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FGF-21 Level is higher in patients with breast cancer, a candidate for a new biomarker?

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ABSTRACT

Aims: Fibroblast Growth Factor 21 (FGF-21) is a member of the FGF family involved in biological processes such as embryonic development. cell growth. morphogenesis. tissue repair. tumour growth and invasion. with mitogenic and cytogenetic activity at 19q13.33.Breast cancer is a deadly and increasing disease in women. and recent studies have shown a relationship between some cancers. including breast cancer. and hormones secreted from adipose tissue.The aim of the present study was the measurement of FGF-21 levels in patients with breast cancer and its association with breast cancer.

Methods: The study included 39 patients with newly diagnosed breast cancer and 39 healthy controls. During the patients' routine blood tests. a venous blood sample was taken and the serum levels of FGF-21 were determined by ELISA.

Results: Demographic and laboratory data were compared between the newly diagnosed breast cancer group and the control group. The control group consisted of 39 participants with a mean age of 52.49 ± 7.02 years. In the patient group. 39 participants with a mean age of 52.15 ± 6.21 years were included in the study. there was no statistical difference regarding age($p>0.05$).In the control group. the mean FGF-21 level was 121.35 ± 88.4 pg/ml. while the mean FGF-21 level in the patient group was 171 ± 117.45 pg/ml. a statistically significant difference was detected(p value=0.036).

Conclusion: FGF-21 is thought to have significant and beneficial effects on glucose. lipid and energy metabolism. as well as slowing the growth of cancer cells. and may later be used as a biological marker for breast cancer.

Keywords: FGF-21, breast cancer, obesity

INTRODUCTION

Breast cancer is the most common malignancy in women and the most common cause of cancer-related death after lung cancer in women. In recent years. there has been an increase in the incidence of breast cancer. and as well as metabolic syndrome. especially in industrialized countries. with the spread of obesity.[1] As a result of that it brought to mind the question of whether there is a relationship between metabolic syndrome and breast cancer.

Metabolic syndrome is characterised by a cluster of metabolic disorders that may be risk factors for diabetes mellitus. coronary heart disease. peripheral vascular disease and cerebrovascular.[2] Metabolic syndrome is thought to be associated with an increased risk of many cancers. including breast cancer.[3] Several hormonal. metabolic and inflammatory mechanisms are known to play a role in the development and progression of breast cancer.[4] Adipocytokines as a carcinogen are being tried to be defined whether there is another link between obesity and cancer. Falk Libby E. et al.[5] investigated the effect of adiponectin on tumor cell proliferation in early stage breast cancer. The effect of different adiponectin isoforms on breast cancer cells was examined and the results of the present study suggested that a spesifik AdipoQ isoform may enhance breast cancerinvasion.possibly via autophagic induction.

Fibroblast Growth Factor (FGF-21) is a member of the FGF family involved in biological processes such as embryonic development, cell growth, morphogenesis, tissue repair, and tumor growth and invasion.[6] If there is no adiponectin in

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the environment; it has been shown that FGF-21 is unable to upregulate glucose uptake alone into the adipocytes. It is known that adiponectin protects against chronic illnesses such as diabetes, obesity and cancer through its anti-inflammatory properties.[7] A few years ago, it was assumed that fatty tissue cells (brown fat tissue), which had been found, converted to energetic heat through mitochondria, leading to weight loss.[8] In 2013; Luo Y et al.,[9] reported that although liver and muscle have received the most attention so far as the two main organs that send FGF21 as a stress signal, other organs may also use the same mechanism to recruit adipocytes in large fat depots or the microenvironment of various tissues. In the microenvironment of tissues containing ectopic or interspersed adipose tissue or adipocytes, such as the breast, bone marrow, and perirenal and epicardial regions, FGF21 serves to alter adipocyte signaling affecting parenchymal cell functions through a paracrine mechanism, and in stressed adipose tissues composed predominantly of adipocytes, by both paracrine and autocrine mechanisms. becomes active.

In line with these findings FGF-21 has significant and positive metabolic effects and anti-carcinogenic properties on breast cancer. In this study we aimed to measure FGF-21 levels in patients with breast cancer and to show their association with metabolic parameters in patients with cancer and healty control group.

