REVIEW

A BIDIRECTIONAL RELATIONSHIP BETWEEN MENOPAUSE AND DIABETES MELLITUS

Lakshmi Prasanna S, Dhivya K*, Gnana Chaitanya C, Divyasree P, Nazma M

Department of Pharmacy Practice; Sri Venkateswara College of Pharmacy, Chittoor- 517127

Submitted on: 27.02.18; Revised on: 10.03.18; Accepted on: 21.03.18

ABSTRACT

Menopause is described as a transition from the state of reproductivity to infertility. It is clinically diagnosed by estimating cessation of spontaneous menstruation over a period of 12 months. Estrogen governs insulin production capacity of the pancreatic islet cells as well as glucose homeostasis by several possible pathways in animal models. In the liver, estrogen regulates insulin sensitivity by activating glycogen synthetase and glycolytic enzymes; aromatase knockout is an enzyme responsible for estrogen biosynthesis which upon inactivation, mice develops insulin resistance due to estrogen deficiency which was reversed by estrogen therapy. Estrogen receptor possesses roles in cellular glucose uptake by governing glucose transporter (GLUT) and also modulates insulin receptor substrate-1 phosphorylation. In women insulin resistance may contribute to hyper-androgenism and an ovulatory dysfunction through several pathways. The compensated phase of insulin resistance stimulates the testosterone biosynthesis of human ovarian theca cells from women with polycystic ovarian syndrome which induces the earlier or late menopause. Thus this review elucidates a bidirectional relationship between diabetes mellitus and menopause.

KEY WORDS: Menopause, Diabetes mellitus, Insulin, Estrogen

Corresponding Author: K. Dhivya
E-mail: divyapharmd@gmail.com

Indian Research Journal of Pharmacy and Science; 16(2018)1280-1287;
Journal Home Page: https://www.irjps.in
DOI: 10.21276/irjps.2018.5.1.6

INTRODUCTION

Menopause is described as a transition from the state of reproductivity to infertility. Normally, women attains natural menopause between the age of 45-55 years[1]. It is clinically diagnosed by estimating cessation of spontaneous menstruation over a period of 12 months.[2] Natural menopause is not a rapid change but an ever shifting process that occurs over multiple years. In 2001, States of Reproductive Aging Workshop (STRAW) formulated a specific nomenclature. In 2011, STRAW 10 reassembled in order to formulate a more comprehensive staging system, which is regarded as a gold standard in characterising the changes associated with reproductive aging, i.e. from menopause to post-menopause[3,4].Epidemiologicalstudies revealed that African American and Latina women have natural menopause about 2 years earlier than those of white women. In contrast, Asian women and Caucasian women seem to possess similar age at menopause, despite Thai women were reported to have a lower median age i.e. 49.5 years at menopause and Filipino Malay women have been reported to have an earlier average age at natural menopause at 47-48 years[5-7].During early foetal development, germ cells differentiate into oogonia within the ovaries and these germ cells develop into oocytes at puberty but few are depleted through atresia and ovulation[8]. Lessen the count of oocytes leads to reduced inhibin secretion which decreases the ovarian negative feedback on follicle-stimulating hormone (FSH). The consequent elevation in FSH level leads to increased follicular recruitment and an accelerated follicular loss with preservation of estradiol levels in early menopausal transition[9, 10]. Eventually, the depletion of follicles results in variable response of ovaries to FSH, resulting in wide fluctuation in estrogen levels and loss of the normal reproductive cycle. When all the ovarian follicles are depleted, the ovary is unable to respond to even high levels of FSH and further reduction in estrogen levels will be seen[11]. The postmenopausal period is hormonally characterized by an elevation in FSH (>30 mIU/mL) and diminished estradiol levels[12]. We have both advantage and disadvantage when the woman attains menopause but disadvantages are more when compared to advantages, sometimes it may lead to life threatening conditions. Vasomotor symptoms, insomnia, mood changes, severe tiredness, stiff painful joints, back pain, body pain, headache, urinary leakage and skin changes are most commonly associated symptoms with the menopause; it even predisposes a woman to develop osteoporosis and an increased risk of cardiovascular disease[13, 14]. As discussed earlier Estradiol (E2) is one of the important hormone involved in female reproductive physiology, gene regulation and plays a crucial role in various physiological and pathological states, including glucose homeostasis and insulin resistance[15]. Several studies have suggested that women with type 1 or type 2 diabetes mellitus (DM) undergo menopause several years earlier than non-diabetic women[16].DM is a metabolic disorder characterized by persistent hyperglycemia as well as abnormality in carbohydrate, protein, and lipid metabolism resulting from defects in insulin secretion, and/or insulin sensitivity and an impaired suppression of glucagon secretion in response to ingested glucose[17, 18]. Thus, diabetes mellitus involves two primary pathogenic mechanisms: (i) a reduction in insulin secretion due to progressive decline in pancreatic islet cell function and inadequate suppression of glucagon secretion; (ii) a decrease in the metabolic responses due to insulin peripheral insulin resistance[19, 20]. This review attempts to highlight the impact of menopause and type II DM on each other.

