Obesity control and liver health in breast cancer: Normalized hepatic elasticity after ketogenic diet

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ABSTRACT

Most socially significant diseases, including breast cancer, are undeniably linked to obesity. Recently, a positive relationship between excessive weight and increased risk of breast cancer poor outcomes has been proved. Liver integrity is an essential point during chemotherapy. Consequently, a hepatic safe therapeutic approach for managing obesity in patients with breast cancer should be initiated. Our study aimed to assess the impact of the ketogenic diet on body mass index (BMI) and to evaluate its safety on liver function in female patients with breast cancer. The study comprised 520 women with ductal breast cancer who underwent a 60-day modified ketogenic diet. BMI, prothrombin time (PT), activated partial thromboplastin clotting time (aPTT), aspartate aminotransferase to platelet ratio index (APRI), and ultrasound liver elasticity was evaluated before and after the diet. The results showed a significant decrease in BMI and an improvement in ultrasound liver elasticity in all the participants after completing the diet. Before the KD, the participants' median BMI was 35.0 kg/m2, and after the 60-day diet, the median BMI was reduced to 30.0 kg/m2. No significant liver parameter changes were found after the diet. In conclusion, we can safely promote the keto diet amongst individuals with an increased chance of developing breast cancer for a better disease prevention.

1. Introduction

A variety of pathologies, such as type 2 diabetes mellitus (T2DM), cardiovascular and cerebrovascular diseases, musculoskeletal disorders, and neoplasms, including breast cancer, are known to be directly related to obesity [1]. Recent scientific data has proved that excessive body weight positively correlates with the risk of postmenopausal estrogen receptor-positive breast cancer development and with poor outcomes for all the breast tumor subtypes. It is generally accepted that obese women have an increased risk for postmenopausal but not pre-menopausal breast cancer [2]. This association could be explained by the elevated circulating estrogens deriving from the peripheral androgen aromatization within the adipose tissue of overweight/obese postmenopausal women. Another theory of the relationship mentioned above presents obesity as a metabolic syndrome-associated factor that increases circulating insulin and insulin-like growth factor (IGF) – both known as mitogens. Part of their action is also mediated by the crosstalk of this

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pathway with that of the estrogen receptor pathway in breast cells. Furthermore, a hypothesis dating from 2004, describes adipocytes as dynamic endocrine cells that secrete various cytokines, polypeptides, and hormone-like molecules (adipocytokines), influencing tumor growth [3].

In order to better control neoplastic growth, oncologists nowadays follow a routine practice of promoting healthy weight loss in breast cancer-affected individuals. According to several preclinical and clinical trials, the ketogenic diet, or simply keto diet (KD), represents a novel therapeutic approach for certain types of cancers, including breast cancer [4,5]. Due to the proven anti-convulsant properties of ketone bodies after crossing the blood-brain barrier, KD was initially used for managing refractory epilepsy in infants and children [5–7]. However, from a medically-monitored tool for treating epilepsy, it was converted to a mainstream dietary weight reduction option [6–9]. KD is a high-fat, low-carb, moderate-protein diet that produces metabolic changes leading to increased levels of free fatty acids and serum ketones and reduced blood insulin, glucose, and glucagon concentrations [6,10]. KD appears to create an unfavorable metabolic environment for the proliferation of breast cancer cells. Moreover, it is proven to restore the hormonal and inflammatory environment of the host, which is thought to suppress tumor growth. Generally, patients with breast cancer can benefit from a KD because it improves biochemical parameters and total body composition.

The present study aimed to assess the impact of ketogenic diet (KD) on weight and its safety referring to the liver function in female patients with confirmed breast cancer. By comparing the values of body mass index (BMI), prothrombin time (PT), activated partial thromboplastin clotting time (aPTT), aspartate aminotransferase to platelet ratio index (APRI), and ultrasound liver elasticity before and after the KD, the analysis is believed to reveal some intriguing data concerning the possible effect of KD on the liver integrity of women with breast cancer – a key factor for following a safety, uncomplicated chemotherapy.

2. Materials and methods

The present prospective study was conducted in the Complex Oncology Center of Plovdiv, Bulgaria. It comprised 520 women with diagnosed ductal breast cancer who underwent a 60-day modified ketogenic diet with very low carbohydrate, medium fat, and 20% protein content. In all the participants, body mass index (BMI), prothrombin time (PT), activated partial thromboplastin clotting time (aPTT), aspartate aminotransferase to platelet ratio index (APRI), and ultrasound liver elasticity was evaluated before and after the diet.

