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Original article

A Study on the role of High fructose diet induced type 2 diabetes and preneoplastic uterine inflammation in female rats

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ABSTRACT

Introduction: Dysregulated insulin levels plays a role in the occurrence of metabolic syndrome. Collected data indicates a link between insulin and preneoplastic state. Thus the present study aimed to explore the possible role of insulin in the pathogenic events of preneoplastic inflammation of uterus in an experimental model of type II DM in female rats induced by high fructose diet. Materials and Method: 24 female rats were randomly into control group (I) , Diabetic group (II). Animals were sacrificed ,blood samples were collected for serum glucose, triglycerides, FFA, insulin and HOMAIR and IGF1. Uteri were dissected for detection of IGF and adiponectin. Results: Diabetic groups showed significant increase in serum glucose, triglycerides, free fatty acid, insulin, IGF1 and HOMAIR levels. Dissected uterus tissues showed significant decrease in receptor gene expression of adiponectin and marked increase in IGF1 receptor gene expression. Conclusion: Insulin-IGF1 axis positively correlate with preneoplastic uterus inflammation especially associated with obesity.

Introduction

The prevalence of metabolic syndrome is increasing. Available data suggested that using dietary intervention as an integral part of future approaches to prevent and treat diabetes ,obesity and its metabolic consequences (Rolls, 2010). Emerging studies are now characterizing a possible link between visceral obesity and the increased risk of tumors (Doyle et al., 2012). Visceral obesity leads to chronic inflammation and disturbance in the production of adipokines ,cytokines, sex steroids and a pro-coagulant insulin resistant state collectively known as the metabolic syndrome(Doyle et al., 2012). Prospective findings recently associated visceral adiposity specifically with the development of cancer in either sex. Indeed, the obese-state is thought to be a pro-tumorigenic environment and contributes also to insulin resistant state with the resultant excess of circulating glucose, FFA and insulin levels. Elevated levels of pro-inflammatory adipokines including TNF-α, IL-6 and IL-1 result in an imbalance between increased inflammatory stimuli and decreased anti-inflammatory mechanism leading to persistent low -grade inflammation .These adipokines may even affect the body handling of glucose (Ouchi et al., 2011).In this issue they are thought to be involved in the pathogenesis of insulin - resistance which is an adaptive response to raised FFA, thus relating to the extent of visceral adipose tissue deposits. Since the rates of lipolysis are higher in visceral adipocytes, thus the risk of developing insulin resistance is related to the size of visceral fat deposits. The insulin resistance status is characterized by increased risk of carcinomas of breast, prostate and uterus. Thus it was proposed that insulin may act as a mitogenic agent directly on target pre-neoplastic cells or might initiate changes in endogenous hormone metabolism (Donohoe et al., 2011). Adiponectin is a protein, which is produced by the adipocytes and regulates energy homeostasis, glucose and lipid metabolism (Tao et al., 2002). Adiponectin also correlates with systemic insulin sensitivity and was found to be reduced in diabetic patients (Kadowaki et al., 2006). It also has anti-inflammatory effect (Ouchi and Walsh et al., 2007).It has anti-cancer effect and inhibits endometrium cancer (Qiaoli et al., 2011).Guided by the above findings the present study signed to detect the role of insulin- IGF-1 axis in the progression of pre-neoplastic inflammation induced in female rat model. Furthermore , the study aimed to investigate the risk carried by hyper insulinemia in type 2 diabetic patients induced by high carbohydrate diet in the deterioration of the inflammatory processes in attempt to find the insulin- cancer link.

Materials and Method:

The study was carried out in the Animal House of Physiology and Biochemistry Department, Faculty of Medicine, Cairo University. 24 adult female albino rats of average body weight ranging from 150-200 grams comparative to age 10-12 weeks were purchased and included in this study. The animals were housed in wire-mesh cages. During this period, they were left to acclimatize to the normal environmental conditions as regards dark/light cycle, degree of temperature and relative humidity for few days before the experiment. Meanwhile, all the rats were given free access to food and water. Eventually, the rats were randomized into two main groups. Control group (n=12)in which rats received ordinary animal chow for 8 week and Diabetic group (n=12).

