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Butyric acid plasma level upregulation in breast cancer

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Abstract

Background

In Egypt, breast cancer (BC) has the highest mortality rate in women in comparison to other types of cancer, where its prevalence is high among all cancer types. Butyric acid has been reported to have an anti-cancer effect. Thus, the present study aims to explore if there is any significant alteration in butyric acid levels in breast cancer patients and their relatives compared to healthy (control) women.

Methodology and results

Twenty women with a history of BC in their families (relatives) and 34 healthy females who acted as a healthy control group were included in this research in addition to the 24 females diagnosed with BC (patients). High-performance liquid chromatography was used to assess the level of butyric acid quantitatively using the ion exchange separation method. According to our findings, the mean plasma level of butyric acid in BC patients and women having a family history of BC (relatives) is significantly higher than that in healthy females (control). That may further be used as a biomarker for early screening of BC.

Conclusion

Butyric acid plasma level is a suggested biomarker that may be used in the early screening of BC.

Introduction

Among women's tumors, BC is one of the most prevalent and deadly types [1]. Numerous internal and external variables contribute to the development and occurrence of breast cancer [2]. The chance of survival rises with early detection [3]. Tumors that spread through the blood and lymphatics tend to have poorer prognoses and distant metastases. This makes it important to have breast cancer screening programs that that are clear and evident [4].

Dysregulation of the cellular metabolism is one of cancer's most significant features [5]. Normal metabolite levels are altered, and aberrant metabolites are produced, as a result of cancer cells' metabolic reprogramming, which promotes unchecked proliferation. The final products of biological metabolism, these modified metabolites are referred to as aberrant metabolites because they are highly sensitive to both biological activity and pathological circumstances [6]. Research has indicated that high dietary fiber consumption lowers the risk of colorectal cancer [7, 8]. Short-chain fatty acids, or SCFAs, are byproducts of the digestive fibers' natural bacterial fermentation in the intestinal lumen [9].

Although this link is not always present, dietary fiber is said to exhibit an epidemiologically negative association with lower bowel malignancies. Uncertainty surrounds the exact mechanism underlying the health advantages of a high-fiber diet, particularly in terms of colon cancer prevention. Ausman came to the unclear conclusion that there is no proof that dietary fiber prevents colon cancer in his examination of the relationship between dietary fiber and cancer [10]. On the other hand, the cancer-preventive benefits varied significantly throughout the in vitro and in vivo investigations where various forms of dietary fibers were employed [11].
However, recent studies have shown that butyric acid has a variety of effects on isolated cells [12, 13]. Particularly, there is a lot of interest in its capacity to alter nuclear architecture and induce colon cancer cells to undergo apoptosis. Acetylation and phosphorylation of the nuclear histones are two important

posttranslational alterations that butyric acid affects and alters the structure of chromatin. In the case of malignant colonic cells, butyric acid overcomes their resistance to regular programmed death and can also change the differentiation state of cells [14].

Materials and methodology

The current study, a case-control study, was carried out in the period between March (2021) and December (2022) in the Biochemistry and General Surgery departments, Faculty of Medicine, Assiut University, Assiut.

There were 78 participants in this research, and they were then divided into the following three groups (GRPs):

GRP number (1**)**
Twenty-four females who have a previous diagnosis of BC.

GRP number (**2**)
Twenty women (relatives of group 1) with a history of BC in their families.

GRP number (3)
Thirty-four healthy women made up GRP (3) (the control group).

Sample collection and handling

Three ml of antecubital venous blood were drawn from all subjects and injected into a heparin-containing tube for the separation of plasma to be used in the butyric acid profile and metabolite assessment.

Assay of butyric acid

Plasma amino acids and metabolites, including plasma butyric acid, were determined in the unit of the Metabolic and Genetic Disorders (MGDU), Faculty of Medicine, University of Assiut, using high-pressure liquid chromatography (HPLC) using the innovative automatic amino acid analyzer S 433 provided by Sykam GmbH, Germany, catalog No. 1120001.

Statistical analysis

The statistical package for social science, SPSS version 22, was applied for both data entry and analysis. The mean, standard deviation, median, and range of the data were displayed. ANOVA testing, or post-hoc testing, was utilized for quantitative variables in parametric data. The measurement of correlation between quantitative variables was done using Pearson correlation. The Mann-Whitney test was used to assess quantitative variables between two groups when working with parametric data, and the Kruskal-Wallis test was applied to more than two groups. The Spearman correlation was used to determine the correlation between quantitative variables. The P-value has statistical significance if $P < 0.05$.

Results

Personal data analysis

Table 1 displays the subjects' personal information for the three groups of participants. Regarding age, height, weight, or BMI, the observed results showed no significant difference between the three groups.

Butyric acid plasma level

The mean plasma butyric acid level is displayed in Table (2), showing significantly different butyric acid levels were found between both GRPs (1 and 2) in comparison to GRP (3). Furthermore, a significant difference was observed between the three groups' mean levels of butyric acid, with the patient group having significantly greater levels than the control and relative groups. In addition, butyric acid levels in the relative group were significantly higher than those of the controls.