The inclusion criteria were: a diagnosis of breast cancer; no past or ongoing chemotherapy treatment; body mass index (BMI) ≥ 30 kg/m2; a signed informed consent by each participant. The following exclusion criteria were used: disease progression and chemotherapy initiation; alcoholism, chronic liver disease, hepatitis.

In all the studied women, BMI was calculated. According to the formula (BMI = weight (kg)/height (m)2).

2.1. Laboratory tests

Blood samples for the aforementioned laboratory tests were taken early in the morning after an overnight 12-h fast and were taken for determination to the Laboratory of Complex Oncology Center, Plovdiv. Prothrombin time (PT) and international normalized ratio (INR) tests measure how long a clot forms in a blood sample. Prothrombin is a protein made by the liver. Thus, PT test might also be performed to check for the presence of liver disease. The usual range of INR for a healthy person not using warfarin is 0.8–1.2 [11]. Activated partial thromboplastin clotting time (aPTT) is another assay that characterizes coagulation of the blood. Its value's reference range is between 30 s and 50 s [12]. Aspartate aminotransferase to platelet ratio index (APRI = {(AST/AST upper limit of normal range) x 100}/platelet count (109/L)) is supposed to be a novel accurate index for the prediction of significant fibrosis and cirrhosis [13–19].

2.2. Diagnostic imaging examinations

A set of imaging tests, including a whole-body computed tomography (CT) scan for the breast cancer staging and abdominal ultrasound transient elastography (US TE) exam for assessing the liver elasticity (measured in kPa), was performed before and after the 60-day KD.

The CT protocol is with tube voltage 80–130 kV with dose reduction technology, applied on every patient. Standard abdominal scan was performed, with the patient in supine position, abdomen centered gantry and scan ex-tend from the diaphragms to the iliac crest, in craniocaudal direction. The field of view (FOV) is 350 mm, slice thickness 0.75 and interval 0.5 mm.

Every patient underwent standard B-mode ultrasound examination of the abdomen, and after that point shear wave elastography (pSWE) and two-dimensional shear-wave elastography. A convex C1-8IQ appleprobe transducer was used.

2.3. Statistical analysis of data

Computer software IBM SPSS Statistics for Windows (Version 27.0) was used for the statistical analyses (IBM Corp. 2020, Chicago, IL, USA). The Shapiro-Wilk test was performed to check the normality of the continuously measured variables. All target variables, as well as the patient's age, exhibited non-normal distribution ($p < 0.05$, $p < 0.01$, and $p < 0.001$). As a result, we used the median values and interquartile ranges (IQRs) and the related samples Wilcoxon signed-rank test for paired comparisons of the target variables before and after the ketogenic diet. Frequencies and per-centages (%) were used to represent categorical variables. In order to assess the existing correlations between the studied categorical variables, we performed the Chi-square test. All statistical tests were two-tailed at

a Type I error of 0.05 ($p < 0.05$).

3. Results

The patients' age ranged from 43 to 75 years, with a median of 60 years (IQR = 5.50). Before the KD, the participants' median BMI was 35.0 kg/m2, with a minimum value of 31.0 kg/m2 and a maximum of 45.0 kg/m2. After the 60-day diet, the median BMI was reduced to 30.0 kg/m2 (IQR = 6.0), with individual values ranging from 24.0 kg/m2 to 40.0 kg/m2 (Fig. 1).

Before the KD, all the patients were categorized as obese, with BMI >30.0 kg/m2. After completing the 60-day ketogenic regimen, 30 patients (5.80%) were categorized as normal weight (BMI = 18.5–24.9 kg/m2), 180 patients (34.60%) moved to the overweight range (BMI = 25.0–29.9 kg/m2), and 310 patients (59.60%) remained in the obese category (BMI> 30 kg/m2) (Fig. 2). However, they all were established to reduce their BMI by several units as is shown in Fig. 1.

No significant changes concerning patients' PT ($p = 0.302$), aPTT ($p = 0.132$), and APRI ($p = 1.00$) were observed before and after the 60-day ketogenic diet. A significant reduction of the median values of US transient elastography (TE) liver elasticity after the completion of the diet ($p < 0.001$) was found (Table 1). The individual data revealed a reduction of US TE liver elasticity in 380 of the patients (73%), no change - in 130 patients (25%), and an increase - in 10 patients (2%). Fig. 3 reveals US TE's individual and median change before and after the KD.

