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Original Article

Insulin Resistance and Breast Cancer in Postmenopausal Women

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Abstract

The incidence of breast cancer is increasing in the developing countries due to various preventable risk factors like sedentary life style, higher fat diets and higher body mass index. A major metabolic consequence of these risk factors is the development of insulin resistance. Several studies have demonstrated that insulin may have a role in breast cancer but the results have been inconsistent. Therefore the present study was undertaken to compare serum insulin and insulin resistance in 28 postmenopausal women with breast carcinoma and healthy age matched controls. Fasting plasma glucose level and fasting serum insulin was measured. Insulin resistance was calculated by homeostasis model assessment-insulin resistance (HOMA-IR) method. Based on the descriptive and inferential statistical analysis, there was a significant increase in fasting plasma glucose ($p<0.001$) and serum insulin resistance ($p=0.027$) in cases when compared to controls and insulin levels showed a trend towards increase ($p=0.070$) in the cases compared to controls. Therefore plasma glucose, serum insulin and insulin resistance may have a role in breast carcinogenesis. These findings may provide the basis for insulin related factors to serve as potential targets for breast cancer prevention and risk assessment.

Introduction

Cancer is the leading cause of death worldwide and is the second important cause of death in developing countries (1). In India, breast cancer is the most common cancer of urban women and the second most common cancer of the rural women (2). As India is stepping towards urbanization, leading to life style changes, the number of breast cancer cases in India would also increase (3). While the increasing rates can be attributed to modern family planning practices (maternal age at first child and breastfeeding) and westernized lifestyle (sedentary life, fat diets, higher body mass index) partially, specific etiological factors need to be identified and validated in Indian women (4). Metabolic syndrome and its consequent biochemical derangements may contribute to carcinogenesis. Development of insulin resistance is one of the important metabolic consequences of these life style changes (5). Insulin resistance is a condition where, glucose is not efficiently utilised by peripheral tissues in spite of

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normal insulin levels, especially in the muscle and/or liver cells, leading to hyperinsulinemia (6). Insulin resistance (IR) is strongly associated with obesity (7), but relationship between insulin and breast cancer has been noted in non obese women also (8). Most of the studies (9, 10) are done in diabetic patients but insulin resistance occurs even before patients become frank diabetics. Several studies (11, 12, 13) have demonstrated that insulin and the insulin receptors may have a role in breast cancer but the results have been inconsistent. Studies have included women who were either obese or who were using hormone therapy. Oestrogen levels are also known to be one of the risk factors for breast cancer. Thus our study includes postmenopausal women who are non diabetic, non obese and those who are not taking any hormone therapy. The present study was undertaken to compare serum insulin and insulin resistance in postmenopausal women with breast carcinoma and healthy subjects. This association of insulin resistance and breast cancer would provide insight on the role of insulin in carcinogenesis and may aid in prevention and treatment of breast cancer.

Materials and Methods

The study population included 56 postmenopausal women aged between 40 to 80 yrs from M.S. Ramaiah Teaching and Memorial hospitals, Bangalore. Patients who were diagnosed with breast cancer on the basis of FNAC or biopsy report (14) were selected as cases. The control group included healthy subjects from normal population. The subjects with history of diabetes mellitus, fasting blood sugar (FBS) >126 mg %, hormone replacement therapy, any thyroid abnormalities, any treatment for the breast cancer, chronic liver disease, multiple endocrine neoplasia syndrome, cachexia and malignancies other than breast cancer were excluded.

An informed consent was obtained and there were no financial liabilities on the subjects. Ethical clearance was obtained from ethical committee of M. S. Ramaiah medical college, Bangalore.

A detailed history was taken. Blood pressure, body weight, height, waist circumference and hip circumference were measured. BMI and waist hip ratio were calculated. Systemic examination was done. All the details were recorded manually. Subjects were screened for general physical health to rule out any clinical disorder likely to interfere with the study findings. 5 ml of venous blood was collected after 12 hours overnight fast between 7 pm to 9 am. After centrifugation, the serum was stored at –20°C in Ependorf tubes till the analysis was conducted. Fasting plasma glucose level was measured by glucose oxidase peroxidase method using glucose auto analyser. Fasting serum insulin was measured by ELISA technique under standard laboratory conditions. Insulin resistance was calculated by homeostasis model assessment-insulin resistance (HOMA-IR) method. Homeostatic model assessment (HOMA) is a method for assessing β-cell function and insulin resistance (IR) from basal (fasting) glucose and insulin or C-peptide concentrations. HOMA is one of a family of “paradigm models.” Paradigm models are physiologically based structural models with theoretical solutions adjusted to the population norms. The relationship between glucose and insulin in the basal state reflects the balance between hepatic glucose output and insulin secretion, which is maintained by a feedback loop between the liver and β-cells. The output of the model is calibrated to give normal β-cells function of 100% and normal IR of 1. Once this interrelationship is calculated, one can estimate β-cells function and IR for any pair of plasma glucose and insulin concentrations without having to refit the model (15). The equation used for IR is:

HOMA-IR = [fasting plasma insulin concentration (mU/l) × fasting plasma glucose (mmol/l)]/22.5 (16).