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Diabetes was induced via providing the rats with high fructose diet dissolved in the drinking water at a concentration of 1gram/ml and given in a free access to the animals. At the 4th week blood samples were withdrawn from the retro-bulbar plexus estimation of random blood glucose level. Rats with blood glucose level 200mg/ml were included in the study (Adeyi , 2012).

Sample collection and scarification;

At the end of the planned time for the study (8 weeks) blood samples then collected serum was kept frozen at 80° c, to be assayed later. The following parameters were assessed;

1-Fasting serum levels of glucose.

2-Fasting serum insulin levels and HOMA IR was estimated.

3-Fasting serum levels of triglycerides and free fatty acids.

4-Serum IGF1

Then the animals were sacrified by cervical dislocation (Abdel aziz et al., 2011).

After scarification of the animals a mid-ventral abdominal incision was done then uteri is excised for biochemical assessment for estimation of receptor gene expression of Insulin, Adiponectin, Insulin like growth factor – 1 (IGF-1) by ELISA

Statistical analysis:

Data was coded and entered using the statistical package SPSS (version 12). Data was summarized using mean, standard deviation, and range, for quantitative variables. Comparison between groups was done using ANOVA (analysis of variance), and multiple comparison (post Hoc test), for quantitative variables. Correlation was done to test the relation between quantitative variables. P-values < 0.05 were considered as statistically significant.

Results:

The results of this study showed marked significant increase in the serum levels of glucose in diabetic group compared to the control group (as shown in table 1. Regarding the serum levels of insulin, the estimated levels reflected the experimental procedures applied in group Π (diabetic) increased values compared to the control group I (table 1).

Regarding HOMAIR there was significant increase in group II comparison to group I as shown in table (1).

The results of the study have shown a marked significant increase in the serum levels of Triglycerides and FFA in group II compared to group I as shown in table (2).

Uterine adiponectin receptor gene expression levels revealed a significant decrease in group Π compared to group I as recorded in table 3

There was significant increase in the IGF-1receptor gene expression in group Π compared to I as shown in table 3.

Visceral fat : Significant elevation in the level of Fat in group II in comparison to group I.

Table 1

	Group I (control)	Group II (DM)
Serum glucose	6.18 – 6 mMole	15.18 – 6 mMole
Serum insulin level	8 – 0.57 hIU/L	17.38–3.16hIU/L
Homa IR	2.20–0.31	11.61–2.06

Table 2

	Group I (control)	Group II (DM)
TG	92.27 – 12.87	133.9 – 9.43
FFA	3.24–1.34	15.77–4.09

Table 3

	Group I (control)	Group II (DM)
Uterine expression Adiponectin	1.08 – 0.11	0.34– 0.17
Uterine expression IGF1	1.02 – 0.02	9.43–1.43

Discussion:

Diabetes mellitus describes a group of metabolic diseases in which a person has a high blood glucose, either due to inadequate insulin secretion (T1DM) or because the cells do not respond properly to insulin (T2DM) or both (Derr et al., 2009).

The role of insulin and its status are key components in metabolic syndrome a disturbing link may connect the insulin status, to a pre-neoplastic state which may fortell an additional danger: cancer (Giovannucci et al., 2010).In fact, increasing evidence has suggested that this insulin role is related to many cancers as those of liver, pancreas, endometrium and others (Shikata et al., 2013). This evidence also includes studies that examined in particular, the risk of uterine cancer or adenoma in relation to some significant determinants of metabolic syndrome, as well as markers of insulin resistance (insulin and C-peptide) (Guo, 2014). Factors that connect diabetes to cancer are incompletely understood. Thus, the present study was carried out in an attempt to further elucidate some of the possible factors which predispose diabetic patients to the pathogenic events which may eventually lead to cancer initiation, growth and proliferation. To achieve this, an experimental model of diabetes was induced in female rats by providing them high CHO diet of a high glycemic value for 8 weeks (Adeyi, 2012) to achieve a state of hyperinsulinemia and T2DM. The present results confirmed the effectiveness of the experimental model of T2DM, and hyperinsulinemia was reflected by the significant elevation in the serum glucose, insulin level and HOMA IR values compared to those of control. The ability of using white bread and sugar solution in induction of DM may be due to the fact that glucose derived from the high glycemic index-diet can produce persistently high levels of insulin secretion, which ultimately result in post- receptor insensitivity to the released insulin (Adeyi, 2012). Furthermore, it has been well conceived that dietary carbohydrates can increase insulin secretion, which subsequently