The native CT liver density after the KD showed a median value of 63 (IQR = 5.00), with individual variations ranging from 56 to 73.

4. Discussion

As it has been mentioned above, it is now widely accepted that there is a significant relationship between obesity and breast cancer. The link between them could be explained by the presence of increased circulating and local estrogens, altered amounts of adipokines (leptin and adiponectin), disrupted insulin/IGF signaling pathway, modifications within the microbiome, and local and systemic inflammation effects [20,21]. Therefore, weight loss is highly recommended in patients with proven breast cancer, even those with "in situ" lesions. It has been established that most of the drugs used for chemotherapy in patients with breast cancer cause toxic changes, predominantly affecting hepatic cells' mitochondria [22]. Consequently, the weight reduction therapeutic plan in those patients should be selected carefully in terms of preventing liver com-plications development [22,23].

Generally, individuals on keto diets have been shown to lose and keep more weight than those on low-fat diets. Compared to low-fat diets, those that contain high fats are found to suppress the feeling of hunger and to increase metabolism rates in all the sub-jects who follow them [24–27]. Furthermore, it has been proved that achieving and maintaining a normal BMI reduces the risk of breast cancer occurrence.

The findings from the current study showed a significant decrease in BMI values in all the participants after completing the diet, as 40.4% were found to improve their BMI category. Only 5.8% of the studied patients normalized their BMI values after the diet - an expected result because all the participants were initially categorized as obese (BMI >30.0 kg/m2). The results are promising – they confirm the Warburg effect of the KD, which causes starvation of the cancer cells, making them more vulnerable to chemotherapy and radiation [28].

The present study's data is similar to that described in the meta-analysis of Haobin Zhao et al. [29], who aimed to summarize the effects of ketogenic diets on cancer patients in ten controlled trials. It revealed a significant effect of ketogenic diets on body weight (SMD 1.83, 95% CI 2.30 to 1.35; $p < 0.00001$) and fat mass (SMD 1.52, 95% CI 1.92 to 1.07; $p < 0.00001$) and no significant effect on blood glucose, insulin, or lipid profile except triglycerides (TG). It was found that KD did not affect liver and kidney function except
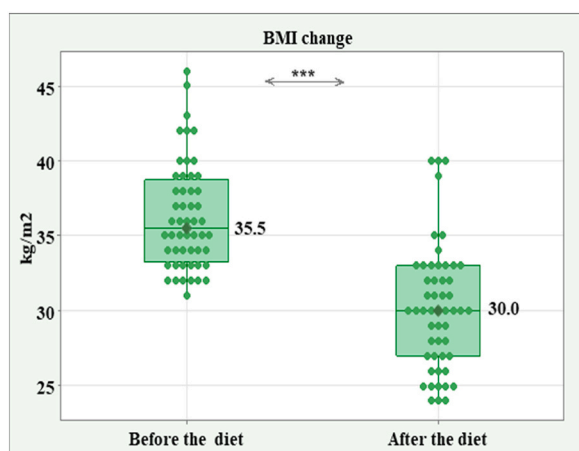

Fig. 1. Individual and median BMI values in the studied patients before and after the KD.
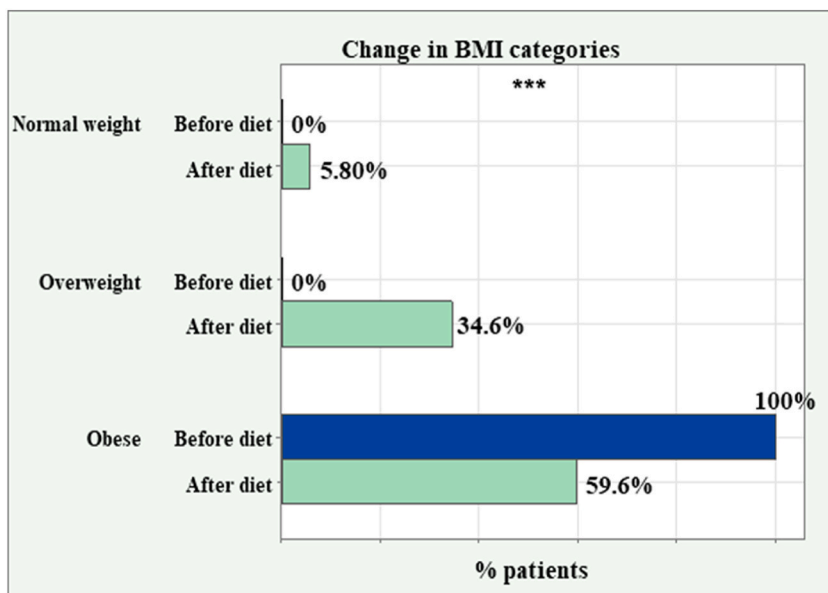
Fig. 2. Changes of BMI categories among the studied patients before and after the KD.