INSULIN RESISTANCE

Insulin induces glucose uptake by stimulating the expression of glucose transporter 4 (GLUT4)[21]. During post-prandial phase, plasma glucose level is high, increased insulin secretion controls glycaemia by binding to its receptors on the cell surface facilitating increased glucose uptake into the cell[22]. Insulin receptor consists of two α subunits and two β subunits. α subunits are located on the cell surface and comprise of insulin binding site, whereas β subunits on trans membrane are responsible for signal transduction. When insulin binds to external α subunit, it stimulates auto phosphorylation of the β subunit at multiple tyrosines which results in activation of insulin signal transduction. This phosphorylation cascade results in translocation of vesicles containing GLUT4 to the cell membrane[23, 24]. On binding to the cell membrane, GLUT4 forms a tri-dimensional structure which enables facilitated diffusion of glucose into the cell. Any alteration in these mechanisms such as insulin signal transduction,

expression of GLUT4 and/or translocation to the cell membrane – results in insulin resistance[25, 26].

ACTION OF ESTRADIOL AT ITS RECEPTOR

Estradiol (E2) exerts its action by binding to estrogen receptor (ER)[27]. Later, another isoform of ER was discovered, it was named ER β and the former ER is now called ER α. In humans, ER α is located on chromosome 6expressed in the uterus, vagina, ovaries, oviduct, pituitary and mammary glands, it is also present in the hypothalamus, brain, bone, liver and cardiovascular system, whereas ER β is located on chromosome 14 which is dominant isoform in the prostate, salivary glands, testis, ovary, vascular endothelium, smooth muscle, immune system and certain neurons of the central and peripheral nervous system[28, 29]. Binding of E2 activates ERs which act as transcriptional modulators by binding to specific sequences (estrogen response elements, EREs) in the promoter region of target genes[30]. Studies revealed differential actions of ER α and ER β which is activation of ER α causes an increase in length and number of neurites, whereas ER β activation induces neurite elongation alone. On the other hand, a few studies demonstrated distinct and sometimes opposite effects of ER α and ER β which forms heterodimers that interact with EREs[31, 32].

MENOPAUSE INDUCED DM

Epidemiologic studies shown the incidence of glucose intolerance and type 2 DM in peri-menopausal women are7.0–10.3% and is 4.8–6.4% respectively[33]. Researchers found that women who started menopause early were 3.7 times more likely to develop DM whereas women who had a normal onset of menopause were more than twice as likely to be diagnosed with DM[34].

Effects of Estrogen on Glucose Metabolism

Estrogen governs insulin production capacity of the pancreatic islet cells and also possesses beneficial effects on the energy metabolism as well as glucose homeostasis by several possible pathways in animal models which are explained clearly in the following paragraphs.

(1) In the liver, estrogen regulates insulin sensitivity by activating glycogen synthetase and glycolytic enzymes; it also acts by modulating the uptake of glucose by peripheral target tissues. Experimental and clinical studies rationalise insulin resistance to be a result of estrogen deficiency or alterations in ER signal transduction process[35, 36].Animal experiments exhibited an increased risk of diabetes on account of ovarectomy and estrogen therapy improves the insulin response to glucose overload. E2 administration seems to enhance the insulin secretion in response to glucose overload by acting on G protein- coupled estrogen receptor (GPER) in rat pancreas and islet cells of mouse. These data conclude that individuals with estrogen deficiency have diminished insulin secretion[37, 38].

