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Evaluation of the Ki-67 and CA 15-3 as a potential biomarker in breast cancer and type 2 diabetes

Israa J. Mnahi, Bushra F. Hasan
Department of Chemistry, College of Science for Women, University of Baghdad, Iraq

Breast cancer (BC) is the most common cancer in women worldwide and the primary cause of cancer-related mortality. Ki-67 is a nuclear protein that serves as a key marker for cellular proliferation. The expression of this marker during all active phases of the cell cycle, expressed as the percentage of positively stained tumor cells, provides valuable prognostic and predictive information in BC. CA 15-3 is a circulating tumor marker which is primarily associated with BC. It is a soluble form of the MUC1 glycoprotein, which is overexpressed and shed into the bloodstream by malignant breast epithelial cells.
The objective: **to study the impact of hyperglycemia on the blood concentrations of tumor markers Ki-67 and CA 15-3 and the role of these biomarkers in women with BC and type 2 diabetes (T2DM).**
Materials and methods**. The study included 100 women who were divided into three groups. 1 group included 32 women with T2DM and BC, 2 group included 34 women with BC, and 3 group (control group) – 34 healthy women. The levels of tumor markers (CA 15-3 and Ki-67), body mass index, age, stage of cancer, duration of T2DM, and glycosylated hemoglobin (HbA1c) were estimated in the three groups.**
Results**. The serum levels of Ki-67 and CA 15-3 in women with T2DM and BC were significantly higher than those in women with BC ($p < 0.0001$), serum Ki-67 level was significantly higher in women with T2DM than in the control group in contrast, and the level of HbA1c was significantly higher in women with T2DM and BC more than BC women and control group.**
Conclusions**. Women with T2DM have a higher risk of BC development than women without diabetes therefore estimating the level of tumor markers Ki-67 and CA 15-3 can be used as diagnostic biomarkers in women with T2DM represents a promising strategy for improving cancer treatment outcomes.**
Keywords: *CA 15-3, Ki-67, type 2 diabetes mellitus, breast cancer, HbA1c.*

Визначення Ki-67 та CA 15-3 як потенційних біомаркерів при раку молочної залози та цукровому діабеті 2-го типу

Israa J. Mnahi, Bushra F. Hasan

Рак молочної залози (РМЗ) є найпоширенішим видом раку в жінок у всьому світі та найчастішою причиною смертності, пов'язаної з раком. Ki-67 – це ядерний білок, який є ключовим маркером клітинної проліферації. Експресія цього маркера протягом усіх активних фаз клітинного циклу, виражена як відсоток позитивно забарвлених пухлинних клітин, надає цінну прогностичну та предикативну інформацію при РМЗ. CA 15-3 – це циркулювальний онкомаркер, який переважно пов'язаний із РМЗ. Це розчинна форма глікопротеїну MUC1, який надмірно експресується та виділяється в кровотік злоякісними епітеліальними клітинами молочної залози.
Мета дослідження: вивчення впливу гіперглікемії на концентрацію в крові онкомаркерів Ki-67 та CA 15-3 та визначення ролі цих біомаркерів у жінок із РМЗ та цукровим діабетом 2-го типу (ЦД2).
Матеріали та методи. У дослідження включено 100 жінок, які були розділені на три групи. До 1-ї групи увійшло 32 жінки з ЦД2 та РМЗ, до 2-ї – 34 жінки з РМЗ, до 3-ї (контрольна група) – 34 здорові жінки. Були оцінені рівні онкомаркерів (CA 15-3 та Ki-67), індекс маси тіла, вік, стадія раку, тривалість ЦД2 та глікований гемоглобін (HbA1c) у трьох групах.
Результати. Рівні Ki-67 та CA 15-3 у сироватці крові у жінок із ЦД2 та РМЗ були значно вищими, ніж у жінок із РМЗ ($p < 0{,}0001$), рівні Ki-67 у сироватці крові були значно вищими у жінок із ЦД2, ніж у контрольній групі, а рівень HbA1c у жінок із ЦД2 та РМЗ був значно вищим, ніж у жінок із РМЗ та контрольної групи.
Висновки. Пацієнтки із ЦД2 мають вищий ризик розвитку РМЗ, ніж жінки без діабету, тому оцінювання рівня онкомаркерів Ki-67 та CA 15-3, яке можна використовувати як діагностичні біомаркери у жінок із ЦД2, є перспективною стратегією для покращення результатів діагностики та лікування раку.
Ключові слова: *CA 15-3, Ki-67, цукровий діабет 2-го типу, рак молочної залози, HbA1c.*

