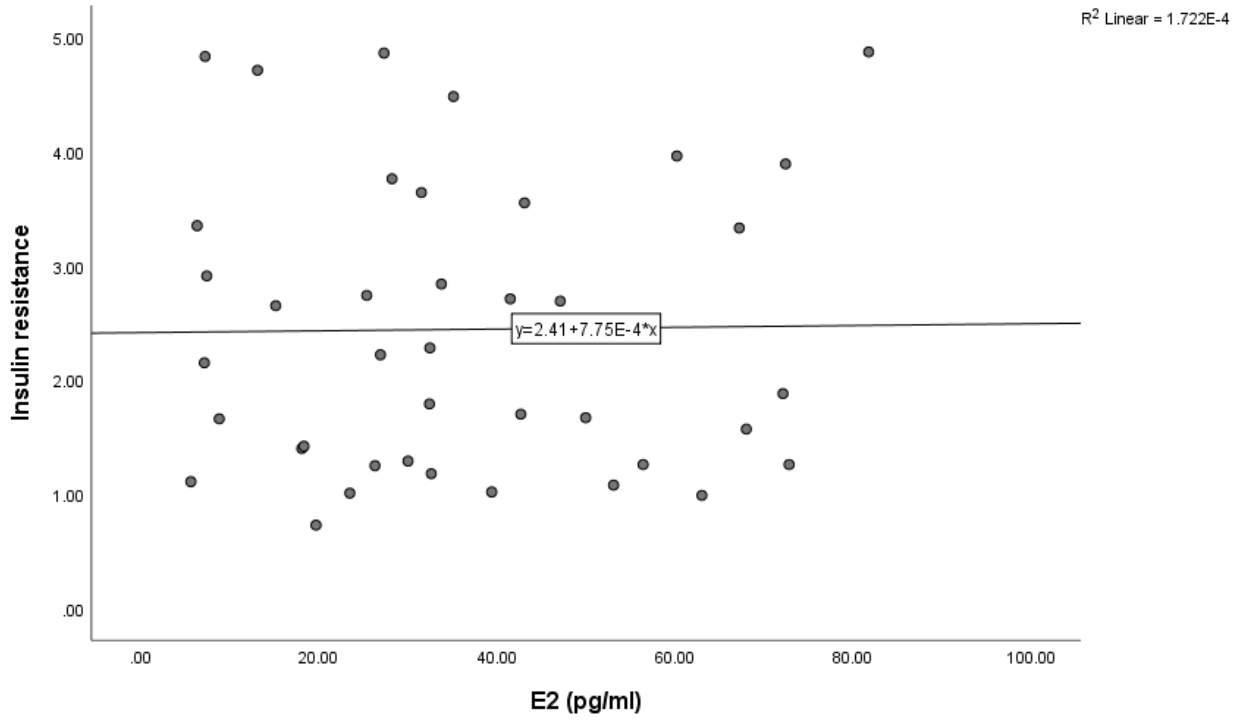

Figure (2): Correlation between E2 and insulin resistance among menopausal women (P-value >0.05)

