ORIGINAL ARTICLE

ASSOCIATION OF IRON DEFICIENCY WITH HYPERINSULINEMIA IN BREAST CANCER

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Background: Iron deficiency was found to sensitize insulin action and associated with increased risk of diabetes in breast cancer women. This prospective study was designed to examine the association of the level of insulin with haemoglobin, as this association may increases the risk of diabetes in breast cancer women. **Methods:** Fifty breast cancer women with age range 35 to 50 years were included in the study. Twenty age-matched control subjects with no history of any disease were taken as controls. Data based on age, BMI and family history were collected. Diabetic breast cancer women and women with family history of diabetes were excluded. Level of haemoglobin and insulin was estimated by standard methods. Homeostasis model assessment HOMA-insulin resistance index was calculated. **Results:** Mean age of patients was 40 years. BMI of the patients was non-significantly increased. Level of haemoglobin was non-significantly decreased in patients as compared to controls. Level of serum insulin was non-significantly increased in patients as compared to the controls. Increased insulin resistance was observed in patients when compared with control subjects. **Conclusion:** Insulin resistance may be responsible for hyperinsulinemia which in turn increases the risk of diabetes in breast cancer. Future research is needed to clarify the underlying mechanism.

Keywords: Iron deficiency, hyperinsulinemia, breast cancer

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INTRODUCTION

Breast cancer is a group of diseases based on different behavioural and molecular characteristics whose pathogeneses are expected to differ.[1] There is a complex interacting mechanisms by which insulin may promote breast cancer development and progression, instead of initiation and neoplastic transformation of the breast tissue. Insulin exerts a significant mitogenic action in breast cancer cell. It is also an anti-apoptotic agent and endocrine regulator of breast cancer-associated adipokines that are related with paracrine and autocrine growth control.[2]

The concentration of Insulin receptors (IR) is higher in breast cancer tissues than in normal breast tissues, and directly related to tumour size, grade, and mortality.[3] It is therefore possible that the interaction between insulin and IR influences breast cancer development through modification of growth and differentiation of breast cell lines.[4] However a study found that there is no link of insulin with breast cancer.[5]

Hyperinsulinemia is found in both premenopausal and postmenopausal breast cancer women.[5,6] It induces proliferative tissue abnormalities via stimulation of DNA synthesis and cell proliferation. However, it is stated that increased circulating insulin may be a weak predictor of type 2 diabetes in breast cancer women.[4] Despite the presence of hyperinsulinemia, studies demonstrated that compromised β-cell function is present in prediabetics years before the onset of type 2 diabetes.[7]

Besides regulation of the metabolic pathway, insulin also stimulates cell mitosis and migration and inhibits apoptosis, effects that may increase insulin resistance, resulting altered insulin-regulated metabolic pathways.[2] It is suggested that abnormal insulin signaling may be involved in breast cancer aetiology.[8] It is proposed that insulin resistance causes hyperglycemia that may foster cancer development by providing an amiable environment for the growth of malignant cell clones.[9]

Iron has a role in the tumour micro-environment. It is suggested that imbalance of iron responsive element/iron regulatory proteins is a main reason of tumor cell survival.[10] Iron deficiency and macroenvironment in breast cancer women may lead to metastasis especially to lymph node and recurrence of cancer.[11,12]

Temporal iron deficiency was found to sensitize insulin action[13] and associated with increased risk of diabetes[14]. An iron deficiency may stabilize hypoxia via the formation of vascular endothelial growth factor results, angiogenesis. It is proposed that angiogenesis is necessary for tumor to grow, and has an important role in tumour progression and recurrenc.[11]

Iron deficiency is also associated with increased reactive oxygen species (ROS).[15] This ROS have a direct effect on circulating insulin results in decrease binding of insulin to the insulin receptor.[3] Increase iron deficiency in breast cancer women with increase BMI is due to inflammatory nature of obesity which might increased hepcidin levels that decreases dietary iron absorption.[16]

For understanding the biochemical mechanisms by which insulin influences breast cancer progression provide some novel approaches to chemotherapy. This prospective study was designed to examine the association of the level of insulin with haemoglobin, as this association may increases the risk of diabetes in breast cancer women.

PATIENTS AND METHODS

Fifty breast cancer women with age range 35 to 50 years were taken from the Oncology Department of local hospital Lahore. Duration of study was two months from March to May 2014. Twenty age-matched control subjects with no history of any disease were taken as controls. Data based on age, BMI and family history were collected. Diabetic breast cancer women and women with family history of diabetes were excluded from all patients. Level of haemoglobin was determined by analyzer. Serum insulin level was estimated by ELIZA technique. Homeostasis model assessment (HOMA)-insulin resistance index was calculated.[17]

RESULTS

Demographic characteristics and variation in the level of haemoglobin and insulin in breast cancer women and controls were noted (Table-1). Mean age of patients and control was 40 years. BMI of the patients was non-significantly increased compared to BMI of controls. Level of haemoglobin was non-significantly decreased in patients compared to controls. On the other hand level of serum insulin was non-significantly increased in patients compared to controls. Increased insulin resistance was observed in patients when compared with control subjects.

Table-1: Demographic characteristics and variation in haemoglobin level and insulin in breast cancer patients and controls

Variables	Patients	Control
Age	40.2±7.8	40±4.3
BMI (Kg/m^2)	28.5±2.5	23.4±2.1
Haemoglobin (gm/dl)	10.12±1.8	12.1±2.1
Serum Insulin (µUI /l)	8.09±6.29	5.19±5.66
Insulin Resistance	2.8	1.03

DISCUSSION

In the present study, mean age of patients was 40 years. Another study[4] reported that increase insulin levels are common in every age group. They found that high insulin level in breast cancer and other women is due to sedentary life style.[4]

We observed that BMI of the patients was non-significantly increased compared to BMI of control subjects. Data of van Kruijsdijk RC *et al*[18] indicate that increase BMI appears to affect pancreatic response to a glucose stimulus. Mulcahy N[19] found that insulin resistance also increases BMI.

Decreased level of haemoglobin is a good indicator of iron deficiency which was observed in our study. According to a study iron deficiency may be related to the insulin action and associated with increased risk of diabetes.[13] Another study proposed that iron deficiency stabilizes hypoxia and causes angiogenesis which is important for the growth of tumour and its progression.[11]

The present study observed hyperinsulinemia in breast cancer women. A study found that women with the highest insulin levels had 1.5-fold higher risk of developing breast cancer than women with the lowest insulin levels.[20] The insulin-cancer hypothesis suggests that chronic hyperinsulinemia leads to decreased level of insulin-like growth factor (IGF) binding proteins, leading to increased tissue level of IGF-I which plays a major role in the development and progression of cancers. Additionally increased endogenous insulin levels have been related with a worse prognosis for breast cancer patients.[21]

We observed an increased insulin resistance in patients when compared with control subjects. According to a study hyperinsulinemia with insulin resistance also has been postulated to increase the risk of breast cancer.[1,22] Insulin resistance may promote cancer risk via decreased sex-hormone binding globulins leading to excess oestrogen and stimulation of oestrogen-dependent tumours or inflammation.[19] High fasting serum insulin levels and indices of insulin resistance were associated with a poor prognosis in women with early breast cancer.[23] It is proposed that when insulin resistance with hyperinsulinemia is present, the ability for stimulation of the PI3K pathway by insulin is lost, but insulin-induced prenylation of Ras protein is increased.[24]

CONCLUSION

Insulin resistance may be responsible for hyper-insulinemia which in turn increases the risk of diabetes in breast cancer. Future research is needed to clarify the underlying mechanism.

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