Descriptive and inferential statistical analysis has been carried out in the present study. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters.

Results

The variables like age, height, weight, BMI, waist circumference, hip circumference and waist to hip ratio of the cases and controls did not differ

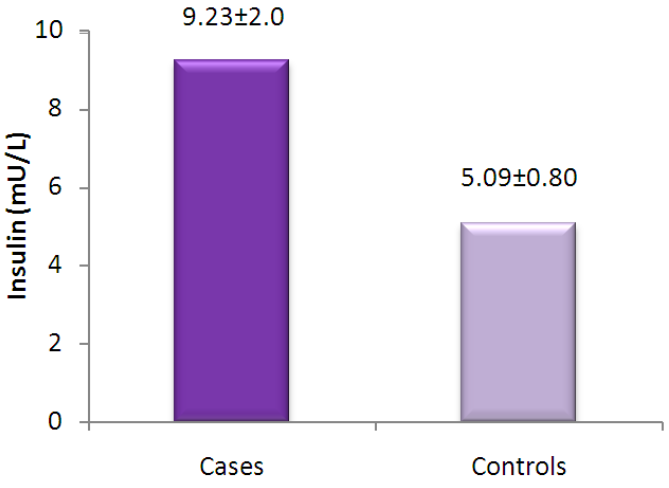
TABLE I : Comparison of Study variables between Cases and Control in Postmenopausal women.

Variables	*Cases (n=28)*	*Controls (n=28)*	*P value*
Age in years	62.75±6.95	61.32±5.65	0.402
Duration in months	7.98±6.93	–	–
Height (cm)	1.54±0.04	1.56±0.05	0.043*
Weight (kg)	62.36±11.05	62.93±8.25	0.827
BMI (kg/m^2)	26.36±4.01	25.89±3.35	0.635
Waist circumference (cm)	83.14±7.91	81.61±8.87	0.497
Hip circumference (cm)	99.5±11.36	96.61±12.31	0.365
Waist to hip ratio	0.84±0.05	0.85±0.05	0.443
Insulin (mU/L)#	9.23±2.09	5.09±0.80	0.070+
FBS mmol/l	5.81±0.61	4.92±0.36	<0.001**
Insulin resistance#	2.37±0.53	1.11±0.17	0.027*

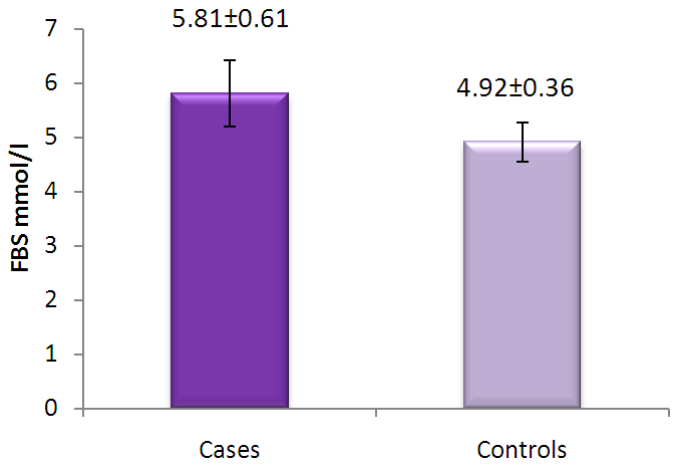
#presented as Mean±SE otherwise as presented Mean±SD.

