How to Cite:
Hussin, S. J., Hilal, N. N., & Hussein, S. Z. (2022). The changes of serum irisin levels in postmenopausal breast cancer women. *International Journal of Health Sciences*, *6*(S6), 7007–7015. https://doi.org/10.53730/ijhs.v6nS6.11973

The changes of serum irisin levels in postmenopausal breast cancer women

Shaymaa Jamal Hussin
Kirkuk Health Directorate, Medical Lab, Kirkuk, Iraq
Email: Sheimaa.a@st.tu.edu.iq

Nihad N. Hilal
Chemistry Department, College of Medicine, Tikrit University, Iraq
Email: drnehad76@tu.edu.iq

Sura Zahim Hussein
Salah Aldeen Health Directorate, Clinical Biochemistry Unit, Tikrit, Iraq
Email: dr.sura2012@yahoo.com

Abstract---Breast cancer (BC) is a malignant neoplasm characterized by abnormal cell growth of breast tissue in an uncontrolled pattern and their ability to infiltrate and invade normal tissue locally. Irisin plays an important role in the occurrence, development, and metastasis of different tumors. The aim of this study to evaluate the changes of serum levels of irisin in postmenopausal breast cancer women and compared with control group. Serum samples were collected from 90 women were 30 of these women were control and 60 women were breast cancer patients attending to cancer center in Kirkuk city- Iraq from November 2021 to April 2022 . Postmenopausal breast cancer women ages were above 46 years, who were proved to be suffering from breast cancer whether a unilateral or bilateral breast affected who agree to participate in this study. Irisin levels for postmenopausal breast cancer women were (77.11±25.91) ng/ml and control (17.35±5.05) ng/ml respectively with a highly significant increase (P≤0.01) when compare with healthy control. These results suggest that irisin can be used in the early diagnosis, differential diagnosis, and prognosis of breast cancer.

Keywords---irisin, breast cancer, serum, postmenopausal.

Introduction

Breast cancer is one of the malignant neoplasms and the most prevalent type of cancer among women all over the world. Breast cancer is a disease with

heterogeneous characteristics. Clinically and based on cellular markers, it can be classified into three subtypes depending on the characteristics of gene expression: ER (estrogen receptor) an/or PR (progesterone receptor), HER2+ (breasts cancer with human epidermal growth factor receptor 2 positive), and TNBC (triple-negative breast cancer) [1,2]. About 70% of breast cancer cases are ER+ or PR+ and the HER2+ (also abbreviated as ERBB2+) can be seen in 15-20% of cases. All these receptors are proteins on the plasma membrane cells. The TNBC is about 15% of breast cancer cases and in this type, no proteins are on the surface of plasma membrane cells [3]. Tumors of breast generally begin from ductal hyper-proliferation and progress to benign tumors or metastatic cancer by various carcinogens as a result of continuous stimulation. Tumor microenvironments, such as stromal influences, play important role in the initiation and progression of the breast cancer. The mammary gland can transformed into a tumor, when exposes stroma to carcinogens, and not the extracellular or the epitheliums [4]. Breast cancer remains one of the most common malignancies in women, as the incidence of it is increasing continuously all over the world. The number of women who suffer from this disease is still increasing, especially in those countries that previously had a relatively low rate of breast cancer because these countries nowadays adopt Western lifestyles for reproductive behavior. The high incidence of breast cancer is closely related to genetics, family histories of breast cancer and environmental factors, behavioral habits, culture of knowledge, reproductive factors, menstruation at an early age, menopause, age of women at first birth and miscarriages. Its etiology and causative factors are complex and interlinked[5].

Irisin is one of novel myokines with 112 amino acids (12587 Da), which was identified in recent years. The “myokines” are a family of hormones secreted by muscles. They participate in several physiological and pathological processes, for example, lipid metabolism and cancer progression. Currently, irisin was found to improve the quality of skeleton and its serum concentration in patients with breast cancer was lower than healthy participants [6]. In addition, there still remains a debate about its role in metabolic syndrome (MetS). The circulating irisin levels were positively associated with the higher body mass index (BMI) or fasting insulin. However, the different roles of serum irisin for MetS were presented in Chinese and White or Black individuals [7].