METHODS

The study was carried out with the permission of Ankara Abdurrahman Yurtaslan Oncology Hospital Research and Training Center Ethics Committee (Date: 04.05.2016. Decision No: 2016- 5378). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This study was conducted between newly diagnosed stage 1-2 breast cancer patients who applied to Ankara Abdurrahman Yurtaslan Oncology Hospital between January 2016 and August 2016, and a control group of the same age group without a diagnosis of cancer who applied to the internal medicine outpatient clinics of Ankara Training and Research Hospital. Thirty-nine patients aged between 40-70 years who were diagnosed with breast cancer stage 1 and 2 and 39 healthy volunteer female patients were included in the study.

Demographic and charactheristic features including age. body mass index (BMI). waist and arm circumference of the all participants were gathered. Arm circumference was measured. Participants were evaluated with detailed physical examination and laboratory findings were collected. From all patients 5 cc blood was taken after eight hours of fasting in the morning hours. Blood obtained was centrifuged at 3000 rpm for 10-20 minutes after clotting was anticipated. Glucose. blood urea nitrogen (BUN). creatinine. uric acid. albumin. sodium(Na). potassium(K). calcium(Ca). phosphorus(P). aspartate aminotransferase (AST). alanine aminotransferase (ALT). gamma glutamyl transferase (GGT). alkaline phosphatase (ALP). bilirubin. Total cholesterol. High Density Lipoprotein (HDL-C). Low Density Lipoprotein (LDL-C). triglyceride(TG). complete blood count (CBC). thyroid function tests (TFT). anti-TPO. high sensitivity C- reactive protein (hs-CRP). erythrocyte sedimentation rate (ESR) levels were studied in the biochemistry laboratory of our hospital on the Beckman Coulter LH780 device by enzymatic colorimetric method (Cobas c501. Roche. Japon). Serum FGF-21 level was determined by enzyme-linked immunosorbent assay (ELISA) method using Biovendor Research and Diagnostic Products (antibody coated 96-well plate human FGF-21) ELISA kit. Biomedical Technologies Inc. Absorbance measurements were performed at 450 nm on a USA ELx800 (Biotek Instruments. INC.) Microplate reader. According to the ELISA kit prospectus; for the measurement of FGF-21 levels. serum samples were diluted 1: 2 by buffer dilution prior to analysis. The standard curve range for analysis was 30 1920 pg / ml. sensitivity 7 pg / ml. intraassay and interassay change were 3.0-4.1% and 3.6-3.9%. respectively.

Stastistical Analysis

The data were analysed using SPSS 22.0 (Statistical Packages for Social Sciences). Arithmetic mean. standard deviation (SD). number and percentage (%) were used as descriptive statistical parameters of the central criteria. The kolmogorov-simirnov test was used to check the normal distribution of the data. If the difference between the breast cancer group and the control group was appropriate with normal distribution. the independent student T test was performed for the continuous variables. chi-squared test or fisher's exact test was used to compare the two categorical variables. In the groups with and without breast cancer. dietary fat. physical activity, menopausal status and frequency distributions of categorical data were used, and the chi-squared test was used between groups. Correlation analysis was performed using the pearson correlation rank test. The significance level was accepted as p-value <0.05.

RESULTS

The demographic and laboratory data of the newly diagnosed breast cancer patient group and the control group were compared. The patient group was evaluated preoperatively. The control group consisted of 39 participants with a mean age of 52.49±7.02 years. In the patient group. 39 participants with the mean age of 52.15±6.21 years were included in the study. No statistical difference was observed regarding age between these two groups (p>0.05). In the control group. the mean FGF-21 level was 121.35±88.4 pg / ml. while the mean FGF-21 level in the patient group was 171±117.45 pg / ml and statistically significant difference was detected (p value=0.036). In Figure it was shown the changes of the FGF-21 levels in the patient and the control group. Arm circumference measurements were 34.15±6.11 cms in the control group and 31.38±3.65 cms in the patient group and it was found significantly different (p value =0.018). BMI and waist circumferences of control and patient groups were similar(p>0.05).

Total cholesterol, uric acid, LDL, TG, TSH, total bilirubin. ESR levels were also similar and there were no statistical difference (p>0.05). Whereas no significant difference was found for white blood cell. platelet count. and hemoglobin

levels (p>0.05). On the other hand creatinin,ALT, HDL, C albumin, free thyroxin, direct bilirubin, CRP and arm circumference measurements were significantly different between the patient and control group (p<0.05). All these finding were detaild in the Table .

