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ORIGINAL ARTICLE

Evaluation of diagnostic and predictive value of serum adipokines: Leptin, resistin and visfatin in postmenopausal breast cancer

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Summary Obesity is a well-known risk factor for cancer. The associations of obesity with postmenopausal breast cancer (PBC) have been previously proven in clinical studies. The mechanisms underlying these associations remain unexplained completely, however, adipose tissue as an endocrine organ producing adipokines may interfere with cancer development. The aim of this study is to investigate the diagnostic and predictive value of serum levels of leptin, resistin and visfatin with inflammatory and tumour markers in relation to anthropometrics, clinicopathological features of PBC. This study included 298 postmenopausal Saudi females categorised into three groups. One hundred and ten BC patients with age matched, 89 healthy control (HC) and 99 females with benign breast lesion (BBL). For all subjects CA15-3, hsCRP, resistin, visfatin and leptin were measured by ELISA. Serum levels of leptin, resistin and visfatin were significantly higher in BC compared to BBL and HC groups ($p < 0.05$). Their levels were also significantly higher in advanced TNM stage, tumour size, LN invasion, histological grade and negative ER or PR cases. The most significant predictor of leptin level was ER ($p < 0.05$). While for resistin and visfatin level the most significant independent predictor was LN invasion. ROC analysis for serum leptin revealed AUC = 0.795; 95% CI, 0.724—0.866. Resistin showed AUC = 0.875; 95% CI, 0.821—0.928. Meanwhile, visfatin greater than 12.2 ng/mL demonstrated a sensitivity and specificity of 97.6% and 92.6%, respectively and AUC = 0.724; 95% CI, 0.643—0.804. In conclusion serum leptin, resistin,

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and visfatin levels could be considered of potential diagnostic value for PBC and they would be independent predictors of LN invasion and ER negative PBC cases.

Introduction

Breast cancer (BC) is the second most common cancer worldwide and the most common neoplasia among women [1]. Obesity is a well-known risk factor for BC, and obese women are likely to have metastatic BC and poor prognosis [2]. Risk factors associated with BC death worldwide included overweight/obesity and physical inactivity [3]. Interestingly association between obesity and the risk of BC differed according to menopausal status [4—7]. Obesity-induced breast carcinogenesis may be correlated to adipokines produced by adipose tissue, oestrogens, insulin and insulin-like growth factors. All are believed to be involved in mammary tumorigenesis [8,9].

Adipokines, as leptin, visfatin and resistin are produced by different fat depots, including subcutaneous, visceral and mammary adipose tissues and they may act on breast tissue in an endocrine, paracrine and autocrine manner [10,11]. Leptin has been proposed to play a role in hormone-dependent malignancies, such as breast and endometrial cancers, by activating the enzyme aromatase [12]. Leptin gene was found to be expressed in normal breast epithelium, in BC cell lines as well as in solid tumours. Leptin was found to be over-expressed in the majority of BC cases [13]. Some authors found that serum leptin was associated with BC regardless of the menopausal status, while others described a negative correlation between leptin and BC in the premenopausal, and a positive correlation in postmenopausal women [4]. Regarding visfatin, it was also found to be significantly elevated in patients with PBC [14,15].

Elevated visfatin expression in BC tissues was reported to be associated with more aggressive cancer behaviour, poor survival as well as adverse prognosis [16]. Resistin is synthesised in cells other than adipocytes, predominantly in macrophages and monocytes particularly in the visceral adipose tissue characterised by a high metabolic turnover [17]. Elevated resistin levels caused by genetic or environmental factors such as obesity, inflammation and diet may play a pivotal role in the pathogenesis of insulin resistance, metabolic syndrome, type 2 diabetes, atherosclerosis, hypertension, cardiovascular disease and several malignancies such as breast, gastric, colorectal and oesophageal cancers [18]. High level of resistin was reported to be associated with the risk of BC [19—21], wherein this relationship was independent of age, BMI, status of menopause [22]. Our team have reported that serum resistin, leptin, and visfatin levels as risk factors for PBC may provide a potential link with clinicopathological features and they are promising to be novel biomarkers for postmenopausal BC [4]. Our aim in this study is to investigate the interrelationship, diagnostic and predictive value of serum levels of leptin, resistin and visfatin with inflammatory and tumour markers in relation to anthropometrics, clinicopathological features of BC as a novel biomarkers emphasising their interrelationship and role on PBC patients.

Subjects and methods

Study populations

Two hundred and ninety-eight postmenopausal Saudi female subjects were enrolled in our study. Studied subjects were considered at postmenopausal state at the time of blood collection if they had no menstrual cycles in the last 12 months, or reported a bilateral oophorectomy. Serum follicule-stimulating hormone (FSH) was used to confirm the postmenopausal status. Postmenopausal women with FSH levels $\geq$ 40 IU/L were included in the study [14]. Others who were not fulfilling these criteria were excluded. Study populations comprised BC patients group, who were recruited from King Abdulla Medical City and El-Noor hospital (Makkah, KSA) during the period from April 2010 until September 2014. BC patients were newly diagnosed and histopathologically-confirmed BC with no prior surgical, chemotherapy or radiotherapy BC treatment so that any influence of treatment was unlikely. Benign breast lesion (BBL) group and postmenopausal healthy control (HC) group were age matched with BC group and any query or suspected case was confirmed to have a