(2) Aromatase knockout (ArKO) is an enzyme responsible for estrogen biosynthesis which is found in mice. Upon inactivation of ArKO, mice develop insulin resistance due to estrogen deficiency which was reversed by estrogen therapy[39].Insulin safeguards glucose homeostasis in case of normal insulin sensitivity[40]. ERs possess vital roles in the metabolism of glucose in liver. In ER-α receptor knockout (ERKO) animal, hepatic insulin resistance is linked with reduced glucose uptake in skeletal muscles. These findings admit that estrogen receptor- α plays a significant role in the regulation of glucose homeostasis and insulin sensitivity in mice[41- 43].Estrogen receptors are newly recognized crucial players in glucose metabolism. These receptors regulate insulin induced cellular glucose uptake through regulation of the tyrosine phosphorylation of insulin receptor protein[22].

(3) ERs possess important roles in cellular glucose uptake by governing cytoplasmic vesicles containing glucose transporter (GLUT)which leads to GLUT4 expression and translocation[44]. In ovarectomized rats, an increased amount of GLUT1 protein is observed in the blood–brain barrier through estradiol substitution. In rats with immature uterus, estradiol therapy induces a fourfold raise in GLUT1 protein content and increased glucose uptake. In polycystic ovarium syndrome (PCOS) cases (characterized by ovarian overproduction of testosterone), insulin induced glucose uptake was reduced owing to decreased amounts of GLUT4 on adipocyte membrane[45, 46]. Mice that are insulin resistant possess deficiency of ER-α shows impaired glucose tolerance and obesity, affecting both male and female. In contrast, ER-β activation might have a diabetogenic

effect and opposes the action of ER-α. Theoretically, a continuously adjusted balance between ER-α and ER-β maintains the ideal GLUT4 expression and glucose homeostasis[47-49].

(4) E2 at elevated concentration is competent of inhibiting insulin signalling in adipocytes through modulation of insulin receptor substrate-1 (IRS-l) phosphorylation[41]. As insulin possesses metabolic effects in addition to mitogenic effects, inhibition of excessive insulin receptor signal by estrogen can be a safety impact against pathological glucose uptake and cell proliferation.

(5) Estrogenpossess crucial role in regulation of growth hormone (GH) activity through inhibitory effects on its secretion and on cellular GH receptor functions. These observations suggest a close correlation between estrogen and their antidiabetogenic as well as anticancer capacities by regulating GH-insulin like growth factor (IGF)-I axis[50-52].

Effects of Estrogen on Lipid Metabolism and Fat Deposition

Estrogen possesses affirmative regulatory effects on the maintenance of serum lipid levels, insulin sensitivity of adipocytes and distribution of body fat. Premenopausal women usually exhibit lowered atherogenic serum lipid level compared to postmenopausal cases. In such case, estrogen therapy may reduce the risk of cardiovascular disease by changing plasma lipid profile[53, 54].In aged rats, estradiol administration improved the liver impairment parameters by lowering the level of lipid peroxidation[55]. In cultured hepatocytes, an androgen receptor mediated antagonism of estrogen-dependent low-density lipoprotein receptor (LDLR) transcription reveals antagonistic associations of vascular diseases and sexual steroids with lipid metabolism[56]. Hence, estrogen plays a crucial role in energy homeostasis, insulin sensitivity and immune responses by regulating the total body mass, regional body fat distribution and metabolism of fat. In healthy premenopausal women, central and abdominal adipocytes express elevated insulin sensitivity than men which means a lower risk for insulin resistance in these women. However, menopause ensues in increased central adiposity and elevated levels of fasting glucose level suggesting a higher risk for cardiovascular, metabolic diseases and malignancies[57, 58].Obesity is an excessive deposition of adipose tissue which predisposes patients to a variety of diseases such as cardiovascular dysfunction, diabetes mellitus and malignancies. Obesity and overweight are important concomitant factors of insulin resistance and altered equilibrium of male and female sexual hormone levels in women[59]. Correlations between increased body weight and estrogen action usually remain controversial. Few authors reveal linear correlation between high body mass index (BMI) and elevated serum estrogen levels, while others depict associations between higher androgen concentrations and central adiposity both in pre- and postmenopausal subjects[60]. Estrogen predominantly induces adipose tissue deposition in gluteo-femoral region; on the other hand increased androgen level typically induces intra-abdominal fat accumulation. Usually women with excessive levels of circulatory androgen exhibit central obesity, which is strongly associated with insulin resistance and its complications[61].