stimulate lipogenesis, then cause insulin resistance (Melnik et al., 2011). This fact is further supported in the current findings by the significant increase in the visceral fat adiposity estimated in the hyperinsulinemic rats. Conflicting results demonstrated that high-CHO content in the diet is protective against insulin resistance and diabetes compared to the high- fat diet (PoPkin et al., 2012). Studies, found that hyperglycemia due to high-sugar diet is positively correlated with increased risk of cancers particularly those associated with the gastrointestinal tract (Masur et al., 2011).Moreover, certain experimental cancers were observed to behave more aggressively with excessive intake of high CHO-content diet (Park et al., 2010). One of aspects of the pathophysiology which associates diabetes and hyperglycemia to cancer is the share status of chronic inflammation explaining the increased risk of cancer associating diabetes (Klement & Kamnerer, 2011). High glucose was also found to alter immune functions since glucose competitively impairs the transport of ascorbic acid into immune cells needed for effective phagocytosis and proper function of lymphocytes (Krone and Ely, 2005). Interestingly, it was detected that high glucose in diet and hyperglycemia is influenced in on WNT/B- catenin signaling; a key cancer- associated pathway (García-Jiménez et al., 2013). Once activated, this B- catenin is a potential transcriptional coactivator targeted to genes involved in proliferation and is a well- known tumor marker of bad prognosis (Singh et al., 2013). WNT-signaling is associated obesity as well. Thus, a diet which elevates blood glucose levels and leads to obesity, has been suggested to provide an additional cause for cancer initiation(Lu et al., 2013). Studies provided evidence that the risk of uterine cancer or adenoma is also strongly related to dyslipidemia. The state of dyslipidemia estimated in our results supports the concept that this metabolic alteration is one of the biomarkers that represents an important pathway for development of cancer (Trabert et al., 2015 , Trabulo et al., 2015 & van de Woestijne et al., 2011). A report suggested lipid peroxidative product; melandialdhyde, may cross- link DNA. This may, in theory contribute to a pre-neoplastic environment (Bielecka-Dąbrowa et al., 2011). Although pro-inflammatory cytokines associating hyperlipidemia were not assessed in this study, yet, supported by the present histopathological examination, a previous report showed lymphocytic infiltration of the colon. As regards to hyperlipidemia observed in this study , FFAs serve as ligands for the toll-like receptor 4 (TLR4) complex that stimulate cytokine production by macrophages, thereby, modulating inflammation (Suganami et al., 2007). Consequently, a potential aim in the present work was to induce T2DM to further explore and evaluate. The role of insulin – IGF-1 axis in the related pathogenic events of this study. Thus, the fact that the inflammation of uterus was far more deteriorated in T2DM. The WNT/B- catenin signaling also has been shown to result in an increase in the expression of incretin hormones (including insulin and IGF-1) expression and secretion (García-Jiménez et al., 2013). This impact was further confirmed and supported by the present findings as regards the hyper-insulinemic state which was displayed via marked increase in the estimated serum levels of insulin and IGF-1. As regards the assessed gene expression of insulin receptors, the current work showed opposing results to the previous study published by singh et al., 2013 since the INS R expression estimated in the experimental groups were observed to be markedly reduced in the uterus . The explanation for the present finding that the pro-inflammatory cytokines induced by hyperglycemia have most likely triggered the insulin resistance as well as decreased the expression of INS-Rs in the affected tissues (Clevers, 2011). A further explanation to clarify the observed INS R gene expression reduction is the presence of the elevated levels of FFAs which induce down regulation of insulin signaling (Hotamisligil, 2006). Guided by findings of several studies, it was concluded that as the duration and severity of T2DM progress, the physicians who often turn the patients to exogenous insulin as means to control hyperglycemia, may eventually risk these patients to cancer-related mortality particularly uterus, compared to patients treated with metformin. Chronic hyperinsulinemia may promote cancer as it exerts its oncogenic potential via abnormal stimulation of multiple cellular signaling cascades that enhance growth factor-dependent cell proliferation and / or directly affect the cell metabolism (Clayton et al., 2011). the elevated receptor expression of IGF-1 in the colon confirm the hypothesis that these IGF-1 receptors may have mediated the proliferative effects of insulin and/or IGF-1 in the inflammed tissues thus predisposing to cancer initiation and promotion compared to control animals (Hursting et al., 2012). Once malignancy develops, insulin receptor expression becomes progressively increased, is able to bind both insulin and IGF-1 (Putche and Curtazar, 2012). As further supported by the present results, hyper-insulinemia may have also triggered a significant increase in IGF-1 production (Doyle et al., 2011).This was reflected by the estimated enhancement in the IGF-1 serum levels in the current work. Although the serum levels of adiponectin have not been estimated in the present work, yet, reports of previous studies have acknowledged a reduced adipocytic expression of adiponectin in pro-inflammatory conditions including the obesity-associated diabetes Ouchi and Walch, 2007). This may add further support to the present findings as regards the significant decline which was depicted in the levels of the adiponectin receptor expression in the uterine tissues. Thus, apart from its anti-inflammatory actions (Ahima, 2006). Adiponectin was also shown to inversely correlate with the risk, stage and grade of adenomas. Through molecular mechanisms, adiponectin can suppress MAPK- mediated mTOR and hinder cell proliferation (Kim et al., 2009).

