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Research Article

Exogenous Insulin Effect on the Initiation of Breast Cancer in Type 2 Diabetes Mellitus Patients

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Abstract

Background: Growing evidence has indicated that women with type 2 diabetes mellitus are at an increased risk of developing breast cancer. However, as a major adjuvant treatment, the influence of hormone therapy such as exogenous insulin on type 2 diabetes mellitus in primary breast-cancer remains controversial.

Objective: To explore the relationship between different types of hypoglycemic medications for diabetes and the factors that may contribute to the initiation of breast cancer.

Methods: The study included 80 blood samples taken from 80 females recruited from Ibn Al-Bitar Center for Cardiac Surgery Hospital in Baghdad, Iraq, between November 2022 and February 2023. They were within an age range of 40 to 70 years. They were divided into three groups according to the treatment strategy and duration of disease as follows: Group 1: (20) patients who take insulin only, Group 2: (20) patients who take metformin with insulin, and G 3: (40) patients on metformin only for less than one year. An enzymatic oxidation technique was used to test the following biochemical parameters for all research groups: Total cholesterol, triglycerides, fasting blood glucose, and high-density lipoprotein cholesterol. Using the Friedewald formula, the very low-density lipoprotein cholesterol and low-density lipoprotein cholesterol were determined. Using an enzymatic process, Insulin levels and Insulin like growth factor-1(IGF-1), Estrogen receptor alpha (ERα) levels, and breast cancer susceptibility protein 1 (BRCA1) were measured with an enzyme-linked immunosorbent assay (ELISA). Glycated hemoglobin (HbA1c) level was measured with a sandwich immunodetection method. Finally, The Homeostasis Model Assessment for insulin resistance (HOMA-IR) was calculated according to the specific formula.

Results: The values for HbA1C%, FBS, and lipid profile showed non-significant differences when compared between study groups. While BRCA-1, estrogen receptor alpha (ERα), insulin, insulin growth factor IGF-1, and HOMA IR All showed significant differences among all groups.

Conclusion: Taking metformin only for less than one year seemed to contribute to higher levels of BRCA-1.

Keywords: BRCA1 protein; Breast cancer; Estrogen receptor alpha; Insulin; Type 2 diabetes mellitus.

Introduction

Diabetes mellitus refers to a multi-etiological metabolic condition characterized by chronic hyperglycemia, lipid and protein metabolism disorders arising from insulin secretion, insulin action, or both. Diabetic patients may suffer from several symptoms, such as excessive thirst, frequent urination, blurry vision, and decreased weight (1). Diabetes can develop to a high level of sugar keto acids, which may be associated with complications and disorders of the large blood vessels that cause several diseases, including stroke, and other disorders (2). Understanding the classical insulin signaling system is crucial to comprehend the pathophysiology and pathophysiological events of type 2 diabetes. The primary hormone for controlling blood sugar is insulin, and in most cases, a healthy balance between insulin secretion and action is what keeps blood sugar levels normal (3). Breast cancer is the most common kind of cancer Worldwide, and the main reason for cancer-related death. Since breast cancer is a complex disease, the exact mechanism by which it starts is unknown. Nonetheless, the pathogenesis of breast cancer involves a complex interaction between hereditary, environmental, and lifestyle variables (4). Made up of two disulfide bridges connecting the α and β chains as a dimer and a third intrachain disulfide bridge in the α chain, insulin is an endocrine peptide hormone consisting of 51 amino acids. Pancreatic beta cells secrete insulin, which is necessary for maintaining healthy levels of lipids and glucose. Along with helping to maintain glucose homeostasis, insulin also supports some other cellular functions, such as the regulation of glycogen production, lipid metabolism, DNA synthesis, gene transcription, amino acid transport, protein synthesis, and degradation (5). Insulin-like growth factor-1(IGF-1) is a polypeptide

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of 70 residues that is divided into A through D domains. The A-C domains are present in proinsulin, but the A and B Domains are the only ones present in mature insulin. Growth hormone controls the majority of the liver's secretion of circulating IGF-1, but various organs can express IGF-1 in an autocrine/paracrine way (6). Insulin-like growth factors are proteins that serve a variety of purposes, including regulating cell differentiation and transformation as well as promoting cell motility, inhibiting apoptosis, and stimulating cell proliferation. Several studies have revealed that malignancies, such as prostate, pre- and postmenopausal breast, lung, thyroid, and colorectal cancers, are linked to elevated levels of IGF-1 (7). One of the main features of type 2 diabetes and obesity is insulin intolerance. Over the past ten years, endoplasmic reticulum (ER) stress has become a significant player in this field, as numerous recent studies have demonstrated its involvement in the initiation of insulin resistance (IR). In addition to acting indirectly by encouraging lipid accumulation, ER stress appears to operate directly as a negative modulator of the insulin signaling pathway (8). Thus the current study tried to explore the relationship between different types of hypoglycemic medications for diabetes and the factors that may contribute to the initiation of breast cancer.