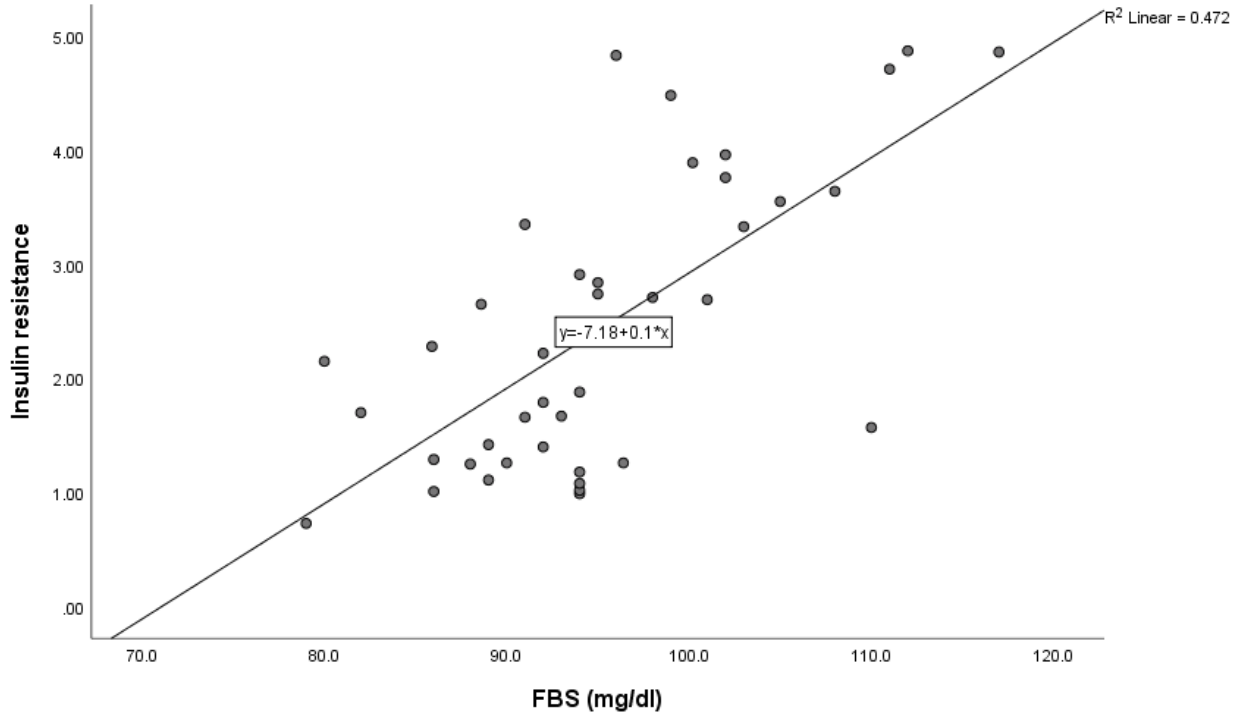

Figure (3): Correlation between fasting blood sugar and insulin resistance among menopausal women (P-value <0.01)

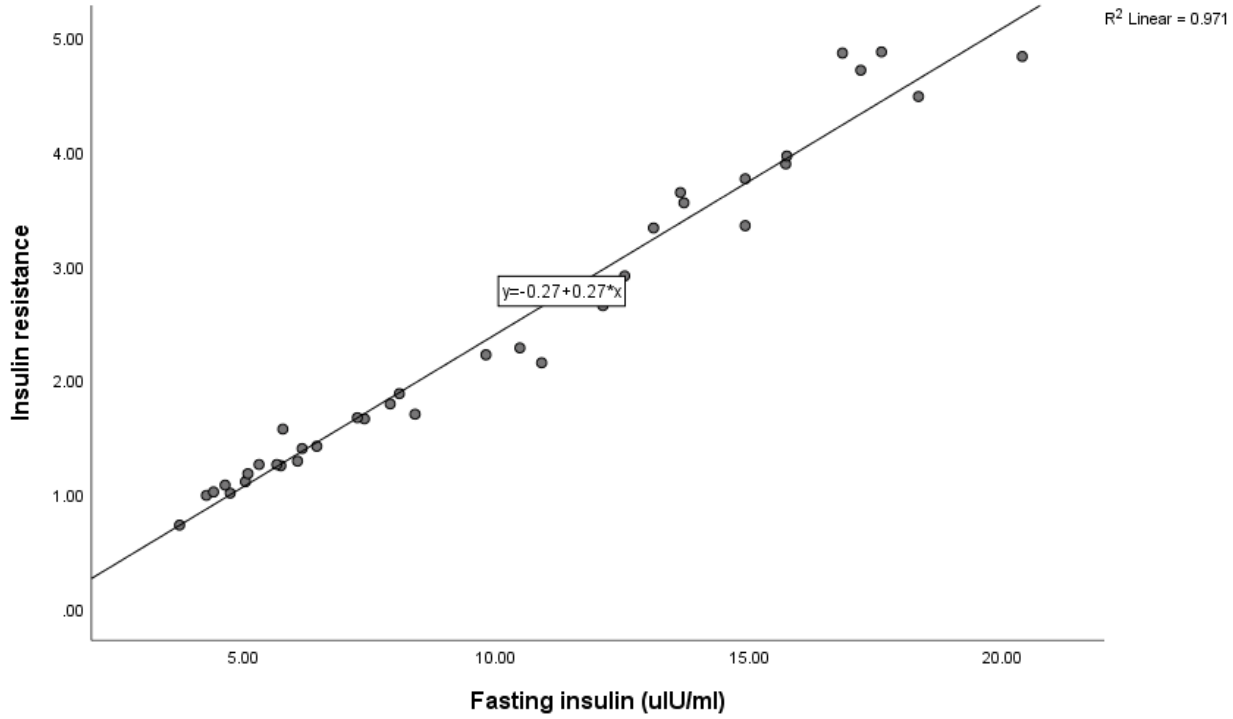

Figure (4): Correlation between fasting insulin and insulin resistance among menopausal women (P-value <0.01)

Discussion

Menopause is characterized by decline in the sex hormones. However, the studied sample mean estrogen level was still within the normal range (lower border) unlike other studies that only included estrogen deficient women below 20 pg\ml in their research like (Kalish et al., 2003, Matsui et al., 2013). Phillips et al. (2008) had normal range estrogen level but the studied sample in this research had higher level of estrogen.