Breast cancer (BC) is a notable global health issue, especially in women with type 2 diabetes mellitus (T2DM) [1]. In recent years, diabetes has become a significant chronic condition globally, with the prevalence of T2DM in Iraq ranging from 8.5 to 13.9%. This contributes to the global upward trend, which anticipates 366 million individuals to have T2DM by 2030 [2]. BC is the most prevalent cancer among women globally and the leading cause of cancer-related mortality in this population. In Iraq, women with BC have the highest prevalence among various cancer types, accounting for 21.2% as reported by the Iraqi Ministry of Health in 2022 [3, 4].

Several types of researches have been conducted to ascertain the link between diabetes and its potential to increase the risk of BC [5, 6]. Several different mechanisms have been suggested to contribute to an elevated BC risk in women with T2DM which is characterized by relative insulin resistance and is closely related to

hyperglycemia leading to higher levels of insulin in the bloodstream which ultimately has growth-promoting effects on cells including BC, oxidative stress and chronic inflammation [1, 7]. Inflammation is a key factor in the development of T2DM through two pathways: obesity, which causes systemic inflammation through macrophage infiltration, and pro-inflammatory cytokine production. Obesity, which leads to metabolic syndrome, hypertension, and dyslipidemia, is positively associated with inflammatory biomarkers [8–10]. Fat production and increased inflammatory markers correlate with T2DM, causing metabolic stress in pancreatic islets and insulin-sensitive tissues such as adipocytes [11, 12].

Malignant tumor screening in clinics is now routine for patients with diabetes, aiding tumor diagnosis and prognosis evaluation. This has clinical significance, reducing mortality and improving patient's quality of life, as tumor marker screening is now widely used [13, 14]. Ki-67 is a nuclear protein that plays a crucial role in cell proliferation and serves as an important prognostic and predictive biomarker in cancer, particularly BC [15]. Ki-67 expression is strongly associated with tumor cell proliferation and growth, making it a valuable marker for assessing tumor aggressiveness. Its presence indicates actively dividing cells, which is a hallmark of cancer [16]. CA 15-3 and MUC1 are the most commonly used serum marker in BC [17] MUC1 appears to play a role in cell adhesion and the high levels present in cancer may be causally involved in metastasis. At present the main uses of CA 15-3 are in preclinically detecting recurrent BC and monitoring the treatment of patients with advanced BC. In a prospective study of 368 patients we show that patients with high preoperative levels of CA 15-3 (>30.4 U/mL). This large transmembrane glycoprotein has shown potential as a prognostic tool [18]. In multivariate analyses, CA 15-3 demonstrated a prognostic impact independent of tumor size and nodal status. CA 15-3 is valuable for monitoring treatment responses in patients with advanced BC [19].

The objective: to explore the impact of hyperglycemia on the blood concentrations of tumor markers Ki-67 and CA 15-3 and the role of these biomarkers in women with BC and T2DM.

MATERIALS AND METHODS

A total 100 Iraqi women took part in the study in the period women between 1st August 2024 and 1st February 2025. The participants were divided into three groups (G): G1 – 32 women with BC and T2DM, G2 – 34 women with BC only, and G3 – 34 healthy controls.