Patients and Methods

The study sample

The participants in the current study were recruited from Ibn AL-Bitar Center for Cardiac Surgery Hospital, and the laboratory procedures were carried out in the College of Science for Women / University of Baghdad. The women included in the study were those with type 2 diabetes who did not have breast cancer. The study included (80) women with an age range of (40-70) years. They were divided into three groups according to the treatment strategy and duration of disease as follows: Group 1: (20) patients who take insulin only, Group 2: (20) patients who take metformin with insulin, and G 3: (40) patients on metformin only for less than one year. A sample of seven milliliters of blood sample was collected from each participant and divided into two tubes; an EDTA tube for HbA1c (Boditech I-chroma, Korea), and a gel tube for BRCA-1, estrogen receptor alpha, insulin, insulin growth factor (ELISA - My Sunlong, China), FBS and lipid profile (measured manually by using a Biosystem Spine kit). The tubes were left for 20-25 minutes at a room temperature of 25 ºC, and were then centrifuged at 2000-3000 rpm for 10 minutes. The separated serum was kept in deep freeze at- 20°C.

Exclusion criteria: Cases with Covid-19, pregnant women, patients with breast cancer, and smokers.

Statistical Analysis

The statistical analysis was done using version 26 of the SPSS program. The group description was presented as medians and mean ± SE. The ANOVA test used to study the differences between the means, in addition to linear regression to study the relationships between variables. The probability value used to determine statistical significance was ($p \leq 0.05$).

Results

Table 1 shows the mean and median age and duration of disease (years) for the participants in the three study groups

Table (1): Mean and median age and disease duration of the study groups

Parameters	Study Groups		
	(1) Insulin only No. (20)	(2) Metformin + insulin No. (20)	(3) Metformin only < 1 year No. (40)
Age (year)	64.4 ± 1.19 (66)	60.2 ± 1.90 (61)	52.3 ± 1.00 (53)
Disease duration (years)	10.00±0.001 (10)	10.00±0.001 (10)	1.6 ± 0.08 (2)

Table 2 shows that the differences in the mean values of FBS, HbA1c%, cholesterol, TG, HDL-C, LDL-C and VLDL-C for the three study groups were not significant. Groups 1 had the highest mean value for FBS and the lowest for cholesterol; group 2 had the highest mean value for cholesterol, TG, LDL and VLDL and the lowest mean value for HDL; and group 3 had the highest mean value for HDL and the lowest mean value for FBS, HbA1C, TG, LDL and VLDL

Table (2): Mean and median values for blood glucose and lipids in the study groups

Parameters	Study Groups			P-value
	(1) Insulin only No. (20)	(2) metformin + insulin No. (20)	(3) Metformin only < 1 year - No. (40)	
FBS -(mg/dL)	234.6±23.52 [a] (219)	222.0±21.24 [a] (195)	187.1±14.49 [a] (159)	0.302
HbA1c%	9.1±0.450 [a] (8.71)	9.1±0.396 [a] (8.70)	7.8±0.211 [a] (7.35)	0.153
Cholesterol (mg/dL)	178.5±11.48 [a] (185.50)	196.3±14.05 [a] (184.5)	180.4±9.43 [a] (180)	0.223
TG (mg/dL)	172.4±13.91 [a] (176)	179.3±14.63 [a] (161.5)	165.5±14.84 [a] (146)	0.984
HDL-C (mg/dL)	36.6±1.92 [a] (36.50)	36.4±1.99 [a] (36.51)	40.7±1.26 [a] (40)	0.129
LDL-C (mg/dL)	107.6±10.61 [a] (110.50)	123.7±13.23 [a] (110)	106.6±9.072 [a] (106)	0.134
VLDL-C (mg/dL)	34.4±2.76 [a] (35)	35.9±2.92 [a] (32.5)	33.1±2.97 [a] (29)	0.982

Table 3 shows highly significant differences among the three study groups in terms of the mean values of parameters relevant to breast cancer and insulin. Group 1 had the highest mean value for IGF-1 and HOMA IR and the lowest mean value for BRCA-1; group 2 had the highest mean value for Erα and insulin; and group 3 had the highest mean value for a

nd the lowest mean value for ‹BRCA-1 and the lowest mean value for Erα, IGF-1, insulin and HOMA IR.