DM INDUCED EARLIER MENOPAUSE

Insulin is a potent effector of human sexual steroid hormone production in the endocrine organs and modulates estrogen signals at receptor level[62]. In women, insulin resistance may contribute to hyperandrogenism and an ovulatory dysfunction through several pathways. Hyperinsulinemia is described as compensated phase of insulin resistance which stimulates the testosterone biosynthesis of human ovarian theca cells in women with polycystic ovarium syndrome (PCOS). This results in excessive androgen and deficient estrogen production.[63] Treatment with insulin sensitizing metformin reduces hyper insulinemia by directly inhibiting androgen overproduction in human ovarian theca cells[64]. In addition, insulin may affect the pituitary gland to favour the secretion of luteinizing hormone (LH) and increases adrenal androgen production by means of an increased adrenal sensitivity to adreno corticotropin. Insulin and insulin-like growth factor-I receptors may synergize with LH to promote androgen production by ovarian theca cells[65]. High risk of endometrial cancer in women with PCOS was presumed to justify the "unopposed estrogen hypothesis" supposing normal or elevated bioavailable estrogen and low level of progesterone. Nevertheless, both obesity and hyper insulinemia in these cases are associated with defective ovarian estrogen and excessive androgen synthesis, thus unopposed high estrogen level cannot be blamed for endometrial cancer risk[66]. Moreover, high estrogen level would be

contradictory to an ovulatory infertility as ovulation may be provoked by excessive estrogen administration. Recently, androgen-excess and the associated metabolic alterations are regarded as common sources of cardiovascular risk and other complications in PCOS cases. Hyperandrogenism explains both an ovulation and hirsutism, which are characteristic disorders in women with PCOS[67].

CONCLUSION

This review suggests that developing DM after menopause is more common than DM induced earlier menopause. But still, both the concepts are considered essential in preventing the occurrence of each other. In postmenopausal women, regular physical activity or estrogen replacement therapy seems to possess more beneficial hypoglycaemic effect evoking their impact on the insulin secretion capacity of β-cells. In diabetic women, controlling blood sugar level and maintaining body weight within normal range helps in preventing attaining earlier menopause and other complications.

REFERENCES

1. Ross, Lauren A, Polotsky, Alex J., Metabolic correlates of menopause: an update., Current Opinion in Obstetrics and Gynecology., 2012; 24(6): 402–407.
2. Morabia A, Costanza MC., International variability in ages at menarche, first live birth, and menopause. World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives., Am J Epidemiol., 1999; 150(5): 546.
3. Takahashi TA, Johnson KM., Menopause., Med Clin North Am., 2015; 99(3): 521-34.
4. Siobán DH, Margery G, Janet EH, Roger L, Pauline M, Robert WR, Sherry S, Patrick MS, Tobie JV., Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging., Menopause., 2012; 19(4): 387–395.
5. Gold EB1, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, Skurnick J., Factors associated with age at menopause in a multi-ethnic population of women., Am J Epidemiol., 2001; 153:865–74.
6. Chompootweep S, Tankeyoon M, Yamarat K, Poomsuwan P, Dusitsin N., The menopausal age and climacteric complaints in Thai women in Bangkok.,Maturitas., 1993; 17:63–71.
7. Ellen BG., The Timing of the Age at Which Natural Menopause Occurs., Obstet Gynecol Clin North Am., 2011; 38(3): 425–440.
8. Hall JE., Neuroendocrine changes with reproductive aging in women.,SeminReprod Med., 2007; 25(5): 344-51.
9. William ER, Wendy JK, and Jessica MM., Biomarkers of Ovarian Reserve.,Biomark Insights., 2008; 3: 259–268.
10. Burger HG, Dudley EC, Hopper JL., The endocrinology of the menopausal transition: a crosssectional study of a population-based sample., J Clin Endocrinol Metab., 1995; 80: 3537–45.
11. Soule MR, Bremner WJ., The menopause and climacteric: endocrinologic basis and associated symptomatology., J Am Geriatrics Soc., 1982; 30: 547-561.
12. Henry GB., Diagnostic role of follicle-stimulating hormone (FSH) measurements during the menopausal transition- an analysis of FSH, oestradiol and inhibin., Eur J Endocrinol., 1994; 130: 38-42
13. Patricia AR, Sarah LK, Nancy ER., Postmenopausal Symptoms in Female Veterans with Type 2 Diabetes: Glucose Control and Symptom Severity., J Womens Health (Larchmt)., 2015; 24(6): 496–505.
14. Deborah G., Management of Menopausal Symptoms., N Engl J Med., 2006; 355: 2338-2347.
15. Elwood VJ, Herbert IJ, Alicia AW, Cheryl AF., Estrogen action: a historic perspective on the implications of considering alternative approaches., Physiol Behav., 2010; 99(2): 151–162.
16. Nilsson S, Mäkelä S, Treuter E, Tujague M, Thomsen J, Andersson G, Enmark E, Pettersson K, Warner M, Gustafsson JA., Mechanisms of estrogen action., Physiol Rev., 2001; 81(4): 1535-65.

