Fasting plasma glucose and body mass index as predictors of neoadjuvant chemotherapy response in breast cancer

Meme kanserinde neoadjuvan kemoterapi yanıtlarını öngörmede belirleyici olarak açlık kan şekeri ve vücut kitle indeksi

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Abstract

Aim: Obesity is a well-known modifiable risk factor for breast cancer. Impaired fasting glucose is a component of metabolic syndrome and a significant risk for diabetes. We aimed to research the effect of these two major components of metabolic syndrome on neoadjuvant chemotherapy (NAC) response in breast cancer.

Methods: We conducted 161 patients who had received NAC from January 2016 to January 2022. Fasting plasma glucose levels were measured at least two times and BMI was recorded before starting NAC. Impaired fasting glucose is defined as plasma glucose levels of 100 to 125 mg per dL. Analyses were compared into two groups according to FPG levels below or above 100 mg/dl and according to BMI obese (BMI30≥ kg/m2), or non-obese (BMI <30 kg/m2). The pathologic response was evaluated, and patients were divided into five groups according to the Miller-Payne grading system classified from grade V to I, complete pathologic response, loss of more than 90% of tumor cells, reduced 30% and 90% of tumor cells, lost less than 30% of tumor cells, and had no reduction in cellularity and no change malignant cells respectively

Results: In the pathologic responses, 70.8% of patients with impaired fasting glucose levels were grade 1 non-reduction with NAC. Disease free-survival was shorter in the group that had impaired fasting glucose than in the group that had normal fasting plasma glucose (FPG) (p=0.031). In univariate analysis clinical stage 3 (p <0.001), postmenopausal status (p=0.037), human epidermal growth factor receptor 2 (HER-2) negativity (p<0.001), estrogen receptor (ER) positivity (p <0.001), progesterone receptor (PR) positivity (p <0.001) rate were higher in grade 1 unresponsive patients compared to patients with pathological response grade 2, grade 3 and grade 4. In multivariate analysis showed that fasting plasma glucose, clinical stage, HER-2 status, and ER status were independent predictor factors for pathological complete response (pCR). BMI had no impact on pCR. Our trial showed that the ratio of pCR in patients with impaired fasting glucose was 2.5 times lower than that in patients who had normal FPG levels [HR: 2.5, 95%CI 1.08–5.92, p = 0.03].

Conclusion: Fasting plasma glucose significantly impacted both pCR and recurrence.

Keywords: Blood glucose; breast cancer; neoadjuvant therapy

Öz

Amaç: Obezite, meme kanseri gelişiminde etkili olabilen değiştirilebilir bir risk faktörüdür. Bozulmuş açlık glikozu ise metabolik sendromun bir bileşenidir ve diyabet gelişimi için önemli bir risk faktörüdür. Metabolik sendromun bu iki ana bileşeninin meme kanserinde neoadjuvan kemoterapi (NAK) yanıtı üzerindeki etkisini araştırmayı amaçladık.

Yöntemler: Ocak 2016'dan Ocak 2022'ye kadar NAK alan 161 meme kanseri hastasını geriye dönük olarak inceledik. Açlık plazma glukoz (APG) seviyeleri en az iki kez ölçüldü ve NAK'a başlamadan önceki vücut kitle indeksileri (VKİ) kaydedildi. Bozulmuş açlık glukozu, 100 ile 125 mg/dl plazma glukoz seviyeleri olarak tanımlandı. Analizler, APG seviyelerine göre 100 mg/dl'nin altındaki ve üzerindeki veya VKİ'ye göre obez (VKİ 30≥ kg/m²) ve obez olmayan (VKİ <30 kg/m²) olacak şekilde karşılaştırılarak yapıldı. NAK yanıtları Miller-Payne derecelendirme sistemine göre, grade 1 yanıtsız, grade 2 %30'dan az, grade 3 %30 ile %90 arası, grade 4 %90'dan fazla yanıt ve grade 5 patolojik tam yanıt (pTY) olacak şekilde sınıflandırıldı.

