Relationship of High Molecular Weight Adiponectin with Female Breast Cancer

Alia Banori[1], Ejaz Hassan Khan[2], Ahmad Rafiq[3], Mohsin Shafi[4], Sadaf Durrani[5] and AmbreenAli[6]

[1]Department of Pathology, Khyber Medical College, Peshawar & IRNUM Hospital, Peshawar, [2]Department of Pathology, Northwest School of Medicine, Peshawar, [3]Department of Chemical Pathology, Khyber Medical College Peshawar, [4]Department of Pathology, Khyber Medical College Peshawar, [5]Department ofBiochemistry Khyber Medical College Peshawar, [6]Pak International Medical College, Peshawar.

ABSTRACT

Background: Role of serum adiponectin level is very important in the prediction of cancer. Regarding breast cancer, adiponectin's role is still under-investigation among women of pre and postmenopausal stage of life.
Objective: To determine serum levels of HMW adiponectin in female patient of breast cancer.

Methods: This is a case control study.This study consisted of 300 female subjects. Among which 150 consisted of patients having breast cancer and 150 consisted of normal healthy females as a control.This study was conducted in IRNUM Hospital Peshawar, Khyber Pakhtunkhwa (KPK). The duration of the study was 12 months i.e. from March 2016 to March 2017. Fasting blood samples were obtained from the participants and were analyzed for serum adiponectin level.

Results: Significantly low adiponectin level was observed in cases than in controls with (P= 0.001). No significant difference was found in blood sugar level among both the groups (P=0.28). Significantly high level of serum insulin was found in patients having breast cancer as compared to control with (P= 0.02).

Conclusion: The current study shows that serum adiponectin level is markedly decreased in breast cancer patients. It shows an inverse relationship with breast cancer, suggesting its protective role in breast cancer.

Keywords: Adiponectin, High Molecular Weight Adiponectin, Breast cancer

Introduction

Adiponectin, a peptide hormone has been recently identified and is secreted by adipose tissue. Adiponectin has anti- obesity, insulin sensitizing, anti-inflammatory, anti-hyperlipidemic and anti-cancer activities.[1,4,6] It has three structural forms. The most important active form of adiponectin is the High Molecular Weight (HMW) form.[2,3] Due to its important roles in health, it has become a focus of attention for researches.

Adiponectin leads to suppression of proliferation and migration of endothelial cells and macrophages. By causing increased apoptosis and decreased neovascular proliferation, adiponectin causes impaired growth of cancer cells leading to cell death.[5]

CORRESPONDENCE AUTHOR
Dr. Alia Banori
Email Address: alia.banori@yahoo.com
Mobile: 03339312729

Adiponectin causes decreased production of estrogen in the adipose tissue by decreasing aromatase activity.[3]

A significant inverse relationship of breast cancer risk with serum adiponectin has been revealed by several epidemiological studies. Miyoshi et al obtained low serum adiponectin levels in breast cancer patients.[6]

Adiponectin is an important risk biomarker and is increasingly emerging as attractive chemo- protective target in female breast cancer due to its preventive role in breast cancer. Studies have shown association of low total adiponectin level with female breast cancer, but it has not been clearly determined whether HMW Adiponectin has more active role than total adiponectin.[7,8,9]

Breast cancer is the most commonly occurring cancer in females and it is the leading cause of cancer related mortality among women worldwide [4,6,11]. It has been estimated that 1.67 million of women were diagnosed with breast cancer, accounting for about 25% of all cancers diagnosed in 2012 according to "World Health Organization" (WHO).[4,10] Itis considered to be the second highest cause of cancer related deaths.