17. Anees AS, Shadab AS, Suhail A, Seemi S, Iftikhar A, Kapendra S., Diabetes: Mechanism, Pathophysiology and Management-A Review., Int. J. Drug Dev. & Res., 2013; 5(2): 1-23.
18. Ozougwu JC, Obimba KC, Belonwu CD, Unakalamba CB., The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus., Journal of Physiology and Pathophysiology., 2013; Vol. 4(4), pp. 46-57.
19. Carrera B. CA, Martínez M. JM., Pathophysiology of diabetes mellitus type 2: beyond the duo "insulin resistance-secretion deficit"., Nutr Hosp., 2013; 28(2): 78-87
20. Michael S, Barry JG, Timon WH., Type 2 diabetes: principles of pathogenesis and therapy., Lancet., 2005; 365: 1333–46.
21. Louise C, Shian-Huey C, and Alan RS., Insulin Signaling and the Regulation of Glucose Transport., Mol Med., 2004; 10(7-12): 65–71.
22. Saltiel AR, Pessin JE., Insulin signaling pathways in time and space., Trends Cell Biol., 2002; 12(2): 65-71.
23. Masato K, Jose AH, Kenneth MY, Ronald KC., The Structure of Insulin Receptor and Its Subunits EVIDENCE FOR MULTIPLE NONREDUCED FORMS AND A 210,000 POSSIBLE PRORECEPTOR., The Journal of Biological Chemistry., 1982; 257(17): 10392-10399.
24. Furtado LM, Somwar R, Sweeney G, Niu W, Klip A., Activation of the glucose transporter GLUT4 by insulin., Biochem Cell Biol., 2002; 80(5):569-78.
25. Gwyn WG, Geoffrey DH., The glucose transporter family: structure, function and tissue-specific expression., Biochem. J., 1993; 295: 329-341.
26. Sumera K, David HA, Patricia FL., Hepatic expression and cellular distribution of the glucose transporter family., World J Gastroenterol., 2012; 18(46): 6771–6781.
27. Amjad F., Structural and Functional Diversity of Estrogen Receptor Ligands., Curr Top Med Chem., 2015; 15(14): 1372–1384.
28. Hye RL, Tae-Hee K, Kyung-Chul C., Functions and physiological roles of two types of estrogen receptors, ERα and ERβ, identified by estrogen receptor knockout mouse., Lab Anim Res., 2012; 28(2): 71–76.
29. Ilaria P, Carlotta G, John AK, Filippo M., Estrogen Receptors Alpha (ERα) and Beta (ERβ): Subtype-Selective Ligands and Clinical Potential., Steroids., 2014; 15(0): 13-29.
30. Bonnie JD, Kenneth SK., Estrogen receptors and human disease., J Clin Invest., 2006; 116(3): 561–570.
31. Planey SL, Kumar R, Arnott JA., Estrogen receptors (ERα versus ERβ): friends or foes in human biology?., J Recept Signal Transduct Res., 2014; 34(1): 1-5.
32. Patrone C, Pollio G, Vegeto E, Eva E, Ivan de C, Gustafsson J, Adriana M., Estradiol Induces Differential Neuronal Phenotypes by Activating Estrogen Receptor α or β., Endocrinology., 2000; 141(5): 1839–1845.
33. Diana J, Andrzej M., Consequences of menopause in women with diabetes mellitus – a clinical problem.,Gynecological Endocrinology., 2005; 21(5): 280–286.
34. Nadel I, Cypryk K, Pertynski T, Sobczuk A, Stetkiewicz T., Studies on the incidence and clinical significance of the metabolic syndrome in postmenopausal women in Lodz region., Pol Arch Med Wewn., 2001;106: 823–828.
35. Franck MJ, Deborah JC, Andrea LH., The Role of Estrogens in Control of Energy Balance and Glucose Homeostasis.,Endocr Rev., 2013; 34(3): 309–338.
36. Suba Z., Low Estrogen Exposure and/or Defective Estrogen Signaling Induces Disturbances in Glucose Uptake and Energy Expenditure., J Diabetes Metab., 2013; 4: 272.
37. Vogel H, Mirhashemi F, Liehl B, Taugner F, Kluth O, Kluge R, Joost HG, Schürmann A., Estrogen deficiency aggravates insulin resistance and induces β-cell loss and diabetes in female New Zealand obese mice.,Horm Metab Res., 2013; 45(6): 430-5.