Irisin is a newly discovered exercise-induced cytokine, produced by the proteolytic hydrolysis of fibronectin type III domain-containing protein 5. It is widely distributed in the human body and is involved in the browning of white adipose tissue, improving insulin resistance, improving cognitive function, and regulating bone metabolism [8]. Recent studies have shown that irisin concentration is elevated in a variety of tumor tissues as compared with that in normal tissues. However, irisin has different effects on the proliferation and apoptosis of tumor cells in breast cancer, lung cancer, and liver cancer through various mechanisms. Irisin plays an important role in the occurrence, development, and metastasis of different tumors, suggesting that irisin can be used as a potential target for tumor diagnosis and treatment [9-11].

Patients and Methods

Venous blood of about (5-10) ml was taken from postmenopausal breast cancer women and control subjects; it was allowed to clot inside a plain tube. After doing centrifugation for 30 minutes at 3000 rpm, the serum was aspirated, then subdivided into aliquots within plastic tubes and kept at (-20 °C) till the time of estimation. From ninety individuals, serum sample was collected; thirty of them were normal and sixty cases were patients with postmenopausal breast cancer women who attended to cancer center in Kirkuk Oncology Center from November 2021 to April 2022.

Inclusion Criteria

The cases includes postmenopausal women with age above 46 years who were proved to be suffering from breast cancer whether an unilateral or bilateral breast affected who agree to participate in this study.

Exclusion Criteria

Each woman was excluded from any following diseases in this study: diabetes mellitus, hypertension, thyroid diseases, severe anemia, benign breast cancer and any tumor or cancer cases. The irisin levels were detected by Enzyme Linked Immunosorbent Assay (ELISA) Sunlong Biotech Company kits with the sandwich method [12]. Statistical analysis was done by using SPSS, 2001 statistical program, and a comparison was made between various groups, which were evaluated by t-test. The level of statistical significance was calculated at ($P<0.05$).

Results

The mean±SD of Irisin levels for breast cancer women were (77.11±25.91) ng/ml and control (17.35±5.05) ng/ml respectively with highly significant increase ($P\leq0.01$) when compared with control group as shown in table (1) and Figure (1). The level of Irisin in all stages of postmenopausal breast cancer women was (112.86±11.93) ng/ml, (87.85±10.01) ng/ml, (64.75±16.91) ng/ml, (51.38±31.99) ng/ml respectively.

Table 1
Levels of Irisin (ng/ml) in Postmenopausal Breast Cancer Women and Controls

Groups	No. of Individuals	Mean ±SD	P value
Breast cancer Women	60	77.11±25.91	
Controls	30	17.35±5.05	*P ≤ 0.01

*P ≤ 0.01: - highly significance

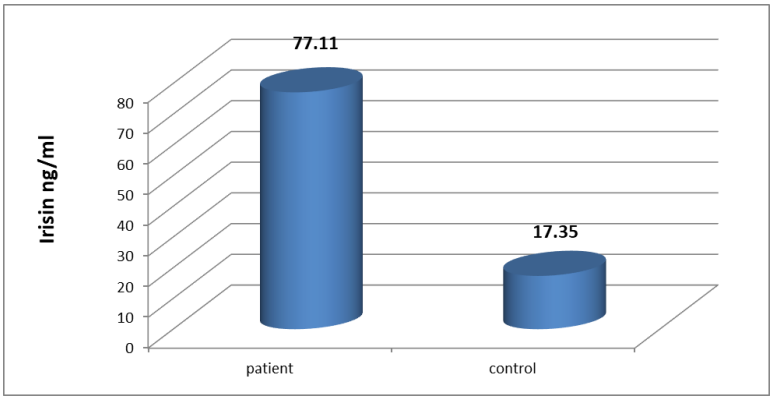

Figure 1. Irisin ng/ml in postmenopausal breast cancer women and controls

The mean±SD of Cholesterol levels for breast cancer women were (179.0±25.36) mg /dl and control (116.13±42.72) mg /dl respectively with highly significant increase (P≤0.01) when compared with control group as shown in table (4.7) and Figure (4.7).