+Suggestive significance (P value: 0.05<P<0.10)* Moderately significant (P value:0.01<P≤0.05)** Strongly significant (P value : P≤0.01)

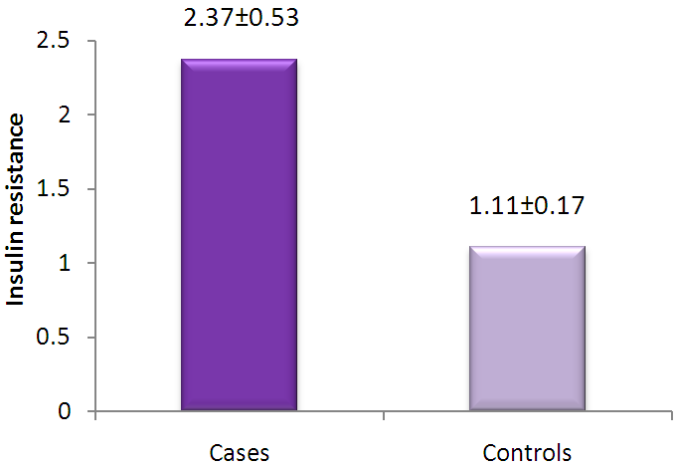
significantly between the cases and controls (p>0.05) (Table I). Serum insulin levels were 9.23±2.09 mU/L (mean±SE) and 5.09±0.80 mU/L (mean±SE) in the cases and controls respectively (Graph 1). The Fasting plasma glucose in the cases and controls was 5.81±0.61 mmol/L (mean±SD) and 4.92±0.36 (mean±SD) respectively which was highly significant (p<0.001**) (Graph 2). The insulin resistance were 2.37±0.53 (mean±SE) and 1.11±0.17 (mean±SE) in the cases and controls respectively which was statistically significant (p = 0.027*) (Graph 3) (Table I).



Graph 1 : Comparison of mean values of insulin between cases and controls.



Graph 2 : Comparison of mean values of fasting blood sugar(FBS) between cases and controls.



Graph 3 : Comparison of mean values of insulin resistance between cases and controls.

Discussion

The present study showed a significant increase in serum insulin resistance (p=0.027) in cases when compared to controls and insulin levels showed a trend towards increase (p=0.070) in the cases compared to controls. Increased insulin resistance is found to be a risk factor to breast cancer. To overcome insulin resistance, insulin secretion increases leading to compensatory hyperinsulinaemia (17).

Cancer is a multifactorial disease, with genetic, environmental and metabolic derangements contributing to carcinogenesis. One of the distinguishing feature of cancer cells is unchecked

replication and immortality. Growth factors play a vital role in the initial development and progression of cancer (12, 18). IGF-I (insulin-like growth factors) exhibits mitogenic and antiapoptotic effects. Most of the IGF-I in the circulation is produced by the liver and is bound to insulin-like growth factor binding proteins (IGFBPs). High levels of circulating insulin decreases levels of insulin like growth factor binding protein, thus increasing the IGF-1. Compensatory hyperinsulinemia due to insulin resistance could induce growth directly or indirectly by increasing the levels of other more potent growth factors (IGF) or it can make cells more sensitive to other growth factors (19, 20, 21). So increased insulin levels and insulin resistance may play a role in the development and progression of breast cancer.

In the present study, fasting plasma glucose in the breast cancer cases was significantly increased ($p<0.001$) compared to controls. This increased level of glucose due to insulin resistance may also play a role in the development of breast cancer by aiding the “selection” of malignant cell clones (22). This finding is in agreement with that of Muti et al who concluded that chronic alteration of glucose metabolism is related to breast cancer development in the year 2002 (22). Cancer cells have been shown to extensively use glucose for proliferation (23). Fasting glucose levels depends on the hepatic gluconeogenesis. Apart from reduction in insulin secretion or insulin sensitivity, which cause increased glucose production and decrease glucose utilization (24), gluconeogenesis is stimulated by counter-regulatory hormones such as adrenal hormones, epinephrine, and cortisol, and by androgens and growth hormones (25, 26). These hormones are determinants of morning fasting glucose, and additional studies are needed to clarify the potential etiological role of these hormones in breast cancer.

In the present study no significant correlation was found between insulin resistance and age, duration of the disease, BMI, waist circumference and waist hip ratio in the breast cancer group. Therefore there is no association between insulin resistance and age, duration of the disease and anthropometric parameters.

Gunter MJ et al have found strong positive association between the risk of breast cancer and fasting insulin levels in non diabetic postmenopausal women (27).

The present study shows that breast cancer patients have significant increase in fasting plasma glucose, serum insulin and insulin resistance compared to controls. Therefore plasma glucose, serum insulin and insulin resistance may have a role in breast carcinogenesis. These findings may provide the basis for insulin related factors to serve as potential targets for breast cancer prevention and risk assessment. Healthy lifestyle may reduce the risk of breast cancer by modifying the risk factors. Since it was a cross sectional study, causal relationship between serum insulin, insulin resistance and breast cancer could not be found which is a limitation of the study. Additional studies are needed to clarify the exact role of glucose metabolism pathways and insulin in breast cancer development.

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