38. Iskra B, Branka K, Tatjana M, Slavica SS, Goran P, Sasha JM, Irfan A, Biljana T., Effects of Hormone Replacement Therapy on Insulin Resistance in Postmenopausal Diabetic Women., Open Access Maced J Med Sci., 2016; 4(1): 83–88.
39. Anisha AG, Henry JP, Dale JH., Estrogen: An Emerging Regulator of Insulin Action and Mitochondrial Function., Journal of Diabetes Research., 2015; Volume 2015.
40. Bryzgalova G, Gao H, Ahren B, Zierath JR, Galuska D, Steiler TL, Dahlman-Wright K, Nilsson S, Gustafsson JA, Efendic S, Khan A., Evidence that oestrogen receptor-alpha plays an important role in the regulation of glucose homeostasis in mice: insulin sensitivity in the liver., Diabetologia., 2006; 49(3): 588-97.
41. Matic M, Bryzgalova G, Gao H, Antonson P, Humire P, Omoto Y, Portwood N, Pramfalk C, Efendic S, Berggren PO, Gustafsson JÅ, Dahlman-Wright K., Estrogen signalling and the metabolic syndrome: targeting the hepatic estrogen receptor alpha action.,PLoS One., 2013; 8(2): e57458.
42. Muraki K, Okuya S, Tanizawa Y., Estrogen receptor alpha regulates insulin sensitivity trough IRS-1 tyrosine phosphorylation in mature 3 T3-L1 adipocytes.,Endocr J., 2006; 53: 841–851
43. Welch RD, Gorski J., Regulation of glucose transporters by estradiol in the immature rat uterus., Endocrinology., 1999; 140(8): 3602-8.
44. Boado RJ, Wu D, Windisch M., In vivo upregulation of the blood-brain barrier GLUT1 glucose transporter by brain-derived peptides.,Neurosci Res., 1999 Sep; 34(4): 217-24.
45. Evanthia DK, Andrea D., Insulin Resistance and the Polycystic Ovary Syndrome Revisited: An Update on Mechanisms and Implications.,Endocr Rev., 2012; 33(6): 981–1030.
46. Handgraaf S, Riant E, Fabre A, Waget A, Burcelin R, Lière P, Krust A, Chambon P, Arnal JF, Gourdy P.., Prevention of Obesity and Insulin Resistance by Estrogens Requires ERα Activation Function-2 (ERαAF-2), Whereas ERαAF-1 Is Dispensable., Diabetes., 2013; 62(12): 4098–4108.
47. Camila M, Guido L, Javad H, Irina M, Mona G, James R., Sowers Loss of Estrogen Receptor α Signaling Leads to Insulin Resistance and Obesity in Young and Adult Female Mice.,Cardiorenal Med., 2012; 2(3): 200–210.
48. Rodrigo PAB, Ubiratan FM, Margaret W, and Jan-AG., Muscle GLUT4 regulation by estrogen receptors ERβ and ERα., Proc Natl Acad Sci., 2006; 103(5): 1605–1608.
49. Leandro FP, Borja G, Juan C. Díaz-C, Flores AM.,Estrogens Regulate the Hepatic Effects of Growth Hormone, a Hormonal Interplay with Multiple Fates., Front Endocrinol (Lausanne)., 2013; 4: 66.
50. Suba Z., Circulatory Estrogen Level Protects Against Breast Cancer in Obese Women., Recent Pat Anticancer Drug Discov., 2013; 8(2): 154–167.
51. Leung KC, Johannsson G, Leong GM, Ho KK., Estrogen regulation of growth hormone action.,Endocr Rev., 2004; 25(5): 693-721.
52. Mohammad Asif., The prevention and control the type-2 diabetes by changing lifestyle and dietary pattern., J Educ Health Promot., 2014; 3: 1.
53. Jee-Yeon Lee, Hye Sun Hyun, Hyang-Gi Park, Ji Hyun Seo, Eun Young Lee, Ji Soo Lee, Dong-Yun Lee, Doo Seok Choi, and Byung-Koo Yoon., Effects of Hormone Therapy on Serum Lipid Levels in Postmenopausal Korean Women., J Menopausal Med., 2015; 21(2): 104–111.
54. Maria LF, Ana GM., Postmenopausal Women Have Higher HDL and Decreased Incidence of Low HDL than Premenopausal Women with Metabolic Syndrome., Healthcare (Basel)., 2016; 4(1): 20.
55. Jun-Wang X, Jun G, Xin-Ming C, Jin-Yan L, Lei D, Ai J, Gui-Ping X., Effects of estradiol on liver estrogen receptor-α and its mRNA expression in hepatic fibrosis in rats., World J Gastroenterol., 2004; 10(2): 250–254.
56. Croston GE, Milan LB, Marschke KB, Reichman M, Briggs MR., Androgen receptor-mediated antagonism of estrogen-dependent low density lipoprotein receptor