A study performed in China revealed that breast cancer proportion has become about half of those in European countries annually[10]. Thus, it is urgent for the identification of new prognostic biomarkers related to breast cancer that help in making early diagnosis, tumor progression monitoring and medical optimization .[4]

Many factors are associated with breast cancer which consists of genetics of an individual person (body makeup), family history, lifestyle, obesity, blood sugar and serum insulin levels. Obesity is the most important factor for breast cancer which nowadays has been ruled out to be a crucial cause of increased prevalence of cancer.[11, 12]

Adiponectin has been determined to have an inhibitory effect on cancer cells proliferation. Therefore, adiponectin in its high serum concentration is considered to have an important role against breast cancer. [13,14,15]

Several epidemiological studies have shown a significant inverse relationship of breast cancer with serum adiponectin but there is scarcity of literature on this topic in our part of the world. So, this study was planned to find out the relationship between breast cancer and serum adiponectin in local context.

Methodology

This study was conducted in IRNUM Hospital Peshawar, Khyber Pakhtunkhwa (KPK). It was approved by the ethical Committee of Khyber Medical College, Peshawar. The duration of the study was 12 months i.e. from March 2016 to March 2017. This case control study consisted of 300 female subjects, 150 subjects were taken as female patients diagnosed with breast cancer and 150 subjects were normal healthy females, taken as control. All the patients were selected from IRNUM Hospital Peshawar. All the control females were selected randomly. All females diagnosed with breast cancer and without any prior treatment were included in the cases. The control group included females with no history of any past or present malignancy and any major chronic illness. A well-informed consent was taken from all the participants. A detailed history was taken and height, weight and BMI (Body mass index in Kg/ height in meters²) of all the participants were recorded on a structured performa.

A volume of 5 ml fasting blood samples was obtained from all the participants after overnight fast. All the samples were centrifuged at 3000 rpm to obtain clear serum. The obtained sera were stored at -70℃ for further analysis.

The variables analyzed for this study consisted of serum adiponectin, serum insulin and blood sugar. Fasting blood sugar was measured on fresh samples while the stored serum was used for the analysis of adiponectin and insulin. ELISA (Enzyme Linked Immunosorbent Assay) Method was used to determine serum HMW Adiponectin using human adiponectin ELISA Kit (cat number: DHWADO), commercially available from "Biovendor Research and Diagnostic Products, Germany". It was based on sandwich enzyme Immunoassay technique. The machine used was ELISA Reader. An ECL (Electro Chemiluminescence) Method was used to analyze serum insulin and was based on sandwich enzyme Immunoassay technique. It was performed on Cobas E411 analyzer. Fasting blood sugar was measured by an Enzymatic Colorimetric method, using a semi auto chemistry analyzer, Micro Lab 300.

Data analysis was carried out using SPSS version 20. Results were expressed as mean±SD. Independent students t-test was used for the comparison of variables between the two groups. By using the Pearson correlation co-efficient r, association between HMW with female breast cancer was found out. Results with p value less than 0.05 were significant.

Results

Table 1: Comparison of General Characteristics and Biomedical Parameters in Both Groups

Parameters	Case Mean ± SD	Control Mean ± SD	P
Age (Years)	45.46±12.95	41.55±9.18	.003*
BMI	26.7±6.09	27.2±5.95	.473
Sugar (mg/dL)	99.58±22.97	96.93±19.97	.287
Insulin(μU/mL)	15.28±10.90	12.67±9.35	.027*
Adiponectin(μg/mL)	3.08±2.15	5.50±8.15	.001*

Note: p* valve <0.5 was considered significant.
(SD = standard deviation)

Table 2: Correlation of Adiponectin with Different Parameters in Both Groups

Parameters	Case		Control	
	R	p	r	p
Age	.148	.070	.048	.557
BMI	-.462	.000**	-.162	.048*
Sugar	-.152	.063	.064	.436
Insulin	-.171	.036*	-.108	.189

*significant at 0.05 level, **significant at 0.01 level.

Comparison of general characteristics and biomedical parameters of the study population, i.e. case and control group are shown in Table 1. Cases show higher mean age (45.46±12.95years) as compared to the control group (41.55±9.18 years) with a significant difference (P= 0.003). No significant difference has been shown regarding BMI. Significant difference has been obtained in serum insulin levels (p=.027). High significant difference was observed regarding serum adiponectin level, which was comparatively lower in cases (3.08±2.15 units) than the control (5.50±8.15) with P- value 0.001.