Bulgular: Bozulmuş açlık glukoz düzeyleri olan hastaların NAK sonrası patolojik yanıtlarının %70.8'i, grade 1 yanıtsız grubundaydı. Bozulmuş açlık glukozu olan hastalarda, hastalıksız sağ-kalım, normal APG'si olan hastalara göre daha kısaydı (p=0.031). Tek değişkenli analizde, klinik evrenin 3 olması (p<0,001), postmenopozal durum (p=0,037), HER-2 negatifliği (p<0,001), östrojen reseptör (ER) pozitifliği (p<0,001), progesteron reseptör (PR) pozitifliği (p<0,001) patolojik yanıtlara göre grade 1 yanıt vermeyen grupta, grade 2, grade 3 ve grade 4 olan hastalara kıyasla daha yüksekti. Çok değişkenli analizde APG, klinik evre, HER-2 (human epidermal growth factor receptor 2) durumu ve ER durumu, patolojik tam yanıt için bağımsız öngörücü faktörler olarak bulundu. VKİ'nin pTY üzerinde etkisi gösterilemedi. Çalışmamız, bozulmuş açlık glukozu olan hastalarda pTY oranının, normal APG seviyelerine sahip hastalardakinden 2,5 kat daha düşük olduğunu gösterdi [HR: 2,5, %95 CI 1.08–5.92, p=0,03].

Sonuç: Açlık plazma glukozunun hem pTY hem de nüks üzerinde istatistiksel anlamlı bir etkisi bulunmaktadır.

Anahtar Sözcükler: Kan şekeri; meme kanseri; neoadjuvan tedavi

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INTRODUCTION

In postmenopausal women, obesity is a well-known modifiable risk factor for breast cancer A high body mass index in premenopausal and postmenopausal women increases breast cancer mortality risk (1). An epidemiologic study showed that high fasting insulin levels are related to increased breast cancer recurrence rate (2). Regulation of fasting plasma glucose is important for treatment response. A retrospective cohort study in patients who were diagnosed with breast cancer and received neoadjuvant chemotherapy (NAC) from M. D. Anderson Cancer Center suggested that patients with diabetes mellitus administrating metformin and NAC have a higher pathological complete response (pCR) rate than diabetics not using metformin. (3). This study shows whether the factor that increases the pCR rates is blood sugar level or the effect of metformin is controversial. Impaired fasting glucose and obesity are two major components of metabolic syndrome and significant risk for diabetes. We planned to investigate the effects of body mass index and fasting plasma glucose on early chemotherapy responses. High blood glucose levels and obesity may reduce pathological responses after NAC. Therefore, we compared fasting plasma glucose and BMI at diagnosis with pathological responses of patients receiving NAC.

METHODS

Patients

Retrospectively, we searched for study participants who had known fasting plasma glucose, weight, and height before chemotherapy initiation if they were age 18, had histologically confirmed Stage II or III breast cancer, and were scheduled for neoadjuvant chemotherapy from January 2016 to January 2022. BMI (kg/m²) was calculated as weight divided by the square of height (m2), and patients were divided into two groups obese (BMI ≥30 kg/m²), and non-obese (normal/overweight (BMI <30 kg/m²)). Fasting plasma glucose levels were measured at least two times and the lower level was recorded. Impaired fasting glucose is defined as plasma glucose levels of 100 to 125 mg per dL (4), so analyses were compared into two groups according to FPG levels of more than 100 mg/dl or less than 100mg/dl.

Human epidermal growth factor receptor 2 (HER2), and Hormone receptors were tested according to the ASCO/CAP guideline recommendations. Immunohistochemistry (IHC) test results of more than 1% for Estrogen receptor (ER), and progesterone receptor (PR) were accepted as ER and/or PR-positive (5). IHC results also defined HER2 were 3+ positive, 2+ suspected, and 1+ negative. Fluorescence in situ hybridization testing was performed when the results were 2+ with the IHC test (6).

The pathologic response was evaluated, and patients were divided into five groups according to the Miller-Payne grading system classified from grade V to I, complete pathologic response, loss of more than 90% of tumor cells, reduced 30% and 90% of tumor cells, lost less than 30% of tumor cells, and had no reduction in cellularity and no change malignant cells respectively (7). İstanbul Medeniyet University, Goztepe Research, and Training Hospital Ethics/Institutional Review Board approved this study (date: 30.03.2022, decision no: 2022/0175).