Although table 1 showed normal fasting blood sugar and insulin level since the participants do not suffer from diabetes. There mean values was higher than other studies has found (Kalish et al., 2003, Phillips et al., 2008). Insulin resistance in the studied sample was high like other studies (Oya et al., 2014). Since the reduction of estrogen level in postmenopausal period leads to reduction in the protective effect of estrogen against insulin resistance as the estrogen improve insulin sensitivity and suppress gluconeogenesis.

In table (2) significant positive correlation of BMI with fasting blood sugar and insulin level. BMI has positive correlation with insulin level at P- value <0.01. BMI considered the main contributor to changes in fasting blood sugar and insulin levels in postmenopausal women. Kalish et al. (2003) and Chu et al. (2006) has found similar correlation. For this reason, it was expected to have similar correlation between BMI and insulin resistance. Obesity plays a major role in changes that occur in insulin sensitivity. Kalish et al. (2003) and Chu et al. (2006).

In table (2) showed significant positive correlation between estrogen with fasting blood sugar but non-significant negative correlation with insulin level. Also, positive non-significant correlation between estrogen level and insulin resistance. This might be due to the weaker effect of estrogen and stronger effect of BMI in postmenopausal women. This results also shown in (Kalish et al., 2003) while (Matsui et al., 2013).

In addition, table (2) has shown positive correlation between fasting blood sugar and insulin levels and positive correlation between insulin level and insulin resistance. This suggests that in postmenopausal women insulin has higher effect than fasting blood sugar on insulin resistance. This was also similar to (Kalish et al., 2003).

Conclusion

The main factor that affect insulin resistance in menopausal women is body mass index. Estrogen loose its protective effect against insulin resistance as it dramatically decrease after menopause.

References

A.M. CYBULSKA, D. S.-M., S. WIEDER-HUSZLA, M. PANCZYK, A. JURCZAK, E. GROCHANS 2023. Diagnostic markers of

insulin resistance to discriminate between prediabetes and diabetes in menopausal women. *European Review for Medical and Pharmacological Sciences*.

AMISI, C. A. 2022. Markers of insulin resistance in Polycystic ovary syndrome women: An update. *World J Diabetes,* 13**,** 129-149.

CHU, M. C., COSPER, P., ORIO, F., CARMINA, E. & LOBO, R. A. 2006. Insulin resistance in postmenopausal women with metabolic syndrome and the measurements of adiponectin, leptin, resistin, and ghrelin. *American Journal of Obstetrics and Gynecology,* 194**,** 100-104.

DE PAOLI, M., ZAKHARIA, A. & WERSTUCK, G. H. 2021. The Role of Estrogen in Insulin Resistance: A Review of Clinical and Preclinical Data. *The American Journal of Pathology,* 191**,** 1490-1498.

GALMÉS-PASCUAL, B. M., MARTÍNEZ-CIGNONI, M. R., MORÁN-COSTOYA, A., BAUZA-THORBRÜGGE, M., SBERT-ROIG, M., VALLE, A., PROENZA, A. M., LLADÓ, I. & GIANOTTI, M. 2020. 17β-estradiol ameliorates lipotoxicity-induced hepatic mitochondrial oxidative stress and insulin resistance. *Free Radical Biology and Medicine,* 150**,** 148-160.

JELENIK, T. & RODEN, M. 2013. How Estrogens Prevent From Lipid-Induced Insulin Resistance. *Endocrinology,* 154**,** 989-992.

KALISH, G. M., BARRETT-CONNOR, E., LAUGHLIN, G. A. & GULANSKI, B. I. 2003. Association of Endogenous Sex Hormones and Insulin Resistance among Postmenopausal Women: Results from the Postmenopausal Estrogen/Progestin Intervention Trial. *The Journal of Clinical Endocrinology & Metabolism,* 88**,** 1646-1652.

KHALILOV, R. & ABDULLAYEVA, S. 2023. MECHANISMS OF INSULIN ACTION AND INSULIN RESISTANCE. *Advances in Biology & Earth Sciences,* 8.

LOBO, R. A. & GOMPEL, A. 2022. Management of menopause: a view towards prevention. *The Lancet Diabetes & Endocrinology,* 10**,** 457-470.