Table 2
Levels of Cholesterol (mg /dl) in Postmenopausal Breast Cancer Women and Controls

Groups	No. of Individuals	Mean ±SD	P value
Breast cancer Women	60	179.0±25.36	
Controls	30	116.13±42.72	*P ≤ 0.01

*P ≤ 0.01: - highly significance

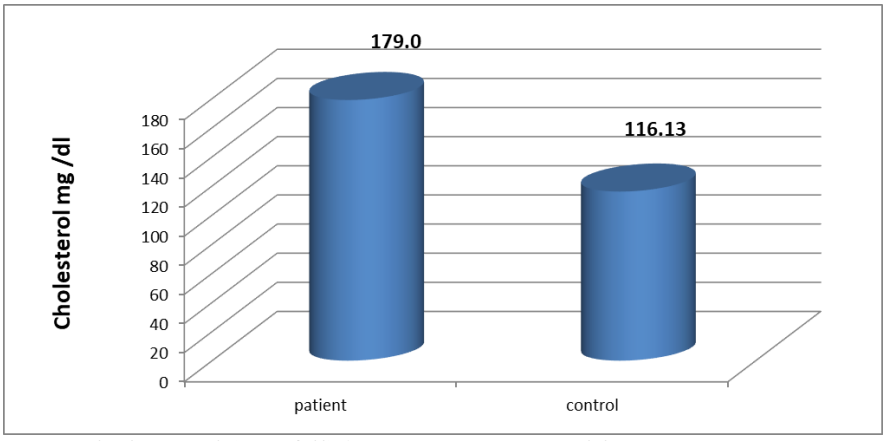

Figure 2. Cholesterol (mg /dl) in postmenopausal breast cancer women and controls

The mean±SD of Triglyceride levels for breast cancer women were (147.3±41.54) mg/dl and control (118.03±34.99) mg/dl respectively with no significant increase (P > 0.05) when compared with control group as shown in table (4.8) and Figure (4.8).

Table 3
Levels of Triglyceride (mg/dl) in Postmenopausal Breast Cancer Women and Controls

Groups	No. of Individuals	Mean ±SD	P value
Breast cancer Women	60	147.3±41.54	
Controls	30	118.03±34.99	***P > 0.05

***P > 0.05: - no significance

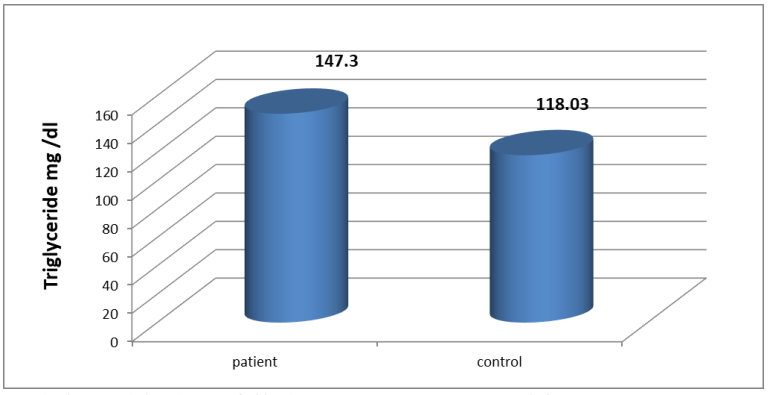

Figure 3.T riglyceride (mg /dl) in postmenopausal breast cancer women and controls

The mean±SD of HDL levels for breast cancer women were (47.03±8.8) mg /dl and control (51.0±5.0) mg /dl respectively with no significant decrease (P > 0.05) when compared with control group as shown in table (4.9) and Figure (4.9).

