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Original Research Article

The effect of BMI on cardiac biomarkers during trastuzumab treatment in HER2-positive breast cancer in Iraqi patients.

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Abstract: ***Background***: The body mass index, or BMI, is a crucial metric for evaluating obesity and its possible effects on health. Because trastuzumab carries a risk of cardiotoxicity, it is crucial to comprehend the relationship between BMI and cardiac biomarkers in patients with HER2-positive breast cancer. ***Objective***: The purpose of this study is to examine how body mass index affects cardiac biomarkers during trastuzumab treatment in Iraqi patients with HER2-positive breast cancer, particularly troponin and CK-MB. ***Methods***: Over the course of a year, 100 Iraqi women with HER2-positive breast cancer who were only receiving trastuzumab treatment participated in a cross-sectional observational study. Based on their BMI, the participants were divided into three groups: normal weight, overweight, and obese. To measure the levels of highly sensitive troponin and creatine kinase MB (CK-MB), blood samples were obtained. To compare biomarker levels across various BMI categories, statistical analysis was carried out using one-way ANOVA and independent t-tests. ***Results***: The study found that the mean levels of CA 15-3, CK-MB, and troponin varied across BMI categories, but none of the differences reached statistical significance ($p > 0.05$). Specifically, CA 15-3 levels were highest in the normal weight group, while CK-MB and troponin levels showed a slight increase with higher BMI, suggesting a potential but not statistically significant trend towards elevated cardiac stress markers in overweight and obese patients. ***Conclusion***: Differences in cardiac biomarkers based on BMI, according to the observed trends, indicate that higher BMI may be associated with increased levels of cardiac stress markers during trastuzumab treatment. Further research is needed to explore the implications of these findings and the potential need for monitoring cardiac function in patients with varying BMI undergoing trastuzumab therapy.

Keywords: BMI, Troponin, CK-MB, Trastuzumab, her2 positive breast cancer.

INTRODUCTION

1.1. Body mass index overview

Body mass index (BMI) is one of the ways to measure obesity in the population. Other ways to measure obesity include the waist-to-hip ratio, the percentage of body or visceral fat, and waist circumference. Body mass index (BMI) can be calculated using mathematical operations that use height and weight values to estimate a person's health status. The measurement of BMI can be utilized to assess the likelihood of developing long-term diseases like cancer, diabetes, hypertension, and depression.(Khanna et al., 2022).

BMI is calculated as weight [kg]/height [m2]. The World Health Organization (WHO) classifies patients as underweight (less than 18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (more than 30.0 kg/m²).(Martel et al., 2018).

Breast cancer (BC) is the most prevalent type of cancer and the primary cause of cancer-related death for women globally, making it a serious public health issue. For this reason, the scientific community has

given it particular attention.(Benson & Jatoi, 2012; Duffy, 2013)

Increased intracellular tyrosine kinase activity and signal transduction pathway activation result from elevated HER2 levels on cell surfaces (caused by the amplification of the HER2 gene [HER2] or overexpression of the HER2 protein); this, in turn, inhibits apoptosis and promotes cell growth, cell division, angiogenesis, and metastasis. About 15–25% of breast cancers have either gene amplification or overexpression of the HER2 protein. Trastuzumab is recommended for the treatment of early HER2-positive breast cancer and as the adjuvant in the treatment of metastatic HER2-positive breast cancer. (Garnock-Jones et al., 2010).

1.2. Trastuzumab in HER-2 positive breast cancer

Trastuzumab is a humanized monoclonal antibody (mAb) that targets the extracellular domain of the HER2 tyrosine kinase receptor. Patients with HER2-overexpressing breast cancers are currently eligible for it in both the metastatic and adjuvant settings.(Valabrega et al., 2007).

1.2.1. Trastuzumab mechanisms of action

Trastuzumab blocks the ligand-independent HER2–HER3 heterodimerization that takes place when HER2 is overexpressed, stopping the proteolytic cleavage of the HER2 extracellular domain and the creation of the active p95HER2 fragment, and interacting with Fc receptors on immune effector cells to cause antibody-dependent cellular cytotoxicity (ADCC) -positive tumors. These activities lead to the downregulation of signaling pathways, including mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt). This ultimately leads to increased nuclear import, stabilization of the CDK inhibitor p27, decreased angiogenic factor production, and a compromised DNA damage response.(Maximiano et al., 2016).