In conclusion: The study implies that a complex network of factors working through insulin –IGF1 axis contribute to a strong link which connects this axis to deterioration of the ongoing inflammation lead to cancer initiation and development of diabetes associated colitis. It is then concluded that further studies are required to implement more effective therapeutic strategies for diabetes associated gonads tumors . To attain this clinical studies should be taken to decrease chronic hyperinsulinemia and insulin resistance thus offering a general approach for prevention of cancer.

REFERENCES:

1. Abdel Aziz MT1, El-Asmar MF, El-Ibrashy IN, Rezq AM, Al-Malki AL, Wassef MA, Fouad HH, Ahmed HH, Taha FM, Hassouna AA, Morsi HM Effect of novel water soluble curcumin derivative on experimental type- 1 diabetes mellitus (short term study). Diabetol Metab Syndr. 2012 Jul 4;4(1):30. doi: 10.1186/1758-5996-4-30.

2. Adeyi AO, Idowu BA, Mafiana CF, Oluwalana SA, Ajayi OL, Akinloye OA. Rat model of food-induced non-obese-type 2 diabetes mellitus: comparative pathophysiology and histopathology. Int J Physiol Pathophysiol Pharmacol. 2012;4(1):51-8. Epub 2012 Feb 28.

3. Ahima RS Adipose tissue as an endocrine organ. Obesity (Silver Spring). 2006 Aug;14 Suppl 5:242S-249S.

4. Bielecka-Dąbrowa A1, Hannam S, Rysz J, Banach M. Malignancy-associated dyslipidemia. Open Cardiovasc Med J. 2011;5:35-40. doi: 10.2174/1874192401105010035. Epub 2011 Feb 24.

5. Clayton PE1, Banerjee I, Murray PG, Renehan AG. Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. Nat Rev Endocrinol. 2011 Jan;7(1):11-24. doi: 10.1038/nrendo.2010.171. Epub 2010 Oct 19.3.

6. Clevers H1 The cancer stem cell: premises, promises and challenges. Nat Med. 2011 Mar;17(3):313-9. doi: 10.1038/nm.2304.

7. Derr RL1, Ye X, Islas MU, Desideri S, Saudek CD, Grossman SA.

8. Association between hyperglycemia and survival in patients with newly diagnosed glioblastoma. J Clin Oncol. 2009 Mar 1;27(7):1082-6. doi: 10.1200/JCO.2008.19.1098. Epub 2009 Jan 12. Donohoe CL1, Doyle SL, Reynolds JV. Visceral adiposity, insulin resistance and cancer risk. Diabetol Metab Syndr. 2011 Jun 22;3:12. doi: 10.1186/1758-5996-3-12

9. Doyle SL, Donohoe CL, Lysaght J, Reynolds JV. Visceral obesity, metabolic syndrome, insulin resistance and cancer. Proc Nutr Soc. 2012 Feb;71(1):181-9. doi: 10.1017/S002966511100320X. Epub 2011 Nov 3.