Including criteria: all diabetic patients were on metformin treatment. The three groups were matched in age, body mass index (BMI), and cancer stage (stages 1 and 2).

The American Joint Committee on Cancer (AJCC) TNM staging system, 8th edition, was used to determine the stages of BC. This method assigns a clinical stage between 0 and IV based on tumor size (T), lymph node involvement (N), and metastasis presence (M). To provide a more accurate prognostic stage grouping, biological markers such as tumor grade, HER2 (Human Epidermal Growth Factor Receptor 2) expression, and hormone receptor status (ER – estrogen receptor, PR – progesterone receptor) were taken into account in addition to anatomical factors. Based on standard diagnostic imaging, biopsy results, and surgical pathology, all clinical and pathological staging was carried out by certified oncologists and pathologists.

Excluded criteria: pregnant women, patients with pancreatitis, obstruction in bile ducts, acute and chronic inflammatory periods and patients suffering from autoimmune diseases.

The three groups of subjects were observed and compared in terms of the levels of tumor markers CA 15-3 and Ki-67 and the parameters BMI and HbA1c. A total of 100 whole blood samples were collected at Baghdad Teaching Hospital / Medical City, and Al-Amal Tumor Center. In the morning, five milliliters of blood was collected from all subjects and; divided in to two parts: two milliliters placed in an EDTA (Ethylenediaminetetraacetic acid) tube for measuring glycated hemoglobin (HbA1c) was assessed by boronated affinity chromatography (BAC) and three milliliters was transferred into gel tubes to obtain the serum by centrifugation at a force of 3000 × g for 10 minutes, and stored in a deep freeze at a temperature of –20 °C until used to measure CA 15-3 and Ki-67 level by the quantitative sandwich enzyme immunoassay technique (ELISA). The height and weight of the subjects were recorded, and their BMI was calculated based on the measurement results.

The data were statistically analyzed using IBM SPSS Statistics 25.0, and the individual correlation test was used to highlight the difference between CA 15-3 and Ki-67 and other parameters within the patient groups. One-way analysis of variance was used to analyze the data, which is a statistical method used to identify significant differences between the groups. A p-value < 0.05 was considered statistically significant. Receiver operating characteristic curve methodology was employed to examine the optical cut-off values for serum CA 15-3 and Ki-67. The correlation between these two indices was analyzed. Univariate analysis was performed to analyze the general clinical data of the patients and the factors influencing complications.

RESULTS AND DISCUSSION

In the Table 1 there is a comparison of the different demographic and clinical parameters between the three patient groups. These groups were classified according to their medical condition.

Comparison of tumor markers between the three groups. Serum levels of Ki-67 and CA 15-3 were significantly elevated in G1 and G2 compared to those in the control group ($p < 0.0001$; Table 2).

Comparison of HbA1c level among the three groups. HbA1c level in the diabetic G1 was significantly higher than those in the BC (G2) and control groups (G3; $p < 0.05$; Table 3).

As shown in Table 4 a correlation analysis was conducted for patients with BC and T2DM. The analysis revealed a significant positive correlation between the two important markers: Ki-67 and CA 15-3. The tumor markers CA 15-3 and Ki-67 were positively correlated with each other in the G2 (Table 5).

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Table 1

Comparison of demographic and clinical parameters across groups in cancer and diabetes patients

Parameters		G1 (n = 32)	G2 (n = 34)	G3 (n = 34)
Age (years)	Mean ± std. error	57.6 ± 1.5	54.3 ± 1.3	49.1 ± 1.7
	Lower 95% CI of mean	54.5	51.5	45.5
	Upper 95% CI of mean	60.7	57.1	52.7
	p-value	0.001		
BMI (kg/m^2)	Mean ± std. error	29.80 ± 0.95	31.8 ± 1.1	29.1 ± 0.9
	Lower 95% CI of mean	27.9	29.4	27.2
	Upper 95% CI of mean	31.7	34.4	31.0
	p-value	0.17		
Duration of diabetes (years)	Mean ± std. error	6.9 ± 1.3	–	8.6 ± 1.0
	Lower 95% CI of mean	4.1	–	6.6
	Upper 95% CI of mean	9.4	–	10.6
Duration of cancer (years)	Lower 95% CI of mean	1.3	2.2	–
	Upper 95% CI of mean	2.8	4.4	–
	Lower 95% CI of mean	4.1	–	–
	Upper 95% CI of mean	9.4	–	–

Note: CI – confidence interval.