1.3. Trastuzumab cardiotoxicity

Cardiotoxic side effects, such as cardiac insufficiency, are a significant problem with trastuzumab treatment. According to suggested theories, interfering with HER4 causes an increase in reactive oxygen species (ROS), which causes endothelial dysfunction in the coronary vasculature and cardiac failure as a result of cardiomyocyte death.(Zeglinski Bsc et al., 2011)

Because HER2 antagonism disrupts neuregulin (NRG)/HER2+ ligand receptor signaling in the medulla, it can cause cardiotoxicity by increasing blood pressure and sympathetic nerve output, decreasing NRG, and increasing norepinephrine (NE). The cumulative dose has no bearing on the heart damage caused by trastuzumab. When treatment is stopped, it is frequently reversible (type II medication) and, if necessary, can be tolerated once more following recovery. Patients receiving concomitant anthracycline therapy are more likely to experience trastuzumab cardiotoxicity. Additional risk factors include being over 50, having a history of cardiovascular disease, having classic risk factors, and having a high body mass index.(Patanè, 2014)

Aim of the study: The study aims to investigate the effect of body mass index on the troponin and CK-MB during trastuzumab treatment in her2 positive breast cancer patients.

2. patients, materials, and methods

2.1. study design and participation

Cross-sectional observational study for 1 year, from August 2024 to August 2025. 60 Iraqi women with HER2-positive breast cancer who were exclusively being treated with trastuzumab were included in the study, from the national teaching hospital in Al-Najaf Governorate. The University of Kerbala College of Pharmacy's Scientific Committee granted ethical approval for the project. After being fully told about the goals of the study, each participant gave their informed consent.

2.2. Sample Collection

3 mL of blood was centrifuged for about 10 minutes at a sufficient speed (e.g., 3000 rpm) to separate the components of serum. The biochemical levels of important markers, such as highly sensitive troponin and creatine kinase MB, were then examined in the serum.

2.3. Biomarker Analysis

A chemical analyzer was used to determine the levels of highly sensitive troponin and creatine kinase MB in the collected serum samples.

2.4. statistical analysis

Appropriate software was used for statistical analysis. Continuous variables between two groups were compared using an independent t-test, while comparisons between three or more groups were done using a one-way ANOVA test.

RESULTS

The study analyzed the levels of the following laboratory biomarkers—CA 15-3, CK-MB, and troponin across different Body Mass Index (BMI) categories in a sample of 60 patients. The participants were divided into three groups based on BMI: normal weight (A: 18.5–24.99 kg/m²), overweight (B: 25–29.99 kg/m²), and obese (C: >30 kg/m²), while there was no one in the underweight group. The results, presented as mean ± standard deviation (SD),

were compared using a one-way ANOVA test, with statistical significance set at $p < 0.05$. Table 1 Description of laboratory biomarkers of the studied patients according to BMI (n=100).

A one-way ANOVA test was used with a significant p-value of less than 0.05. Results are presented as mean ± SD

Parameter	A:18.5-24.99	B:25-29.99	C:>30	P value
ca 15-3 U/ml	20.02±14.95	16.45±7.43	16.09±8.40	0.298
CK-MB ng/ml	0.95±0.38	1.25±0.81	1.14±0.51	0.637
Troponin pg/ml	7.25±2.81	8.70±7.76	8.92±7.02	0.219

The level of tumor marker CA 15-3 (U/ml) exhibited the highest mean value in the normal-weight group (20.02 ± 14.95) compared to the overweight (16.45 ± 7.43) and obese (16.09 ± 8.40) groups. However, the observed differences were not statistically significant ($p = 0.298$). This suggests that BMI may not have a substantial impact on CA 15-3 levels.

Regarding creatine kinase-MB (CK-MB), a marker of myocardial injury, showed slightly higher levels in overweight (1.25 ± 0.81 ng/ml) and obese (1.14 ± 0.51 ng/ml) individuals compared to the normal-weight group (0.95 ± 0.38 ng/ml). Despite this matter, the differences were not statistically significant ($p= 0.637$). This could imply that while higher BMI may be associated with marginally elevated CK-MB levels, the effect is not strong enough to be clinically significant in this study.

Another cardiac biomarker, high-sensitivity troponin (pg/mL), displayed an increasing elevation from the normal weight (7.25 ± 2.81) to the overweight (8.70 ± 7.76) and obese (8.92 ± 7.02) groups. Although the p-value (0.219) did not reach statistical significance, the pattern suggests that higher BMI may be weakly associated with elevated troponin levels, possibly indicating subclinical cardiac stress in individuals with excess weight.