Table (3): Mean and median values for breast cancer and insulin related variables in the study groups

Parameters	Study Groups			P-value
	(1) Insulin only No. (20)	(2) metformin + insulin No. (20)	(3) Metformin only < 1 year - No. (40)	
‹BRCA-1 (ng/ml)	3.1±0.76 [bc] (3.12)	3.3±0.19 [c] (3.01)	3.5±0.19 [c] (3.96)	0.0001*
Estrogen Receptor Alpha (ERα) (pg/ml)	446.6±18.62 [b] (437.7)	473.1±28.67 [b] (458.50)	404.7±15.15 [ab] (442.90)	0.0001*
IGF-1 (ng/ml)	7.5±0.36 [c] (7.34)	7.1±0.46 [bc] (6.49)	6.6±0.45 [bc] (7.13)	0.0001*
Insulin (mU/L)	2.0±0.06 [bc] (2.04)	2.3±0.16 [c] (2.18)	1.8±0.07 [ab] (1.90)	0.0001*
HOMA IR	1.2±0.12 [b] (0.98)	1.2±0.11 [b] (1.10)	0.8±0.07 [ab] (0.69)	0.005*

* *a, b, c are Significant variants that denoted by different small letters, and non-significant variations are denoted by identical small letters*

Discussion:

Type 2 diabetes mellitus is a metabolic disorder marked by persistently elevated blood sugar levels. Gender and age have an impact on diabetes management. Due to their many medical disorders involving the heart and kidneys, women and people over 60 years of age are more affected, which restricts and hinders medical treatment (9). Potent hormone insulin stimulates many signaling pathways, some of which are essential to the biology of cancer. Insulin can either directly or indirectly increase the risk of cancer by influencing the levels of other modulators, including hormones, adipokines, and the insulin-like growth factor-1 (IGF-1) (10).The higher level of BRCA-1 in the third group than other groups in the current study is in agreement with Samuel et al (11) who found that BRCA-1 protein levels increase in patients taking metformin for less than one year because metformin can activate the AMP-activated protein kinase (AMPK) pathway, which is a signaling pathway that regulates cell growth and metabolism. The AMPK pathway has been shown to increase BRCA-1 gene

expression. Metformin may also reduce BRCA-1 protein degradation. Metformin can inhibit the activity of the proteasome, which is a complex that degrades proteins. This could lead to an increase in BRCA-1 protein levels. The result agrees with Boucher et al., who noticed a slight increase in the concentration of BRCA-1 protein in the first group. From various studies, it has been found that insulin can increase the level of BRCA-1 protein (12). This effect may be happening through the insulin receptor signaling pathway. Insulin stimulates a series of signal molecules through binding with its receptor which ultimately enhances expression of BRCA-1 gene (12). Again, insulin and metformin might have complementary effects on levels of BRCA-1 protein. As such, the joint influence created by these two medications outweighs their separate accomplishments (13).

The current study agrees with other studies which have shown that high levels of ERα are found in patients taking insulin for more than a decade, in their breast and endometrial tissue. This might be due to the fact that cells grow after being stimulated by insulin and ERα serves as a growth factor receptor (14). Other studies have found that those patients who have higher levels of ERα in their breast and

endometrial tissue are at risk if they develop cancer. This is because estrogen can promote cancer cell growth. In addition, elevated expression of ERα among patients taking metformin and insulin may carry numerous clinical implications. For instance, since ERα is a target for breast cancer therapy, these hormone therapies can then be better suited for patients whose levels of such proteins go up. Moreover, there are various other physiological processes including cardiovascular health, cognition as well as bone metabolism where ERα plays a role (15). Thus, alterations in the levels of ERα can have more far-reaching effects on the overall wellbeing of individuals who do use metformin along with insulin.