Association of serum adiponectin with various parameters of the studied group has been shown in Table 2 by using Pearson correlation coefficient r. BMI showed strong negative association with adiponectin in both cases and control groups. Serum insulin level was significantly inversely associated with adiponectin among the cases (r=- 0.171, P=0.036).

Discussion

Adiponectin is a peptide hormone which is secreted by adipose tissues and it possess important anticancer activity. It may has a role in female breast cancer development[16]. The present study was focused on possible relationship of adiponectin and related risk factors (like obesity, insulin and diabetes) with female breast cancer.

The mean age of the case group in the present study was a little higher as compared to control showing a relationship of breast cancer with middle age i.e. in pre- menopausal age. Ahmed et al Showed similar results in their study [17]. Higher serum insulin level was obtained in patients having breast cancer than the control group with a significant difference. Previous studies also showed the same results. Shahar et al conducted a study on Malaysian women and showed a high fasting blood glucose and high insulin levels among the cases.[18] Kang et al and Sattin et al obtained similar results.[19,20]Calle et al obtained high insulin

levels in his study which is consistent with the results of our study. [21, 22]

Low levels of serum HMW adiponectin was found among the cases as compared to control in the present study with a high significant difference. Similar results were obtained by Cat et al with low adiponectin and high serum insulin levels which is consistent with our study.[22]

BMI showed a negative association with adiponectin in both the cases and control in the present study, proving that increased BMI is one of the risk factor for breast cancer.[23] Grossman et al and Minataya et al demonstrated that hyperinsulinemia was associated with hypoadiponectinemia.[23,24, 25,] We obtained similar results in our study.

Limitations of Study

We included newly diagnosed cases of breast cancer females in both premenopausal and post-menopausal states which is a strength of this study. However, the study could be performed on a bigger sample size and from multiple institutes.

Conclusion

The present study confirms a relationship of low HMW adiponectin with breast cancer. High serum insulin levels were also observed in this study. Moreover, a negative association was observed between adiponectin levels and serum insulin and BMI.

Further studies are recommended to investigate the role of HMW adiponectin with female breast cancer on genetic levels.

References

1. V, Farabad E, Azadbakht L. Serum Adiponectin level and different kinds of cancer: a review of recent evidence. ISRN oncology. 2012 Nov 18; 2012.
2. Minatoya M, Kutomi G, Shima H, Asakura S, Otokozawa S, Ohnishi H, et al. Relation of serum Adiponectin levels and obesity with breast cancer: a Japanese case-control study. Asian Pac J Cancer Prev. 2014;15(19):8325-30.
3. Tian YF, Chu CH, Wu MH, Chang CL, Yang T, Chou YC, et al. Anthropometric measures, plasma adiponectin, and breast cancer risk. EndocrRelat Cancer. 2007;14(3):669-77.
4. GU L, Cao C, Fu J, Li Q, Li D, Chen MY. Serum Adiponectin in breast cancer. Medicine (Baltimore). 2018;97(29):e11433.

5. Mantzoros C, Petridou E, Dessypris N, Chavelas C, Dalamaga M, Alexe DM, et al. Adiponectin and breast cancer risk. J Clin Endocrinol Metab. 2004;89(3):1102-7.

6. Yu Z, Tang S, Ma H, Duan H, Zeng Y. Association of serum adiponectin with breast cancer. Medicine (Baltimore). 2019;98(6):e14359.

7. Jarde T, Caldefie-Chezet F, Goncalves-Mendes N, Mishellany F, Buechler C, Penault-Llorca F, et al. Involvement of Adiponectin and leptin in breast cancer: clinical and in vitro studies. EndocrRelat Cancer. 2009;16(4):1197-210.

8. Liu LY, Wang M, Ma ZB, Yu LX, Zhang Q, Gao DZ, et al. The role of Adiponectin in breast cancer: a meta-analysis. PLoS One. 2013;8(8):e73183.