transcription in cultured hepatocytes., Endocrinology., 1997; 138(9): 3779-86.
57. Shidfar F, Alborzi F, Maryam S, Marzieh N., Association of waist circumference, body mass index and conicity index with cardiovascular risk factors in postmenopausal women.,Cardiovasc J Afr., 2012; 23(8): 442–445.
58. Eliza BG, Wei S., Gender Differences in Insulin Resistance, Body Composition, and Energy Balance.,Gend Med., 2009; 6(1): 60–75.
59. Xavier PS., The Medical Risks of Obesity., Postgrad Med., 2009; 121(6): 21–33.
60. Linda EG, Tuan AD, Robert AS., An Estrogen Model: The Relationship between Body Mass Index, Menopausal Status, Estrogen Replacement Therapy, and Breast Cancer Risk., Computational and Mathematical Methods in Medicine Volume., 2012; (2012): 792375.
61. Mi-Jeong L, Yuanyuan W, Susan K., Adipose Tissue Heterogeneity: Implication of depot differences in adipose tissue for Obesity Complications., Fried. Mol Aspects Med., 2013; 34(1): 1–11.
62. Catherine GB, Marie-Claude B, Andréanne T, Jean-Patrice B., Insulin and hyperandrogenism in women with polycystic ovary syndrome., J Steroid Biochem Mol Biol., 2010; 122(0).
63. Andrea D., Insulin Resistance and the Polycystic Ovary Syndrome: Mechanism and Implications for Pathogenesis., Endocrine Reviews., 1997; 18(6): 774–800
64. Attia GR, Rainey WE, Carr BR., Metformin directly inhibits androgen production in human thecal cells.,FertilSteril., 2001; 76(3): 517-24.
65. Bergh C, Carlsson B, Olsson JH, Selleskog U, Hillensjo T., Regulation of androgen production in cultured human thecal cells by insulin-like growth factor I and insulin.,FertilSteril., 1993; 59(2): 323-31.
66. Key TJ, Pike MC., The dose-effect relationship between unopposed oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk., Br J Cancer., 1988; 57: 205–212.
67. Christakou C, Diamanti-Kandarakis E., Role of androgen excess on metabolic aberrations and cardiovascular risk in women with polycystic ovary syndrome., Women's Health., 2008; 4: 583–594.

CONFLICT OF INTEREST REPORTED: NIL ; SOURCE OF FUNDING: NONE REPORTED