Conclusion:

Taking metformin only for less than one year seemed to contribute to higher levels of BRCA-1. The ERα signaling by IR and IGF1 is amplified by elevated insulin and IGF-1 levels in females with T2DM. These observations and predictions imply that diabetes, and specifically T2DM, may contain mechanisms for the formation or production of cancer through the use of T2DM medications that affect ERα and IGF-1 levels.

Authors' Declaration: We confirm that all the Figures and Tables in the manuscript are ours. Besides, the Figures and images, which are not ours, have been given permission for re-publication attached to the manuscript. Authors sign on ethical consideration's Approval-Ethical Clearance: The project was approved by the local ethical committee in (College of Science, University of Baghdad) (On October 27, 2022).

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Authors' Contributions: Hanan H. Hassan & Perry H. SaifUllah: Study conception, Hanan H. Hassan & Perry H. SaifUllah Study design. Hanan H. Hassan Acquisition of data. Hanan H. Hassan: Analysis, Interpretation of data, Supervision, Validation, Visualization, Writing- reviewing and editing of manuscript. Hanan H. Hassan & Perry H. SaifUllah: Study conception, Investigation, Methodology, Acquisition of data analysis, Interpretation of data, Writing-drafting of manuscript.

References:

1. Sadeghi A, Niknam M, Momeni-Moghaddam MA, Shabani M, Aria H, Bastin A, et al. Crosstalk between autophagy and insulin resistance: evidence from different tissues. Eur JMR. 2023; 28(1):456. https://doi.org/10.1186/s40001-023-01424-9.

2. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. The lancet. 2017; 389 (10085): 2239-51. (17)30058-2. https://doi.org/10.1016/S0140-6736

3. Hameed AS, Khaleel FM, Rahma AM. The response of acromegalic patients (Diabetic versus non-diabetic) to Long-acting-repeatable Octreotide (LAR) in the presence or absence of Glutathion S transferase (GSTM1, GSTT1) Genes. JPharmaSR. 2019; 11(2):495-500.URL

4. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer—epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—an updated review. Cancers. 202;13(17):4287 . https://doi.org/10.3390/cancers13174287.

5. Ali SE, Khaleel FM. Assessing the Activity of Renin and GST in the Serum of Ladies Suffering from Polycystic Ovary Syndrome and COVID-19 to Predict the Danger of Cardiac Disease. BSJ. 2023; 20(3) (Suppl.): 0986. https://doi.org/10.21123/bsj.2023.7879.

6. Rahmani J, Montesanto A, Giovannucci E, Zand H, Barati M, Kopchick JJ, et al. Association between IGF-1 levels ranges and all-cause mortality: A meta-analysis. Aging Cell. 2022; 21(2): e13540. https://doi.org/10.1111/acel.13540.

7. Díaz del Moral S, Benaouicha M, Muñoz-Chápuli R, Carmona R. The insulin-like growth factor signalling pathway in cardiac development and regeneration. IJMS Journa. 2021 26;23(1):234. https://doi.org/10.3390/ijms23010234.

8. Wondmkun YT. Obesity, insulin resistance, and type 2 diabetes: associations and therapeutic implications. DMSO. 2020:3611-6. https://doi.org/10.2147/DMSO.S275898.

9. Mustafa SA, Hasan BF, Ibrahim N. Estimation of ferritin, erythropoietin in obese Iraqi type II diabetic patients. BCA. 2019;19(2):3307-12. http://dx.doi.org/10.35124/bca.2019.19.2.3307.

10. Baker C, Retzik-Stahr C, Singh V, Plomondon R, Anderson V, Rasouli N. Should metformin remain the first-line therapy for treatment of type 2 diabetes?. TAEM. 2021; https://doi.org/10.1177/2042018820980225.

11. Samuel SM, Varghese E, Kubatka P, Triggle CR, Büsselberg D. Metformin: the answer to cancer in a flower? Current knowledge and future prospects of metformin as an anti-cancer agent in breast cancer. Biom. 2019; 9(12):846. https://doi.org/10.3390/biom9120846.

12. Gholami M, Klashami ZN, Ebrahimi P, Mahboobipour AA, Farid AS, Vahidi A, et al. Metformin and long non-coding RNAs in breast cancer. JTM. 2023; 21(1):155. https://doi.org/10.1186/s12967-023-03909-x

13. Xue L, Chen F, Yue F, Camacho L, Kothapalli S, Wei G, et al. Metformin and an insulin/IGF-1 receptor inhibitor is synergistic in blocking growth of triple-negative breast cancer. Breast cancer research and treatment. 2021; 185: 73-84. https://doi.org/10.1007/s10549-020-05927-5.