9. Fabian CJ. Adiponectin: a risk biomarker and attractive target for chemoprevention. J Clin Oncol. 2011;30(2):124-6.

10. Fan L, Strasser-Weippl K, Li JJ, St Louis J, Finkelstein DM, Yu KD, et al. Breast cancer in China. Lancet Oncol. 2014;15(7):e279-89.

11. Murillo-Ortiz B, Martinez – Garzo S, Lauderos VC, Velazquez GC, Garcia DS. Effect of Reduced dietary fat on estradiol, adiponectin, and IGF-1 levels in Postmenopausal women with breast cancer. Breast cancer, 2017;9:359-64.

12. Elkum N, Al-Tweigeri T, Ajarim D, Al-Zahrani A, Amer SM, Aboussekhra A. Obesity is a significant risk factor for breast cancer in Arab women. BMC Cancer. 2014;14:788.

13. Wang Y, Lam JB, Lam KS, Liu J, Lam MC, Hoo RL, et al. Adiponectin modulates the glycogen synthase kinase-3beta/beta-catenin signaling pathway and attenuates mammary tumorigenesis of MDA-MB-231 cells in nude mice. Cancer Res. 2006;66(23):11462-70.

14. Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto Y, et al. Adipocyte-derived plasma protein Adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle cell. Circulation. 2002;105(24):2893-8.

15. Waki H, Yamauchi T, Kamon J, Kita S, Ito Y, Hada Y, et al. Generation of globular fragment of Adiponectin by leukocyte elastase secreted by monocytic cell line THP-1. Endocrinology. 2005;146(2):790-6.

16. Ford NA, Devlin KL, Lashinger LM, Hursting SD. Deconvoluting the obesity and breast cancer link: secretome, soil and seed interactions. Journal of mammary gland biology and neoplasia. 2013;8(3-4):267-75.

17. Ahmed SD, Khanam A, Sultan N, Idrees F, Akhter N. Serum Adiponectin Level Association with Breast Cancer Risk: Evidence from a Case-Control Study. Asian Pac J Cancer Prev. 2015;16(12):4945-8.

18. Shahar S, Salleh RM, Ghazali AR, Koon PB, Mohamud WN. Roles of adiposity, lifetime physical activity and serum Adiponectin in occurrence of breast cancer among Malaysian women in Klang Valley. Asian Pac J Cancer Prev. 2010;11(1):61-6.

19. Stattin P, Bjor O, Ferrari P, Lukanova A, Lenner P, Lindahl B, et al. Prospective study of hyperglycemia and cancer risk. Diabetes Care. 2007;30(3):561-7

20. Kang JH, Yu BY, Youn DS. Relationship of serum Adiponectin and resistin levels with breast cancer risk. J Korean Med Sci. 2007;22(1):117-21.

21. Kadowaki T, Yamauchi T. Adiponectin and Adiponectin receptors. Endocr Rev. 2005;26(3):439-51.

22. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer. 2004;4(8):579-91.

23. Grossmann ME, Ray A, Dogan S, Mizuno NK, Cleary MP. Balance of Adiponectin and leptin modulates breast cancer cell growth. Cell Res. 2008;18(11):1154-6.

24. Grossmann ME, Ray A, Nkhata KJ, Malakhov DA, Rogozina OP, Dogan S, et al. Obesity and breast cancer: status of leptin and Adiponectin in pathological processes. Cancer Metastasis Rev. 2010;29(4):641-53.

25. Minatoya M, Kutomi G, Asakura S, Otokozawa S, Sugiyama Y, Nagata Y, et al. Equol, Adiponectin, insulin levels and risk of breast cancer. Asian Pac J Cancer Prev. 2013;14(4):2191-9

Contribution of Authors

- Alia Banori: Conceived the idea, collected samples, experimentation
- Ejaz Hassan Khan: Synthesis and planning of the research.
- Ahmad Rafiq: Active participation in active methodology for the research.
- Dr. Mohsin¬Shafi: Interpretation analysis and discussion.
- Sadaf Durrani: Active participation in Experimentation
- Dr. Ambreen Ali: Data Analysis