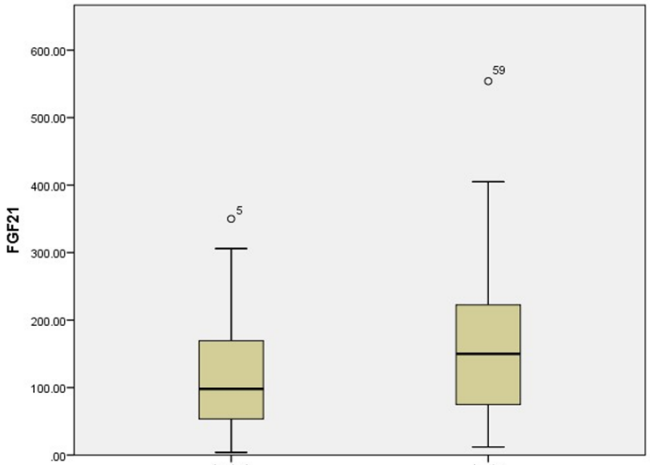

Figure. Serum FGF-21 levels in the patient and control group

Table . Demographic laboratory charactheristics and body measurements of the study population

Mean±S	Patient Group (n=39)	Control Group (n=39)	P Value
Age,year	52.15±6.21	52.49 ±7.02	0.825
BMI, kg/m^2	28.81±5.17	30.44 ±4.11	0.128
Fasting glucose. mg/dl	107±28.69	103 ±9.21	0.386
Creatinin. mg/dl	0.69 ±0.12	0.77 ±0.11	0.001
ALT, u/l	17.66 ±8.69	29.97 ±25.30	0.005
Uric acid, mg/dl	4.52 ±1.23	4.72 ±1.78	0.568
Total cholesterol, mg/dl	201.53 ±42.07	214.46 ±35.77	0.148
LDL-C, mg/dl	127.30 ±34.54	130.38 ±30.10	0.676
HDL-C, mg/dl	44.53 ±9.34	54.58 ±13	<0.001
TG, mg/dl	141.58 ±67.40	156.97 ±86.71	0.384
Calcium, mg/dl	9.40 ±0.71	9.71 ±0.47	0.026
Albumin, g/dl	4.03 ±0.74	4.42 ±0.30	0.003
TSH, mIU/L	1.65 ±1.11	2.02 ±1.12	0.155
ST4, ng/dl	1.06 ±0.30	0.82 ±0.17	<0.001
Total bilirubin, mg/dl	0.65 ±0.39	0.58 ±0.29	0.381
Direct bilirubin, mg/dl	0.25 ±0.19	0.12 ±0.07	<0.001
CRP, mg/L	4.47 ±5.64	0.70 ±0.55	<0.001
ESR,mm/hour	18.74 ±15.40	17.38 ±9.49	0.640
White blood cell,10^3/mm^3	7.36 ±2.38	7.44 ±2.05	0.867
Platelet count,10^3/mm^3	299.74 ±53.14	309.33 ±59.99	0.457
Hemoglobin, g/dl	13.32 ±1.28	12.98 ±1.52	0.285
Waist circumference, cm	98.20 ±12.44	95.38 ±6.38	0.212
Arm circumference, cm	31.38 ±3.65	34.15 ±6.11	0.018
FGF-21, pg/ml	171 ±117.45	121.35 ±88.43	0.036

* Variables were presented as n (%). mean ± SD or median [Q1-Q3]
BMI. Body Mass Index; ALT. LDL-C. Low Density Lipoprotein-Cholesterol; HDL-C. High Density Lipoprotein-Cholesterol; TG. Triglyceride; TSH. Thyroid Stimulating Hormone; FT4. Free thyroid hormone4; CRP. C-Reactive protein ; ESR. Erythrocyte Sedimentation Rate; FGF-21. Fibroblast growth factor 21, pg/ml. picogram/ml;kg/m^2 .kilogram/square meter; mg/l. milligram/litre; mm. millimeter; cm. centimeter