Table 4
Levels of HDL (mg/dl) in Postmenopausal Breast Cancer Women and Controls

Groups	No. of Individuals	Mean ±SD	P value
Breast cancer Women	60	47.03±8.8	
Controls	30	51.0±5.0	***P > 0.05

***P > 0.05: - no significance

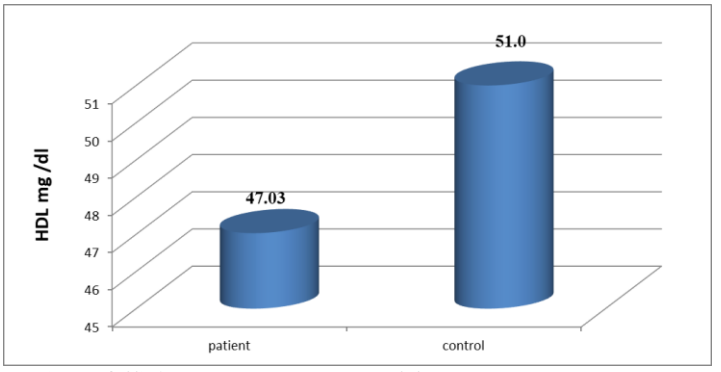

Figure 4. HDL (mg /dl) in postmenopausal breast cancer women and controls

Discussion

This study showed that Irisin was increased in postmenopausal breast cancer women and there was a highly significant difference (P≤0.01) when compared with control group. In this study, the maximum level of Irisin in stage 1 when compared with other stages which estimated that for every one-unit increase in irisin levels, the risk of breast cancer decreases by nearly 90%. Serum levels of muscle- and adipose-tissue-derived molecules, namely, irisin in patients with benign and malignant breast cancer of different stages compared to healthy individuals. Irisin level was closely related to the occurrence of breast cancer and was an independent predictor of breast cancer. Meanwhile, the serum level of irisin was positively correlated with tumor stage. These results suggest that irisin can be used in the early diagnosis, differential diagnosis, and prognosis of breast cancer [13-16].

A positive correlation was found between irisin level and the clinical stage of the tumor. No statistically significant correlation was found with respect to tumor size, lymph node metastasis, and histological malignancy of the tumor. Irisin is an adipomyokine that is involved in the regulation of metabolic processes. It also influences processes related to inflammation, including cancer [17]. The role of Irisin in cancer disease, including many types of malignancies, i.e., breast, lung, gastrointestinal, reproductive tract, and bone cancers, therefore, it is crucial for cancer cell metastasis [13]. During recent years, an increasing number of malignancies of different origins, including colon, endometrial, and postmenopausal breast cancer were shown to be associated with body fat accumulation and sedentary lifestyle. It is reported that moderate exercise may decrease breast cancer risk up to 20–30% [18].

Increased irisin levels may be a result of an increasing energy demandin cancer cells and a switch to glycolysis instead of obtaining ATP from the respiratorychain. Irisin also increases glucose uptake by cells and enhances AMP-activated kinase (AMPK) phosphorylation [15]. Therefore, higher concentrations of irisin may allow cancercells to obtain energy through glycolysis, which could confirm our findings related to theincreased expression of irisin/FNDC5 in BC compared to the controls [19-22]. Changes in concentration of serum lipids in patients with breast cancer will result in an increased production of tumor necrosis factor-alpha (TNF-α) and inhibition of adipose lipoprotein lipase activity by insulin these changes will impair the catabolism of very low-density lipoprotein cholesterol (VLDL-c), which is influenced by dietary fat intake, alcohol consumption, body weight, pregnancy, endogenous hormones, smoking and physical inactivity. Besides this, proliferating cells such as cancer cells have increased requirement of cholesterol and facilitate lipid biosynthesis and metabolism that will finally leads to increased serum cholesterol level in patients with breast cancer. In addition, since cholesterol is transported by low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c), abnormal serum level of LDL-c and HDL-c is associated with breast cancer and its normal serum level is considered as prognostic marker for breast tumor [23].