Statistical analysis

Retrospectively collected data for the study were enrolled and analyzed by version 20.0 of IBM SPSS Statistics (IBM Corp., Armonk, NY). The number of patients and percentage were stated for categorical variables, and the median (range) was stated for continuous variables. Comparisons of categorical variables percentages in groups were made with Pearson Chi-Square Analysis. Disease-free survival (DFS) analysis was performed according to Kaplan-Meier Method. DFS was determined as the time interval between the date of surgery of BC to the time of disease recurrence or metastasis or, to the last follow-up time if no recurrence or metastasis was recorded. The primary outcome was the effect of blood sugar control on pathologic responses and DFS. The secondary outcome was the effect of BMI on pathologic responses. Logistic regression analysis with forward selection was performed for multivariate analysis. All statistical tests were two-sided. The threshold for statistical significance was p value less than 0.05.

RESULTS

The characteristics of the patients were summarized in Table 1. The median age was 48.5 (range 18–78 years). Median BMI was 29.3 kg/m2, 36.8% were obese (BMI

Table 1: Clinical and pathological characteristics of breast cancer patients

Characteristics	n	%
Median age, years	48.5	
Range	18-78	
Menopause status		
Premenopausal	67	41.6
Postmenopausal	94	58.4
BMI at diagnosis, kg/m2 Median range	29.3	
	17.54 – 48.44	
BMI category Normal/underweight, ≤ 25	32	19.9
Overweight, 25 to 30	57	35.4
Obese, >30	72	44.7
Median FPG at diagnosis, mg/dl	100	
Range	74 - 259	
Diabetes Mellitus, n %		
Yes	21	13
No	140	87
Clinical stage		
Stage II	91	56.5
Stage III	70	43.5
Missing		
Type of surgery		
Breast conserving	63	39.1
Modified radical mastectomy	57	35.4
Simple mastectomy	41	25.5
Pathological response miller		
Payne grading		
Grade I, no response	48	29.8
Grade II, response <30%	12	7.5
Grade III, response 30%-90%	36	22.4
Grade IV, response >%90	18	11.2
Grade V, complete response	47	29.2
ER/PR status		
Both negative	47	29.2
Either positive	38	23.6
Both positive	76	42.2
HER-2 status		
Negative	114	70.8
Positive	47	29.2
Ki 67, median	30%	
Range	2 - 98%	

BMI: Body mass index, HER-2: Human epidermal growth factor receptor 2, ER: Estrogen Receptor PR: Progesterone Receptor

≥ 30 kg/m2), median fasting plasma glucose was 100 mg/dl (range 74-259 mg/dl) and 21 patients had a diagnosis of diabetes mellitus. The rate of hormone receptor-positive patients was higher either positive or negative patients in our patients with treated neoadjuvant chemotherapy (Table1).

DFS was shorter in the group that had impaired fasting glucose than in the group that had normal FPG (p=0.031). The survival curve of DFS showed in Figure 1.

Patients with fasting glucose of more than 100mg/dL were diagnosed with impaired fasting glucose. 70.8% of these patients' pathologic responses were grade 1 non-reduction with NAC. In patients with FPG below 100 mg/dL, the rate of grade 1 non-responders was 29.2%. pCR rate was also higher in patients with normal FPG (63.8%) than in patients with impaired FPG (36.2%). This difference was statistically significant.

The proportion of obese patients increases from the 4th-grade group to the 1st-grade group according to the MGP score. Except for patients with pCR, pathological response rates increase statistically significantly as BMI decreases.

Clinical stage 3(p <0.001), postmenopausal status (p=0.037), HER-2 negativity (p<0.001), ER positivity (p <0.001), PR positivity (p <0.001) rate were higher in grade 1 unresponsive patients compared to patients with pathological response grade 2, grade 3 and grade 4 (Table 2).

In patients with pCR, rate of the obesity, impaired FPG, stage 3, premenopausal status, HER-2 negativity, ER positivity, and PR positivity is lower than the rate of

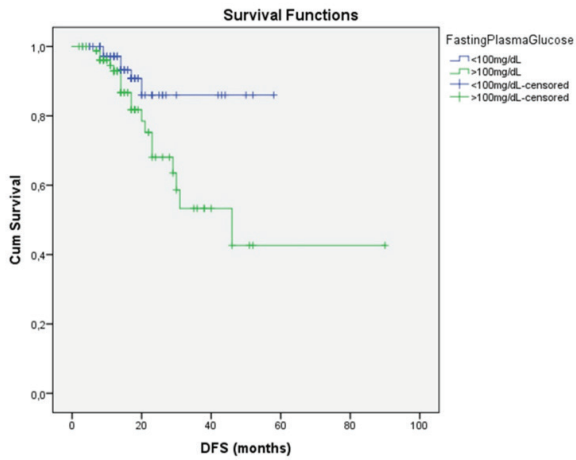

Figure 1: Fasting plasma Glucose on Disease Free Survival (DFS)