10. Foster MT1, Shi H, Seeley RJ, Woods SC. Removal of intra-abdominal visceral adipose tissue improves glucose tolerance in rats: role of hepatic triglyceride storage. Physiol Behav. 2011 Oct 24;104(5):845-54. doi: 10.1016/j.physbeh.2011.04.064. Epub 2011 Jun 12

11. García-Jiménez C1, García-Martínez JM, Chocarro-Calvo A, De la Vieja A.A new link between diabetes and cancer: enhanced WNT/β-catenin signaling by high glucose. J Mol Endocrinol. 2013 Dec 19;52(1):R51-66. doi: 10.1530/JME-13-0152. Print 2014 Feb.

12. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D. Diabetes and cancer: a consensus report. Diabetes Care. 2010 Jul;33(7):1674-85. doi: 10.2337/dc10-0666.

13. Guo S Insulin signaling, resistance, and the metabolic syndrome: insights from mouse models into disease mechanisms J Endocrinol. 2014 Jan 8;220(2):T1-T23. doi: 10.1530/JOE-13-0327. Print 2014 Feb

14. Hursting SD1, Digiovanni J, Dannenberg AJ, Azrad M, Leroith D, Demark-Wahnefried W, Kakarala M, Brodie A, Berger NA. Obesity, energy balance, and cancer: new opportunities for prevention. Cancer Prev Res (Phila). 2012 Nov;5(11):1260-72. doi: 10.1158/1940-6207.CAPR-12-0140. Epub 2012 Oct 3.

15. Hotamisligil GS . Inflammation and metabolic disorders. Nature. 2006 Dec 14;444(7121):860-7.

16. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest. 2006 Jul;116(7):1784-92

17. Karaca T1, Bayiroglu F, Yoruk M, Kaya MS, Uslu S, Comba B, Mis L.Effect of royal jelly on experimental colitis Induced by acetic acid and alteration of mast cell distribution in the colon of rats. Eur J Histochem. 2010 Oct 21;54(4):e35

18. Kim KY1, Baek A, Hwang JE, Choi YA, Jeong J, Lee MS, Cho DH, Lim JS, Kim KI, Yang Y. Adiponectin-activated AMPK stimulates dephosphorylation of AKT through protein phosphatase 2A activation. Cancer Res. 2009 May 1;69(9):4018-26. doi: 10.1158/0008-5472.CAN-08-2641. Epub 2009 Apr 14.

19. Klement RJ1, Kämmerer U.Is there a role for carbohydrate restriction in the treatment and prevention of cancer? Nutr Metab (Lond). 2011 Oct 26;8:75. doi: 10.1186/1743-7075-8-75.

20. Krone CA1, Ely JT. Controlling hyperglycemia as an adjunct to cancer therapy. Integr Cancer Ther. 2005 Mar;4(1):25-31.

21. Lu H1, Ward MG, Adeola O, Ajuwon KM. Regulation of adipocyte differentiation and gene expression-crosstalk between TGFβ and wnt signaling pathways. Mol Biol Rep. 2013 Sep;40(9):5237-45. doi: 10.1007/s11033-013-2623-2. Epub 2013 May 9.

22. Masur K1, Vetter C, Hinz A, Tomas N, Henrich H, Niggemann B, Zänker KS.Diabetogenic glucose and insulin concentrations modulate transcriptome and protein levels involved in tumour cell migration, adhesion and proliferation. Br J Cancer. 2011 Jan 18;104(2):345-52. doi: 10.1038/sj.bjc.6606050. Epub 2010 Dec 21.

23. Melnik BC1, John SM, Schmitz G. Over-stimulation of insulin/IGF-1 signaling by western diet may promote diseases of civilization: lessons learnt from laron syndrome. Nutr Metab (Lond). 2011 Jun 24;8:41. doi: 10.1186/1743-7075-8-41.

24. Onitilo AA1, Engel JM, Glurich I, Stankowski RV, Williams GM, Doi SADiabetes and cancer II: role of diabetes medications and influence of shared risk factors. Cancer Causes Control. 2012 Jul;23(7):991-1008. doi: 10.1007/s10552-012-9971-4. Epub 2012 Apr 25

25. Ouchi N1, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011 Feb;11(2):85-97. doi: 10.1038/nri2921. Epub 2011 Jan 21.