Table 1: participant's data

participant's data	GRP (1) (n= 24)	GRP (2) (n= 20)	GRP (3) (n= 34)	P-Value[1]	P-Value[2]	P-Value[3]
Age: Mean ± SD Range	43.82 ± 5.48 29.0-54.0	42.27 ± 4.32 35.0-55.0	43.37 ± 9.12 25.0-61.0	0.522	0.459	0.565
Weight: Mean ± SD Range	63.58 ± 8.75 48.0-87.0	63.41 ± 9.35 51.0-87.0	63.21 ± 4.85 50.0-73.0	0.609	0.708	0.418
Height: Mean ± SD Range	158.04 ± 5.52 148.0-168.0	161.73 ± 7.85 144.0-171.0	162.82 ± 5.24 148.0-173.0	0.469	0.326	0.787
Body mass index: Mean ± SD (Range)	25.39 ± 2.67 (21.7-31.20)	25.41 ± 2.77 (21.2-32.4)	24.73 ± 2.21 (20.1-28.2)	0.832	0.343	0.483

P (1): GRPs 1 and 2 comparison. **P (2):** GRPs 1 and 3 comparison. **P (3):** GRPs 2 and 3 comparison. To compare amongst several groups, a one-way ANOVA test was employed, followed by a post-hoc test/LSD.

Table 1: butyric acid plasma level of different study groups

	GRP (1) (n= 24)	GRP (2) (n= 20)	GRP (3) (n= 34)	P-value[1]	P-value[2]	P-value[3]
Butyric acid:						
Mean ± SD	23.48 ± 5.74	8.76 ± 7.79	4.97 ± 5.67	0.000*	0.000*	0.027*
(Range)	(6.48-32.45)	(1.20-26.46)	(1.21-35.06)			

P (1): GRPs 1 and 2 comparison. **P (2):** GRPs 1 and 3 comparison. **P (3):** GRPs 2 and 3 comparison. To compare amongst several groups, a one-way ANOVA test was employed, followed by a post-hoc test/LSD.

Discussion

BC continues to be a main worldwide health concern that affects a high number of individuals annually [4]. The annual number of women diagnosed with breast cancer worldwide is estimated to be approximately 1.5 million women [15]. Breast cancer screening has been demonstrated to greatly increase survival rates and is an efficient way to identify the disease in its early stages [16]. Developing novel detection techniques, identifying effective biomarkers, and customizing treatment regimens according to patient profiles are a few of the technical challenges in this field [17]. Together, endogenous and exogenous chemicals create the human metabolome, which represents a person's metabolic atlas.

Short-chain fatty acids (SCFA) engage with the cells that line the intestine and cells of the immune system and have a crucial function in preserving the balance and stability of the intestine and other organs. Recent research indicates that SCFA can modulate immune cells in the intestine, affecting both inflammatory and malignant disorders. SCFA can also regulate gene expression in distant organs by absorbing into the bloodstream, thereby regulating tumor cell apoptosis and proliferation, inhibiting extra-intestinal cell carcinogenesis, and playing an important role in the occurrence and development of malignant tumors [18].

Acetate, propionate, and butyrate are examples of short-chain fatty acids (SCFAs), a class of metabolites generated from bacteria that can act by activating two G protein-coupled receptors known as FFA2 and FFA3, formerly known as GPR43 and GPR41, respectively. Additionally, they can influence other cell targets, including histone deacetylases (HDACs), immunological responses like regulatory T cells (Tregs), the activity of macrophages and dendritic cells, the generation of pro- and anti-inflammatory cytokines, and the growth of plasma B cells [19, 20]. Research revealed that across a range of cancer cell lines, butyric acid inhibits proliferation and promotes differentiation. Colon cancer cells have been observed to induce apoptosis in vitro with the use of butyric acid. Various derivatives or combinations are used instead of butyric acid due to its high clearance rate and procrastinated apoptosis, which have shown decreased efficiency when used alone on neoplastic cells [21].

The current study's findings showed that patients' mean plasma butyric acid levels were significantly higher than those of the control group. Additionally, we observed that patients' butyric acid levels were much higher than those of females with a family history of BC. Studies showed that butyric acid has anticancer properties [22-24] Butyric acid's anticancer properties may also stem from its capacity to impede the growth of cancer cells, trigger cell differentiation and apoptosis, and prevent cell proliferation [25].

In conclusion, butyric acid significantly increases in BC patients, and that may be used in the early diagnosis of BC.

Limitations and recommendations

Limitations include the small sample size and the absence of follow-up. Extensive studies with a higher number of participants and greater follow-up are required to determine whether butyric acid levels are linked to the risk of developing BC in family subjects or not. Monitoring the level of butyric acid in the plasma and inside cancerous cells of BC patients may help with treatment or early diagnosis of BC.

Conflict of interests

There is no conflict of interest. The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

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