Table 1

Laboratory tests and US TE liver elasticity results.

Variables	Mean	IQR	Min.-Max.	p
PT	0.90	0.10	0.80–1.20	0.302
Before diet	0.90	0.10	0.80–1.20	
After diet				
aPTT	35.00	4.75	30.00–47.00	0.132
Before diet	35.00	5.75	29.00–48.00	
After diet				
APRI score	0.30	0.10	0.20–0.50	1.000
Before diet	0.30	0.10	0.20–0.50	
After diet				
US TE liver elasticity	5.60	0.20	5.20–5.80	<0.001
Before diet	5.40	0.20	5.00–5.80	
After diet				

PT - Prothrombin Time; aPTT - Activated Partial Thromboplastin Clotting Time (aPTT); APRI score - The ratio of Aspartate Aminotransferase (AST) divided by the upper limit of the normal AST range multiplied by 100 and then divided by the Platelet (Thrombocyte) Count.

that gamma-glutamyl transferase (GGT) levels were decreased a little. Moreover, no changes in IGF-1 - and TNF-related to tumor growth were established. In conclusion, this analysis shows proof that KD might be used as a safe approach for cancer patients to reduce their body weight and fat mass and improve their quality of life [30].

Recently, four types of ketogenic diets used for treating epilepsy have been described - the classic ketogenic diet, the medium-chain triglyceride diet, the modified Atkins diet, and the low glycemic index treatment. Each of them has less restrictive requirements for fluid, protein, and fat intake [31–33]. There is scientific evidence that eating a high-fat diet might lead to a significant improvement of lipid profile parameters by mainly lowering the concentrations of low-density lipoprotein (LDL) and triglycerides (TG) and increasing those of high-density lipoprotein (HDL) [29,34,35]. In this con-text, Moriconi et al. [33] evaluated different diet strategies for managing the existing cardiometabolic disturbances in patients with diabetes mellitus (DM). They proved that the very low-calorie KD might be a safe and effective tool for fighting obesity, de-glycation, and atherogenic dyslipidemia in individuals with T2DM [35]. Antonio et al. described the effects of KD on semi-professional soccer players [36,37]. In their study, the diet led to significant fat mass loss without detrimental effects on strength, power, and muscle mass. A pilot study published by Li et al. showed that 12-week KD reduced estrogen and progesterone levels in patients with polycystic ovary syndrome (PCOS) [30]. The study reported an additional reduction in serum AST levels. Moreover, positive effects of KD have been established in patients with Alzheimer's disease [33].

The typical liver stiffness values among healthy individuals from the general population are around 5.5 ± 1.6 kPa [43–45]. Age is confirmed to not influence these values, but the presence of both gender and weight differences is proven to have an impact on them. Liver stiffness values are commonly higher in males and subjects with BMI>30.0 kg/m2 [38–40].