DISSCUSION

All patients included in the study had normal cardiac function (LVEF within normal range) due to routine clinical practice that mandates treatment discontinuation upon any sign of cardiotoxicity. Therefore, consider using biomarkers such as highly sensitive troponin I and CK-MB for the early detection of cardiac damage caused by trastuzumab.
Troponin levels can predict adverse cardiac events and a decrease in left ventricular ejection fraction (LVEF) in patients receiving trastuzumab, particularly in those who have previously received anthracyclines. It has been demonstrated that people with elevated troponin levels (≥ 0.08 ng/mL) are more likely to experience trastuzumab-induced cardiotoxicity (TIC) and not recover from it. Elevated high-sensitivity cardiac troponin T (hs-cTnT) levels (> 14) at the conclusion of anthracycline treatment were also associated with a two-fold increased risk of subsequent trastuzumab-induced cardiotoxicity, according to a more recent, larger study. This suggests that troponins are useful for identifying patients who need closer monitoring during trastuzumab therapy because they reflect pre-existing or ongoing cardiac damage. (Dempsey et al., 2021).

Trastuzumab monotherapy carries a notable risk of cardiac dysfunction; this risk is substantially increased when combined with anthracyclines. The cardiotoxicity is linked to mitochondrial dysfunction, oxidative stress, and ferroptosis. Clinical trials have shown that, when used as monotherapy, cardiac dysfunction occurs in 3-7% of patients, while it significantly rises to 28% when trastuzumab is administered concurrently with anthracyclines.(Gao et al., 2024).

High-sensitivity troponin (hs-Tn) is an essential biomarker for identifying treatment-related cardiotoxicity, particularly in the first year following treatment. Hs-Tn measured following four cycles of anti-HER2 medicines (including trastuzumab) is thought to be a significant predictor of cardiotoxicity brought on by chemotherapy followed by anti-HER2 agents (Ahmed et al., 2025).

A study of 3879 patients with baseline high-sensitivity cardiac troponin T (hs-cTnT) values below 30 ng/L who underwent elective coronary angiography due to suspicion of chronic coronary syndrome (CCS) was included. These participants were monitored for any subsequent acute myocardial infarctions (AMIs) until the end of 2009. Patients in higher BMI categories showed a stronger association between hs-cTnT levels and incident acute myocardial infarction compared to those in lower BMI categories. This study indicates that adipose tissue may affect how circulating hs-cTnT relates to the development of myocardial damage and AMI, as shown by an interaction between BMI and hs-cTnT. (Vavik et al., 2021).

Another study of 383 patients also correlates with

highly sensitive troponin and BMI.

The median levels of circulating hs-cTnT in obese people were 8 ng/L, while those in the non-obese group were 6 ng/L/L. They were substantially higher. (Huang et al., 2021).

Ravassa and Kuznetsova et al. show in their study that persistent increases in troponin can lead to clinical cardiac remodeling. They also found that circulating hs-cTnT was associated with early cardiac remodeling before systolic and diastolic functions of the heart were affected. (Ravassa et al., 2015).

On the other hand, a study that examines the relationship between BMI and CK-MB measured infarct size using the study's CK-MB data, and obesity was classified based on BMI. When BMI defined obesity, the study found that peak CK-MB levels and, consequently, estimated infarct size, were similar between obese and non-obese NSEMI (non-stigmatizing elevation myocardial infarction) individuals. (Sungur et al., 2023).

CONCLUSION

This study highlights the relationship between body mass index (BMI) and cardiac biomarkers, specifically troponin and CK-MB, in Iraqi patients with HER2-positive breast cancer undergoing trastuzumab treatment. The observed results suggest a potential association between higher BMI and elevated cardiac stress markers.

The findings underscore the importance of monitoring cardiac function in patients receiving trastuzumab, particularly those with higher BMI, as they may be at an increased risk for subclinical cardiac stress. Given the known cardiotoxic effects of trastuzumab, further research is warranted to explore the implications of BMI on cardiac health in this patient population. Future studies should aim to include larger sample sizes and longitudinal designs to better understand the long-term effects of trastuzumab treatment on cardiac function in relation to BMI.

Conflicts of Interest

The authors declare no conflicts of interest.

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