Table 2

Increased serum levels of CA 15-3 and Ki-67 in women with BC and T2DM

Parameters	Statistical indices	G1 (n = 32)	G2 (n = 34)	G3 (n = 34)
Ki-67 (U/mL)	Percentage	20 (58.8%)	14 (41.2%)	2.420 ± 0.051
	Lower 95% CI of mean	7.4	3.8	2.32
	Upper 95% CI of mean	8.8	5.2	2.53
	p-value	0.0001		
Ca 15-3 (U/mL)	Percentage	32 (60.5%)	16 (30.5%)	9.86 ± 0.15
	Lower 95% CI of mean	32.9	19.7	9.5
	Upper 95% CI of mean	41	28.1	10.2
	p-value	0.0001		

Note: CI – confidence interval.

Table 3

The statistical distribution of HbA1c in all studied groups

Parameter	Statistical indices	G1 (n = 32)	G2 (n = 34)	G3 (n = 34)
HbA1c (%)	Mean ± std. error	7.38 ± 0.25[a, d]	5.65 ± 0.10[d]	5.410 ± 0.059
	Lower 95% CI of mean	6.89	5.43	5.29
	Upper 95% CI of mean	7.88	5.86	5.53
	p-value	0.0001		

Notes: CI – confidence interval; [a] – represented significant analysis between G1 and G3; [d] – represented significant analysis between G2 and G1.

Table 4

Correlation between tumor markers and parameters in patients with BC and T2DM (G1)

Pearson correlation r	BMI	HbA1c	Ki-67	Ca 15-3
Age	–0.09	0.093	–0.134	–0.177
BMI	1	–0.00	0.101	0.131
HbA1c		1	0.104	0.068
Ki-67			1	0.971
Ca 15-3				1

Table 5

Correlation between tumor markers and parameters in G2

Pearson correlation r	BMI	HbA1c	Ki-67	Ca 15-3
Age	–0.062	0.200	–0.178	–0.100
BMI	1	0.313	–0.08	–0.060
HbA1c		1	0.117	–0.129
Ki-67			1	0.966
Ca 15-3				1

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The present study was conducted to investigate the effect of high blood sugar and complications of T2DM on the severity of BC patients and the extent to which tumor marker levels are affected by it. This study provides a comprehensive look at the effect of the level of hyper glycemia on the level of tumor markers and how it can use these markers to assess cancer risk, monitor progression, and guide clinical decisions, particularly for women with diabetes at increased risk. The results demonstrated significantly elevated levels of Ki-67 and CA 15-3 in BC patients with T2DM compared to those in the other study groups.

A. Al-Sarraf et al. focused on Ki-67 as a prognostic marker for breast carcinoma in Baghdad [20]. Ki-67 expression was detected in 75% of the malignant BC cases, with 57.5% exhibiting a high Ki-67 score (≥ 14%). The study also found significant correlations between Ki-67 expression and key clinicopathological factors such as tumor grade and lymph node involvement. The Ki-67 proliferative index has been validated as a crucial marker for assessing tumor aggressiveness and prognosis in BC, particularly for evaluating treatment response [20]. In contrast, the results of another study A. M. Adel ("Clinicopathological Data of Breast Cancer in Diabetic Patients") in Cairo found that diabetic BC patients were often diagnosed at an advanced stage, with 117 diabetic patients compared to 199 non-diabetic patients [21]. However, there was no significant difference in Ki-67 levels between patients with and without diabetes. In the diabetic group, 11.1% had negative Ki-67 expression, whereas 27.4% had positive Ki-67 expression. In the non-diabetic group, 11.1% had negative Ki-67 expression and 30.7% had positive. Ki-67 the study suggests that diabetes does not impact Ki-67 levels in the studied population.