14. Tang ZR, Zhang R, Lian ZX, Deng SL, Yu K. Estrogen-receptor expression and function in female reproductive disease. Cells. 2019; 8(10):1123. https://doi.org/10.3390/cells8101123.

15. Kim JH, Choi YK, Byun JK, Kim MK, Kang YN, Kim SH, et al. Estrogen-related receptor γ is upregulated in liver cancer and its inhibition suppresses liver cancer cell proliferation via induction of p21 and p27. EMM. 2016; 48(3): e213-. https://doi.org/10.1038/emm.2015.11.

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تأثير الأنسولين الخارجي على بدء سرطان الثدي في مرضى السكري من النوع 2

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الخلاصة
الخلفية: تشير الأدلة المتزايدة إلى أن النساء المصابات بداء السكري من النوع الثاني أكثر عرضة للإصابة بسرطان الثدي. ومع ذلك، كعلاج مساعد رئيسي، فإن تأثير العلاج الهرموني مثل الإنسولين الخارجي على داء السكري من النوع الثاني في سرطان الثدي الأولي لا يزال مثيرا للجدل.
الهدف: علاقة الأنواع المختلفة من أدوية السكري بالعوامل التي قد تسهم في بدء الإصابة بسرطان الثدي
المرضى والمنهجية: شملت الدراسة 80 عينة مأخوذة من 80 سيدة تراوحت أعمارهن بين 40 إلى 70 عاما. تم تقسيمهن إلى ثلاث مجموعات حسب استراتيجية العلاج ومدة المرض على النحو التالي: المجموعة الاولى: (20) مريضة يتناولن الأنسولين فقط، المجموعة الثانية: (20) مريضة يتناولن الميتفورمين مع الإنسولين، والمجموعة الثالثة: (40) مريضة يتناولن الميتفورمين فقط لمدة تقل عن عام، وتم جمعهن من مستشفى مركز إبن البيطار لجراحة القلب في بغداد، العراق، بين تشرين الأول 2022 وشباط 2023. تم قياس بعض المعلمات البيوكيميائية لجميع مجموعات الدراسة والتي تشمل: الجلوكوز الصائم والكوليسترول الكلي والدهون الثلاثية والكوليسترول الدهني عالي الكثافة بطريقة الأكسدة الأنزيمية. وباستخدام معادلة فرايدإيوالد، تم تحديد كوليسترول البروتين الدهني منخفض الكثافة وكوليسترول البروتين الدهني منخفض الكثافة. باستخدام عملية إنزيمية، تم قياس مستويات الإنسولين وعامل النمو الشبيه بالإنسولين (IGF-1)، ومستويات مستقبلات هرمون الأستروجين ألفا (ERα)، وبروتين قابلية الإصابة بسرطان الثدي (BRCA-1) باستخدام مقايسة الإمتصاص المناعي المرتبط بالإنزيم (ELISA). تم قياس مستوى الهيموجلوبين السكري (HbA1c) باستخدام طريقة الكشف المناعي للساندويتش. وأخيرا، تم حساب تقييم نموذج التوازن لمقاومة الإنسولين (HOMA-IR) وفقا للصيغة المحددة
النتائج: أظهرت نتائج المجموعات المتعلقة بـ HbA1C%، FBS، وملف الدهون إختلافات غير معنوية عند مقارنتها بين مجموعات الدراسة. في حين أظهرت كل من، BRCA-1، ومستقبلات هرمون الإستروجين ألفا (ERα)، والإنسولين، وعامل النمو الشبيه بالإنسولين IGF-1، ونموذج التوازن لمقاومة الإنسولين HOMA IR ، أهمية بين جميع المجموعات
الإستنتاج: يبدو أن تناول الميتفورمين لمدة تقل عن عام واحد فقط يساهم في ارتفاع مستويات بروتين قابلية الإصابة بسرطان الثدي BRCA-1.
الكلمات المفتاحية: بروتين BRCA-1، سرطان الثدي، مستقبلات هرمون الإستروجين ألفا، الإنسولين، داء السكري من النوع الثاني

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