The exact mechanism of hypertriglyceridemia and decreased HDL concentration in breast cancer patients is not known. However, it has been suggested that

lipoprotein lipase LPL may regulate the clearance of TG from blood to tissue and its activity in adipose tissue decreases in cancer patients contributing to hypertriglyceridemia. Since precursor particles of HDL are thought to derive from lipolysis of TG and the LPL activity decreases in cancer, increased plasma TG may be one of the factors for lower HDL concentration observed in this study [24].

Conclusions

The presumable relationship between irisin and breast cancer was suggested by proving distinguished serum irisin levels of breast cancer patients compared with those of control. The increased expression of irisin in different tumors suggests that it is closely related to the occurrence and development of tumors, making it an attracting new target for tumor prevention research and a marker in early diagnosis of breast cancer.

References

1. Alrawi NN. A review on breast cancer in Iraq and future therapies insights. Baghdad Journal of Biochemistry and Applied Biological Sciences 2022; 3(01):4-16
2. Avgerinos KI, Spyrou N, Mantzoros CS and Dalamaga D. Obesity and cancer risk: emerging biological mechanisms and perspectives. *Metabolism* 2019; 92:121-135.
3. Dos Santos CR, Fonseca I, Dias S, De Almeida JM. Plasma level of LDL-cholesterol at diagnosis is a predictor factor of breast tumor progression. BMC cancer. 2014 Dec;14(1):1-0.
4. E.R Sarhat, S.A. Wadi, B.I. Sedeeq, Th.R. Sarhat and N.A. Jasim.Study of histopathological and biochemical effect of Punica granatum L. extract on streptozotocin -induced diabetes in rabbits .Iraqi Journal of Veterinary Sciences,2019. 33(1):189-194.
5. Entedhar R. Sarhat , Nawal A. Al- Madani , Nazar. A. Naji.Evaluation of Serum Paraoxonase and Lipid Profile in Patients with Chronic Renal Failure Pre and post Hemodialysis. Tikrit Journal of Pure Science 22 (2) 2017:48-53.
6. Entedhar R. Sarhata, Moayad M. Al Anzy, Takea Shaker Ahmed. Study of oxidant-antioxidant status in cerebrospinal fluid of children with meningitis. Eurasian Chemical Communications, 2022, 4(9), 863-869. Link: http://www.echemcom.com/article_148799. Html.
7. Entedhar RS , Husamuldeen Salim Mohammed Saeed. Siham A. Wadi.Altered Serum Markers of Omentin and Chemerinin Chronic Renal Failure Patients on Hemodialysis. Research J. Pharm. and Tech. 11(4): 2018.
8. Guo B, Zhang ZK, Liang C, Li J, Liu J, Lu A, Zhang BT, Zhang G. Molecular communication from skeletal muscle to bone: a review for muscle-derived myokines regulating bone metabolism. Calcified tissue international. 2017 Feb; 100(2):184-92.
9. Hameed EH, Hussein SZ and Abed NAN. Evaluation of Aromatase Activity in Pre and Postmenopausal Breast Cancer Women. wjpmr 2018; 4(9):99-100.
10. Jablońska K, Romanowicz H, Smolarz B, Dzięgiel P, Podhorska-Okołów M . Expression of Irisin/FNDC5 in Breast Cancer. Int J Mol Sci. 2022 Mar 24; 23(7):3530.