Table 2. The relationship between pathologic response and metabolic features of patients

		Pathologic Response						
		Grade 1: No pathologic response	**Grade 2: Minimal response <%30**	**Grade 3: Pathologic response %30-90**	**Grade 4: Near complete response >%90**	**Grade 5: Complete pathologic response**	**Total**	**p value**
		Count %	Count %	Count %	Count %	Count %	Count %	
BMI	<30	27 56.3%	5 41.7%	22 61.1%	10 55.6%	25 53.2%	89 55.3%	0.827
	≥30	21 43.8%	7 58.3%	14 38.9%	8 44.4%	22 46.8%	72 44.8%	
Fasting plasma glucose	<100 mg/dl	14 29.2%	7 53.8%	19 52.8%	10 55.6%	30 63.8%	80 49.7%	0.013
	≥100 mg/dl	34 70.8%	6 41.7%	17 47.2%	8 44.4%	17 36.2%	81 50.3%	
Clinical stage	Stage 2	18 37.5%	3 25.0%	19 52.8%	13 72.2%	38 80.9%	91 56.5%	<0.001
	Stage 3	30 62.5%	9 75%	17 47.2%	5 27.8%	9 19.1%	70 43.5%	
Menopausal status	Pre-menopausal	2 16.7%	15 39.5%	12 33.3%	9 50%	21 44.7%	67 41.6%	0.233
	Post-menopausal	10 83.3%	23 60.5%	24 66.7%	9 50%	26 55.3%	94 58.4%	
HER-2 status	Negative	47 97.9%	11 1.7%	26 72.2%	10 55.6%	20 42.6%	114 70.8%	
	Positive	1 2.1%	1 8.3%	10 27.8%	8 44.4%	27 57.4%	47 29.2%	<0.001
ER status	Negative	18 37.5%	0 0%	4 11.1%	5 27.8%	24 51.1%	51 31.7%	<0.001
	Positive	30 62.5%	12 100%	32 88.9%	13 72.2%	23 48.9%	110 68.3%	
PR status	Negative	22 46.8%	4 33.3%	15 41.7%	8 44.4%	31 66,0%	80 50%	0.110
	Positive	25 53.2%	8 66.7%	21 58.3%	10 55.6%	16 34,0%	80 50%	

BMI: Body mass index, HER-2: Human epidermal growth factor receptor 2, ER: Estrogen Receptor PR: Progesterone Receptor

patients with normal BMI, normal FPG, stage 2, HER-2 positivity, ER, and PR negativity.

In univariate analysis fasting plasma glucose, BMI, clinical stage, HER2 status, ER status, PR status, and Ki-67 had a statistically significant impact on the pCR rate. These results are summarized in Table 3. Logistic regression analysis was performed with significant variables.

Our trial showed that the ratio of pCR in patients with impaired fasting glucose was 2.5 times lower than that in patients who had normal FPG levels [HR: 2.5, 95%CI 1.08–5.92, p = 0.03]. In addition to this clinical stage, Her2 status and ER status were independent predictor factors for pCR. The results of multivariate analysis for independent predictors were summarized in Table 4.

DISCUSSION AND CONCLUSION

Our results showed that impaired FPG is associated with poor response to the neoadjuvant chemotherapy and normal FPG is related to improved DFS. Our study cohort included all breast cancer subtypes: triple negative, hormone receptor-positive, and HER-2 positive. Therefore, it is unclear which breast cancer subtype of fasting blood glucose influences treatment responses. Triple-negative and HER2-positive breast cancer subtypes are associated with high PCR rates and long survival in patients who achieved pCR (8). HER-2 positivity is an independent predictor factor for pCR in our study. In a trial patients with HER-2 positive locally advanced disease with low IGF-1 expression and higher pCR rate with neoadjuvant chemotherapy were associated (9). But metabolic syndrome had no impact on pCR (9). In a mice model trial showed activation in insulin/IGF1R signaling pathway in breast cancer patients and inhibition of this pathway improved paclitaxel outcomes in triple-negative breast cancer (10). In a cell, a culture trial showed that high glucose levels impacted cell-cycle genes and impaired tamoxifen responsiveness in hormone receptor (HR) positive breast cancer (11). Another trial in HR-positive breast cancer suggested clinical benefit from the treatment of everolimus-exemestane more frequently if the patient's FPG levels were below 107 mg/dL compared to