DISCUSSION

Breast cancer is the most commonly diagnosed cancer in women worldwide, with more than 2 million new cases in 2020.[11] Many genetic, reproductive and environmental factors are effective on the development of breast cancer. One of the most important of these factors is the metabolic syndrome. The prevalence of the metabolic syndrome is rapidly increasing all over the world, parallel to that the incidence of breast cancer is also rising.[12] FGF-21 is expressed in the adipose tissue, pancreas, and mainly in the liver. FGF-21 is a powerful regulator of metabolism. It regulates energy balance as well as specific effects on glucose and lipid metabolism. Pharmacological studies in primates and rats have shown that FGF-21 promotes a wide metabolic activity, increases insulin sensitivity, reduces plasma glucose, insulin, lipid levels, promotes the use of fat and energy consumption, and causes weight loss, therefore it has been suggested that this polypeptide may be a promising agent for the treatment of metabolic disorders associated with diabetes and obesity.[13]

It has recently been determined that some members of FGFs, including FGF-15, FGF-19, FGF-21, and FGF-23 play important metabolic roles.14 FGF 21, FGF19 affect glucose, lipid and energy metabolism via KLB and FGFR tyrosine kinase in fat cells and hepatocytes, in addition, obesity and metabolic abnormalities are factors contributing to the progression of breast tumor. Studies on FGFR4 in the liver reveal endocrine FGF21 signaling roles in both metabolic and cellular homeostasis.

In a study, very important results were obtained; it was shown that in obese or diabetic mice; FGF-21 administration decreased glucose, glucagon, lipids, visceral fat, tissue and body weight via increasing insulin sensitivity without changes in movement and diet. Free fatty acids, glucose uptake, HDL have been found to increase. Recombinant therapeutic application of FGF21 has been shown to lower blood sugar, triglyceride levels in diabetic and obese mice, reverse hepatic fat storing, and increase insulin sensitivity.[12] In a study by Zhang et al.,[13] there was a positive correlation between FGF-21 level and the parameters of obesity such as BMI, waist circumference and body fat ratio. FGF-21 concentration was closely related to body weight and amount of adipose tissue. A study provides evidence that increased expression of hepatic FGF21 in lean liver disease promotes breast cancer progression by increasing the anti-apoptotic abilities of breast cancer cells. Similar to our study, we observed overexpression of FGF21 in breast cancer tissues and patients with high FGF21 levels have poorer prognoses. shows. These findings highlight the clinical importance of FGF21 as both a prognostic indicator and a potential target for the treatment of breast cancer.[14]

Cancer-associated fibroblasts are activated fibroblasts that serve as a key component of the tumor microenvironment; FGF-19, FGF-21 and FGF-23 are endocrine FGFs that bind to Klotho and FGF receptors. FGFR1 is often overexpressed in breast and lung cancer, Promoter hypermethylation correlates with poorer survival of patients with gastric cancer, making it an independent prognosis factor.[15,16]

In our study, data such as age, BMI, waist and arm circumference, diet and exercise information, menopause status, comorbidities and medications were used. Our findings showed that FGF-21 levels were significantly higher in patients with early stage (1-2) breast cancer compared to the control group (p:0.036). Creatinine, ALT, HDL, calcium, albumin, fT4, direct bilirubin and CRP levels showed significant differences between the patient and control groups.

In similar studies in the literature, the positive correlation between FGF-21 and obesity, high blood sugar and LDL elevation was not found to be significant in our study. The average BMI of our patient group, in which FGF-21 was found to be significantly elevated, was determined to be overweight as 25.8 kg/m^2.

The strength of our study is that FGF-21 can be used as a biomarker for breast cancer in the future due to its significant and positive effect on glucose, lipid and energy metabolism, as well as its ability to stimulate the growth of cancer cells and cause breast cancer.

When its relationship with stage and treatment response is examined, it is predicted that it can be used as a useful agent in follow-up and treatment.

Limitations

Limitations of the study include a small patient population and the inclusion of only early-stage (stage 1-2) breast cancer patients.

CONCLUSION

It is believed that FGF-21 could be used in the future as a biological marker for breast cancer. as it has a significant and positive effect on glucose. lipid and energy metabolism. as well as slowing the growth of cancer cells. and as breast cancer is considered a metabolic cancer. It is predicted that when the relationship with stage and treatment response is studied. it can be used as a useful agent in follow-up and treatment. Larger randomised controlled trials are needed to clarify our findings.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara Abdurrahman Yurtaslan Oncology Hospital Research and Training Center Ethics Committee (Date: 04.05.2016. Decision No: 2016- 5378).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design. execution. and analysis of the paper. and that they have approved the final version.

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