11. Jedrychowski MP, Wrann CD, Paulo JA, Gerber KK, Szpyt J, Robinson MM, Nair KS and et al . Detection and quantitation of circulating human irisin by tandem mass spectrometry. Cell metabolism. 2015; 22(4):734-40.
12. Jedrychowski MP, Wrann CD, Paulo JA, Gerber KK, Szpyt J, Robinson MM and *et al.* Detection and Quantitation of Circulating Human Irisin by Tandem Mass Spectrometry. Cell Metab. 2015; 22(4):734-740.
13. Kh.G. Washeel, E. R. Sarhat, T.H Jabir.. Assessment of melatonin and oxidant-antioxidant markers in infertile men in Thi-Qar Province. Indian Journal of Forensic Medicine & Toxicology. 2019:13(4) ;1495- 1499.
14. M. S. Hamad , Entedhar R. Sarhat, Salim J. Khalaf, ThuraiaRifaatSarhat , Kasim Sakran Abass .Characteristic Abnormalities In Serum Biochemistry In Patients With Breast Cancer . Sys Rev Pharm 2020;11(11):1967-1
15. Mahde. S. Hamad , E R. Sarhat, ThuraiaRifaat Sarhat, Kasim Sakran Abass.Impact of Serum Adropin and Irisin in Iraqi patients with Congestive Heart Failure. P J M H S.2021;15(2);NO. : 497-499.
16. Mjali A, Jawad SA, Al-Shammari HHJ. Breast Cancer in Middle Euphrates Region of Iraq: Risk Factors, Presenting Symptoms and Time to Medical Help-Seeking. Asian Pac J Cancer Care 2021; 6(3): 243-247.
17. Pinkowska A, Podhorska-Okołów M, Dzięgiel P, Nowińska K. The role of irisin in cancer disease. Cells. 2021 Jun; 10(6):1479.
18. R.S. Entedhar ,. Acute Myocardial Infarction: Melatonin, Apelin, and Visfatin as Predictors of Disease. Diyala J Med. 2017;13(2):11-7.
19. S.E Ahmed , Entedhar R. Sarhat , Neda Awni , ThuraiaRifaat Sarhat, Kasim Sakran Abass. Altered Serum Marker of Adipokines Profile in Breast Cancer Women.Indian Journal of Forensic Medicine & Toxicology, July-September 2021; 15(3):2598-2604.
20. Sarhat Entedhar Rifaat, Khalaf Salim Jasim, Hamad Mahde Salih. A Study of Some biochemical Parameters in blood Serum of Patients with congestive Heart Failure. Indian Journal of Public Health Research & Development.2019: 10(5); 413- 418.
21. Sarhat ER, Rmaid ZJ, Jabir TH (2020) Changes of salivary interleukine17, Apelin, Omentin and Vaspin levels in normal subjects and diabetic patients with chronic periodontitis, Ann Trop Med & Pub Health; 23:S404. DOI: http://doi.org/10.36295/ASRO.2020.23118.
22. Sunlong Biotech Co. Human Elisa kit. Available from: https://www.sunlongbiotech.com/gory.php?id=66. [Accessed 2 December 2020].
23. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2022). Post-pandemic health and its sustainability: Educational situation. International Journal of Health Sciences, 6(1), i-v. https://doi.org/10.53730/ijhs.v6n1.5949
24. Thaib, P. K. P., & Rahaju, A. S. (2022). Clinicopathological profile of clear cell renal cell carcinoma. International Journal of Health & Medical Sciences, 5(1), 91-100. https://doi.org/10.21744/ijhms.v5n1.1846
25. Touvier M, Fassier P, His M, Norat T, Chan DS, Blacher J, Hercberg S, Galan P, Druesne-Pecollo N, Latino-Martel P. Cholesterol and breast cancer risk: a systematic review and meta-analysis of prospective studies. British Journal of Nutrition. 2015 Aug;114(3):347-57.
26. Zhang D, Tan X, Tang N, Huang F, Chen Z, Shi G. Review of Research on the Role of Irisin in Tumors. OncoTargets and therapy 2020; 13:4423.

27. Zomkowski K, Cruz de Souza B, Pinheiro da Silva F, Moreira GM, de Souza Cunha N, Sperandio FF. Physical symptoms and working performance in female breast cancer survivors: a systematic review. Disability and rehabilitation. 2018 Jun 19; 40(13):1485-93.