MATSUI, S., YASUI, T., TANI, A., KUNIMI, K., UEMURA, H., YAMAMOTO, S., KUWAHARA, A., MATSUZAKI, T. & IRAHARA, M. 2013. Associations of estrogen and testosterone with insulin resistance in pre-and postmenopausal women with and without hormone therapy. *International journal of endocrinology and metabolism,* 11**,** 65.

MINH, H. V., TIEN, H. A., SINH, C. T., THANG, D. C., CHEN, C.-H., TAY, J. C., SIDDIQUE, S., WANG, T.-D., SOGUNURU, G. P., CHIA, Y.-C. & KARIO, K. 2021. Assessment of preferred methods to measure insulin resistance in Asian patients with hypertension. *The Journal of Clinical Hypertension,* 23**,** 529-537.

OLATUNBOSUN ST, T. F., GRIFFING GT, SCHADE DS 2020. Insulin resistance. *Medscape*.

OYA, J., NAKAGAMI, T., YAMAMOTO, Y., FUKUSHIMA, S., TAKEDA, M., ENDO, Y. & UCHIGATA, Y. 2014. Effects of Age on Insulin Resistance and Secretion in Subjects without Diabetes. *Internal Medicine,* 53**,** 941-947.

PATARRÃO, R. S., WAYNE LAUTT, W. & PAULA MACEDO, M. 2014. Assessment of methods and indexes of insulin sensitivity. *Revista Portuguesa de Endocrinologia, Diabetes e Metabolismo,* 9**,** 65-73.

PATTI, M. E., BUTTE, A. J., CRUNKHORN, S., CUSI, K., BERRIA, R., KASHYAP, S., MIYAZAKI, Y., KOHANE, I., COSTELLO, M., SACCONE, R., LANDAKER, E. J., GOLDFINE, A. B., MUN, E., DEFRONZO, R., FINLAYSON, J., KAHN, C. R. & MANDARINO, L. J. 2003. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of PGC1 and NRF1. *Proceedings of the National Academy of Sciences,* 100**,** 8466-8471.

PETERSEN, M. S., SHULMAN, G. I. 2018. Mechanisms Of Insulin Action and Insulin Resistance. *Physiological Reviews*.

PHILLIPS, G. B., JING, T. & HEYMSFIELD, S. B. 2008. Does insulin resistance, visceral adiposity, or a sex hormone alteration underlie the metabolic syndrome? Studies in women. *Metabolism,* 57**,** 838-844.

PUROHIT, A. & REED, M. J. 2002. Regulation of estrogen synthesis in postmenopausal women. *Steroids,* 67**,** 979-983.

REAVEN, G. M. 2005. Insulin resistance, the insulin resistance syndrome, and cardiovascular disease. *Panminerva medica,* 47**,** 201-210.

RUYATKINA, L. A., RUYATKIN, D. & SHCHERBAKOVA, L. 2023. Age-dependent aspects of informativeness of surrogate indices of insulin resistance in the

formation of menopausal metabolic syndrome. *Pharmateca,* 30**,** 90-98.

SÁNCHEZ-GARCÍA, A., RODRÍGUEZ-GUTIÉRREZ, R., MANCILLAS-ADAME, L., GONZÁLEZ-NAVA, V., DÍAZ GONZÁLEZ-COLMENERO, A., SOLIS, R. C., ÁLVAREZ-VILLALOBOS, N. A. & GONZÁLEZ-GONZÁLEZ, J. G. 2020. Diagnostic Accuracy of the Triglyceride and Glucose Index for Insulin Resistance: A Systematic Review. *International Journal of Endocrinology,* 2020**,** 4678526.

SATHYA BHAMA C.V., B. S., AND SEETHALAKSHMI A. 2012. Analysis of the degree of insulin resistance in post menopausal women by using skin temperature measurements and fasting insulin and fasting glucose levels: a case control study. *J Clin Diagn Res,* 6**,** 1644-7.

SUNDSTRÖM-POROMAA, I., THU, W. P. P., KRAMER, M. S., LOGAN, S., CAULEY, J. A. & YONG, E.-L. 2020. Risk factors for insulin resistance in midlife Singaporean women. *Maturitas,* 137**,** 50-56.

TALAULIKAR, V. 2022. Menopause transition: Physiology and symptoms. *Best Practice & Research Clinical Obstetrics & Gynaecology,* 81**,** 3-7.

XIANG, D., LIU, Y., ZHOU, S., ZHOU, E. & WANG, Y. 2021. Protective Effects of Estrogen on Cardiovascular Disease Mediated by Oxidative Stress. *Oxidative Medicine and Cellular Longevity,* 2021**,** 5523516.