26. Ouchi N1, Walsh K Adiponectin as an anti-inflammatory factor. Clin Chim Acta. 2007 May 1;380(1-2):24-30. Epub 2007 Feb 2.

.27. Park EJ1, Lee JH, Yu GY, He G, Ali SR, Holzer RG, Osterreicher CH, Takahashi H, Karin M Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell. 2010 Jan 22;140(2):197-208. doi: 10.1016/j.cell.2009.12.052.

28. Popkin BM1, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. Nutr Rev. 2012 Jan;70(1):3-21. doi: 10.1111/j.1753-4887.2011.00456.x.

29. Puche JE1, Castilla-Cortázar I. Human conditions of insulin-like growth factor-I (IGF-I) deficiency. J Transl Med. 2012 Nov 14;10:224. doi: 10.1186/1479-5876-10-224.

30. Rolls BJ: Plenary Lecture 1 Dietary strategies for the prevention and treatment of obesity. Preceedings Nutrit Soc. 2010, 69: 70-79. 10.1017/S0029665109991674

31. Shikata K1, Ninomiya T, Kiyohara Y. Diabetes mellitus and cancer risk: review of the epidemiological evidence. Cancer Sci. 2013 Jan;104(1):9-14. doi: 10.1111/cas.12043. Epub 2012 Dec 6.

32. Singh R1, De Aguiar RB, Naik S, Mani S, Ostadsharif K, Wencker D, Sotoudeh M, Malekzadeh R, Sherwin RS, Mani A. LRP6 enhances glucose metabolism by promoting TCF7L2-dependent insulin receptor expression and IGF receptor stabilization in humans. Cell Metab. 2013 Feb 5;17(2):197-209. doi: 10.1016/j.cmet.2013.01.009

33. Suganami T1, Tanimoto-Koyama K, Nishida J, Itoh M, Yuan X, Mizuarai S, Kotani H, Yamaoka S, Miyake K, Aoe S, Kamei Y, Ogawa Y. Role of the Toll-like receptor 4/NF-kappaB pathway in saturated fatty acid-induced inflammatory changes in the interaction between adipocytes and macrophages. Arterioscler Thromb Vasc Biol. 2007 Jan;27(1):84-91. Epub 2006 Nov 2.

34. Sugiyama M1, Takahashi H, Hosono K, Endo H, Kato S, Yoneda K, Nozaki Y, Fujita K, Yoneda M, Wada K, Nakagama H, Nakajima A. Adiponectin inhibits colorectal cancer cell growth through the AMPK/mTOR pathway. . Int J Oncol. 2009 Feb;34(2):339-44.

35. TaoC1, SifuentesA1, HollandWLRegulationof glucose and lipid homeostasis by adiponectin: effects on hepatocytes,pancreatic β cells and adipocytes. Best Pract Res Clin Endocrinol Metab. 2014 Jan;28(1):43-58. doi: 10.1016/j.beem.2013.11.003. Epub 2013 Nov 15.

36. Trabulo D1, Ribeiro S1, Martins C1, Teixeira C1, Cardoso C1, Mangualde J1, Freire R1, Gamito É1, Alves AL1, Augusto F1, Oliveira AP1,Cremers I1.

37. Metabolic syndrome and colorectal neoplasms: An ominous association. World J Gastroenterol. 2015 May 7;21(17):5320-7. doi: 10.3748/wjg.v21.i17.5320.

38. Trabert B, Wentzensen N , Felix A S., Yang H P., Sherman M E. , and Brinton L A. Metabolic syndrome and risk of endometrial cancer in the United States: a study in the SEER-Medicare linked database. Cancer Epidemiol Biomarkers Prev. 2015 Jan; 24(1): 261–267.

40. Van de Woestijne AP1, Monajemi H, Kalkhoven E, Visseren FL Adipose tissue dysfunction and hypertriglyceridemia: mechanisms and management. Obes Rev. 2011 Oct;12(10):829-40. doi: 10.1111/j.1467-789X.2011.00900.x. Epub 2011 Jul 12.

41. Qiaoli Z, 1 2 Haijian Wu, 3 and Jiang Cao Circulating Adiponectin and Risk of Endometrial Cancer PLoS One. 2015; 10(6): e0129824