A. Zhang et al. provided evidence that Ki-67 is a useful and reliable predictor of recurrence-free survival and a valuable marker for evaluating treatment response to neoadjuvant endocrine therapy in BC patients [22]. The variability of levels changes during treatment and can have prognostic value or could provide information on the effects of therapy. In another investigation of serum Ki-67, increased Ki-67 expression was strongly predictive of lymph node metastasis, so it might be an important marker of aggressive tumors and the probability of metastasis [23]. H. M. Ragab et al. also found that serum Ki-67 levels varied significantly between benign and malignant tumors, reinforcing its role as a prognostic factor that complements traditional indicators such as tumor grade, size, and lymph node involvement [24]. In contrast, another study conducted by X. Yan et al. investigated BC in patients with T2DM and revealed significantly higher Ki-67 expression in individuals with diabetes than in those without diabetes [25]. More Ki-67 positivity was observed in T2DM patients than in the control group (55.9% vs 41.7%). The over-expression of Ki-67 in T2DM patients is higher with an increase in clinical stages, histological grade, and poor prognosis which can strengthen the importance of the Ki-67 important marker in BC progression among diabetic individuals. M. Hasan et al. conducted a study in Saudi Arabia to determine serum tumor marker CA 15-3 in women, who were diabetic as well as non-diabetic persons and had no evidence of neoplasia or any diabetic complications [26]. The research revealed a statistically significant difference in CA 15-3 levels between the two groups, although the levels remained within the normal range (< 37 U/mL) for both diabetic and non-diabetic females. This finding suggests that the serum tumor marker CA 15-3 could be a valuable tool for monitoring purposes in these populations. Interestingly, the study found no correlation between CA 15-3 values and various factors such as age, duration of diabetes, HbA1C, or glucose levels in patients with diabetes. These results contribute to our understanding of CA 15-3 levels which may have implications for BC screening and monitoring in this population [26].

Moreover, S. Fu et al. emphasized that glucose metabolism is an important part of cancer cell metabolism as it provides intermediates and precursors for other metabolic pathways hence tumor cells use more units of glucose than normal cells [27]. The results of another study showed a very high significant correlation between CA 15-3 and Ki-67, suggesting that these markers can be used to diagnose and prognosis BC in women with diabetes, which is in agreement with A. Rasmy et al. [28].

CONCLUSIONS

This study indicates that hyperglycemia can effect on the levels of tumor markers in women with diabetes which may helping to find a promising strategy for improving cancer treatment outcomes. Also, reducing blood sugar level helps prevent the risk of BC. This study underscores the potential of integrating biomarker assessments into routine care for women with diabetes to proactively manage cancer risk.

Ethics aproval and data availability. This study was conducted in accordance with ethical research principles. The datasets generated and analyzed are available from the corresponding author upon reasonable request.

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Conflict of interest. The authors declare no conflicts of interest.

Authors' contributions. The authors were contributed equally in conceptualized the research, collected data, participated in data analysis and write-up, editing and review.

Information about the authors

Israa J. Mnahi – Department of Chemistry, Collage of Science for Women, University of Baghdad, Iraq; tel.: +964 790 150 9718. *E-mail: israa.mnahi2305m@gmail.com*

ORCID: 0009-0000-7248-5260

Bushra F. Hasan – Dr. Assistant Professor, Department of Chemistry, Collage of Science for Women, University of Baghdad, Iraq; tel.: +964 770 217 1238. *E-mail: Bushrafh_chem@csw.uobaghdad.edu.iq*

ORCID: 0000-0002-4766-6120

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