Table 3. Association of complete response and patients' characteristics

Characteristics		Pathologic response		Total	p value
		Non-complete response	Pathologic complete response		
		Count %	Count %	Count %	
Fasting plasma glucose	<100 mg/dl	50 43.9%	30 63.8%	80 49.7%	0.016
	≥100 mg/dl	64 56.1%	17 36.2%	81 50.3%	
BMI	<30	64 56.1%	25 53.2%	89 55.3%	0.43
	≥30	50 43.9%	22 46.8%	72 44.7%	
Clinical stage	Stage 2	53 46.5%	38 80.9%	91 56.5%	<0.001
	Stage 3	61 53.5%	9 19.1%	70 43.5%	
Menopausal status	Pre-menopausal	46 40.4%	21 44.7%	67 41.6%	0.369
	Post-menopausal	68 59.6%	26 55.3%	94 58.4%	
HER-2 status	Negative	94 82.5%	20 42.6%	114 70.8%	<0.001
	Positive	20 17.5%	27 57.4%	47 29.2%	
ER status	Negative	27 23.7%	24 51.1%	51 31.7%	0.001
	Positive	87 76.3%	23 48.9%	110 68.3%	
PR Status	Negative	49 43.4%	31 66,0%	80 50%	0.015
	Positive	64 56.6%	16 34,0%	80 50%	
Ki 67	N, Mean	105 33.4%	44 45.5%	149	0.011

BMI: Body mass index, HER-2: Human epidermal growth factor receptor 2, ER: Estrogen Receptor PR: Progesterone Receptor

Table 4: Multivariate logistic regression analysis of pathologic complete response

Variable	HR (hazard ratio)	95% Cl	p value
Fasting plasma glucose	2.532	1.082 – 5.924	0.032
Clinical stage	4.058	1.567 – 10.512	0.004
HER-2 status	0.213	0.091 – 0.497	0.000
ER status	3.213	1.360 – 7.593	0.008

HR :Hazard Ratio, Cl: confidence interval, HER-2: Human epidermal growth factor receptor 2, ER: Estrogen Receptor

higher FPG (12). On the other hand impact of BMI on the best response was not seen (12).

Tight control of plasma glucose and insulin levels may be important in patients with or without diabetes mellitus. Metformin regulates both blood glucose and insulin levels and is associated with increased pCR in diabetic breast cancer patients (3). The non-diabetic group had also a higher pCR rate compared with the non-metformin diabetic group (3) which suggests the importance of blood sugar level control. A recent mouse model study showed that a low- carbohydrate diet reduced breast cancer in female mice by reducing plasma glucose, insulin, IL-6, TNFα, and prostaglandin E2 (PGE2) (13).

In a study, insulin resistance and PR status had a statistically significant effect on PCR, but no relationship was found with BMI (14). In contrast obesity, and reduced pCR rate in breast cancer had been demonstrated in another trial (15). Retrospective studies on the effect of BMI have conflicting results. A randomized clinical trial demonstrated that increased adiponectin and decreased body fat by exercise reduced the risk of breast cancer in premenopausal women (16).

Our trial suggested BMI did not affect pCR and pathologic response and FPG, clinical stage, Her 2 status, and ER status had a significant effect on the pCR rate. Impaired FPG was also an impact on recurrence and shortened DFS. Retrospective design and one center cohort is limitation of our study. We could not investigate the association between FPG and breast cancer subtypes because of the small cohort. A prospec-

tive randomized trial with a large cohort is needed to define appropriate diet and exercise, controlling FPG and their impact on pCR in breast cancer patients.

The primary outcome of our study was achieved. Fasting plasma glucose had a significant impact on both pCR and recurrence. Fasting plasma glucose, clinical stage, Her2 status, and ER status were independent predictor factors for pCR. BMI had no impact on pCR. Our trial showed that the ratio of pCR in patients with impaired fasting glucose was 2.5 times lower than in patients with normal FPG levels.

Conflict-of-interest and financial disclosure

The authors declares that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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