The current results demonstrated a normalization of the typical liver elasticity with a lowering of the median TE coefficient values from 5.6 to 5.4 kPa due to the 60-day KD obtained by the female patients with breast cancer. The diet was found not to affect the other
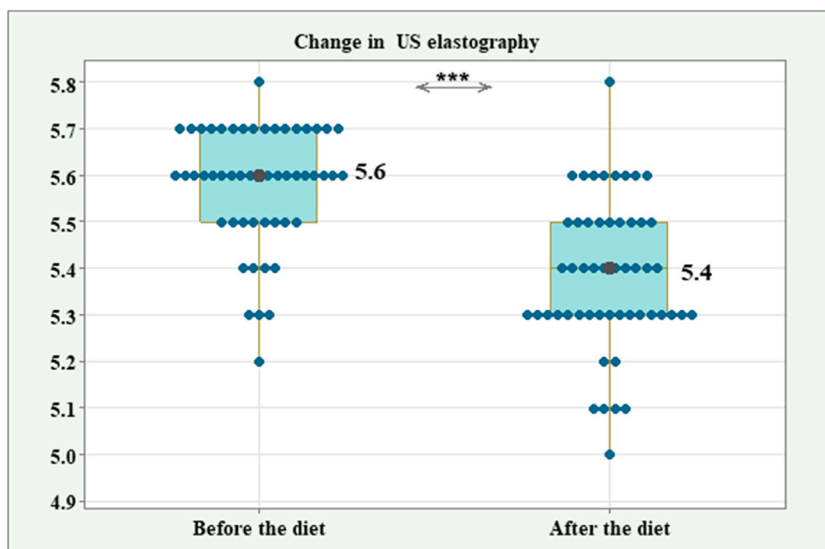
Fig. 3. Individual and median changes of US TE liver elasticity in the studied patients before and after the KD.

tested liver-related laboratory parameters, including PT, aPTT, APRI, and CT liver density (median 63HU). Therefore, KD has been supposed to preserve liver integrity – an essential point for future chemotherapy in breast cancer patients. In conclusion, having the effect of reducing weight as well as to improve liver health, the KD might be promoted among cancer carriers.

In support of the revealed results, several studies which have confirmed the KD's beneficial effect on patients with nonalcoholic fatty liver disease (NAFLD) have existed. Emerging data have shown that KD might rapidly reverse NAFLD and insulin resistance despite increasing circulating nonesterified fatty acids (NEFA) - the primary substrate for the synthesis of intrahepatic triglycerides (IHTG) [41]. Panu Luukkonen et al. [42] presented evidence that hepatic mitochondrial fluxes and redox state were markedly altered during humans' ketogenic diet-induced reversal of NAFLD. A keto-genic diet for 6 days markedly decreased liver fat content and hepatic insulin resistance in ten overweight/obese subjects. These changes were associated with in-creased net hydrolysis of liver triglycerides and decreased endogenous glucose production and serum insulin concentrations. By revealing these data, the authors demonstrated undescribed adaptations underlying the reversal of NAFLD by the ketogenic diet. They highlighted the presence of hepatic mitochondrial fluxes and redox state as potential treatment targets in NAFLD [40–43].

The current research, obtained among a small cohort of female patients with breast cancer, demonstrated that KD had an emphatic beneficial effect both on body weight - a precipitating factor of carcinogenesis, and on liver elasticity – a parameter that evaluates the stiffness of the liver parenchyma, predicting the possibility of cirrhosis development. Recently, it has been suggested that android rather than gynoid obesity in women exert a higher chance of breast cancer occurrence [43]. Thus, the use of body compartments analysis would be very useful for a more precise evaluation of breast cancer risk. Calculating BMI as a metric of adiposity in adults may lead to some methodological bias. It represents a ratio of weight to height and does not distinguish fat mass from lean body mass or subcutaneous adipose tissue (SAT) from visceral adipose tissue (VAT) [43]. In the present study, no waist circumference of the investigated women was monitored before and after the KD. Thus, the lack of sufficient data about the impact of KD on the grade of visceral adiposity (a strong predictor of cancer gene-sis) could be accepted as a limitation of the research.

5. Conclusions

Undoubtedly, the incidence of breast cancer among obese women is on the rise. The link between obesity and breast cancer obliges health professionals to advise affected patients to lose weight. The results show that the ketogenic diet does not worsen liver pa-rameters, just oppositely – it leads to a normalization of liver elasticity assessed by ultrasound elastography. In conclusion, the ketogenic diet represents a safe option for total body weight reduction in breast cancer female patients, even those who re-quire chemotherapy. The current research has dropped the essentials of the topic, but in order to better understand the intimate mecha-nisms by which the KD ameliorates the liver status of female breast cancer patients. Further, more in-depth investigations must be initiated in the future. We can also safely promote the keto diet amongst individuals with an increased chance of developing breast cancer and assure them that it will help reduce weight and improve their liver health. In that regard, the keto diet can assist disease prevention.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Aleksandar Georgiev: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Lyubomir Chervenkov:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation. **Daniela Koleva:** Investigation, Resources, Supervision, Validation, Writing – original draft. **Vanya Anastasova:** Data curation, Resources, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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