ARTIGO ORIGINAL

Association of metabolic alterations with prognostic factors in malignant breast neoplasms

Associação de alterações metabólicas com fatores prognósticos em neoplasias malignas de mama

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Keywords

Breast neoplasms

Metabolic diseases

Prognosis

Cholesterol

Triglycerides

ABSTRACT

Objectives: There are few studies in the literature correlating metabolic alterations with prognostic factors in breast cancer. The aims of this study were to evaluate serum levels of total cholesterol, HDL, LDL, triglycerides and fasting glucose, weight, body mass index and blood pressure, and relate them to prognostic factors (stage, lymph node involvement, histological grade, estrogen and progesterone receptors, ki-67 and Her2/neu) in patients with breast cancer. **Methods:** A retrospective study was conducted in Mastology Service of the Discipline of Gynecology and Obstetrics/Oncologycal Research Institute (IPON) of the Universidade Federal do Triângulo Mineiro (UFTM). We evaluated 100 patients with breast cancer treated at Mastology Clinic (surgical and/or clinical treatment). Serum levels of total cholesterol, HDL, LDL, triglycerides and fasting glucose, weight, body mass index, blood pressure, staging, lymph node involvement, histological grade and immunohistochemical panel (estrogen and progesterone receptors, ki-67 and HER-2/neu) were recorded. Data were expressed as the mean ± standard deviation, and the values were compared by using Student's t-test. P-values less than 0.05 were considered statistically significant. **Results:** Histological grades 1 and 2 were significantly correlated with higher HDL serum levels (p=0.02). Higher levels of triglycerides were found more frequently in grade 3, and highest weight was related to Ki-67 positive, but only with a trend towards significance (p=0.07). **Conclusion:** HDL can be related to prognosis in breast cancer.

Descritores

Neoplasias da mama

Doenças metabólicas

Prognóstico

Colesterol

Triglicerídeos

RESUMO

Objetivos: *Há poucos estudos na literatura relacionando alterações metabólicas com fatores prognósticos em câncer de mama. Os objetivos desse estudo foram avaliar os níveis séricos de colesterol total, HDL, LDL, triglicérides e glicemia de jejum, peso, índice de massa corporal e pressão arterial, e relacioná-los com fatores prognósticos (estadiamento, envolvimento linfonodal, grau histológico, receptores de estrógeno e progesterona, ki-67 e Her2/neu) em pacientes com câncer de mama.* ***Métodos:*** *Um estudo*

*retrospectivo foi realizado no Serviço de Mastologia da Disciplina de Ginecologia e Obstetrícia e Instituto de Pesquisa em Oncologia (IPON) da Universidade Federal do Triângulo Mineiro (UFTM). Nós avaliamos 100 pacientes com câncer de mama tratadas no Serviço de Mastologia (tratamento clínico e/ou cirúrgico). Níveis séricos de colesterol total, HDL, LDL, triglicérides e glicemia de jejum, peso, índice de massa corporal, pressão arterial, estadiamento, envolvimento linfonodal, grau histológico e painel imuno-histoquímico (receptores de estrógeno e progesterona, ki-67 e Her2/neu) foram registrados. Dados foram expressos em média ± desvio padrão, e os valores foram comparados utilizando-se o test t de Student. Valores de p menores que 0,05 foram considerados estatisticamente significativos. **Resultados:** Graus histológicos 1 e 2 foram relacionados significativamente com níveis séricos mais altos de HDL (p=0,02). Níveis mais elevados de triglicérides foram encontrados mais frequentemente em tumores grau 3, e peso mais alto foi relacionado com positividade de Ki-67, mas apenas com tendência à significância (p=0,07). **Conclusão:** Níveis séricos de HDL podem estar relacionados ao prognóstico em neoplasia maligna de mama.*

Introduction

Recent studies have shown a significant association between metabolic syndrome and breast cancer[1]. Moreover, inflammatory and metabolic mechanisms can be related to breast cancer. New adequate and specific biomarkers that prove the relationship between these mechanisms and the prognosis of breast cancer could help in choosing the best adjuvant therapy. Low serum levels of HDL cholesterol, increased fasting glucose and triglycerides, weight gain after menopause, abdominal obesity, hypertension, high dosage of insulin-like growth factor insulin in the blood and other determinants metabolic syndrome appear to be associated with increased risk of developing breast cancer. Still, metabolic and hormonal parameters related to metabolic syndrome appear to directly affect the prognosis of these patients[1-3].

The metabolic syndrome is associated with increased risk of developing cardiovascular disease and diabetes mellitus. Environmental factors, especially abdominal obesity and physical inactivity, are widely implicated, but some individuals are genetically predisposed to insulin resistance. Women treated for breast cancer appear to be at additional risk of metabolic syndrome resulting from excess adiposity and the effect of treatments. The association of lipid accumulation with aggressive behavior was demonstrated in an estrogen receptor negative cancer cell line[4]. Differences in lipid uptake and storage capability may explain the differential effect of a low-fat diet on human breast cancer recurrence. Exogenous cholesterol can confers a proliferative advantage to basal-like breast cancer cells[5].

Malignant neoplasm of breast is the most common cancer in women. The presence of subclinical chronic inflammation and insulin resistance associated with obesity alter the regulation of liponeogenesis in humans, and BRCA1 expression may be involved in this process. Metabolic disorders are very prevalent in the population. The discovery of new prognostic factors

in breast cancer-related metabolic changes could have an impact on follow-up of patients with this disease[3].

There are few studies in the literature correlating clinical and laboratory parameters related to metabolic syndrome with prognostic factors in breast cancer. The hypothesis of this study is the presence of relationship between clinical and pathological factors of poor prognosis with the presence of alterations in the metabolic balance.

Objectives

The aims of this study were to evaluate serum levels of total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides and fasting glucose, weight, body mass index (BMI) and blood pressure, and relate them to prognostic factors (stage, lymph node involvement, histological grade, estrogen and progesterone receptors, ki-67 and Her2/neu) in patients with breast cancer.

Methods

A retrospective study was conducted in Mastology Service of the Discipline of Gynecology and Obstetrics of Oncologycal Research Institute (IPON) of the Universidade Federal do Triângulo Mineiro (UFTM). We evaluated 100 patients treated at Mastology Clinic with confirmed histologic diagnosis of breast cancer. Surgical and clinical treatments have been conducted. The pathological paraffin and immunohistochemical panel (estrogen and progesterone receptors, ki-67 and Her2/neu) were performed by experienced pathologists of Special Pathology Discipline of the UFTM. The study was reviewed and approved by the Ethics Committee of the UFTM.

Immunohistochemistry was considered positive for Her2/neu when the immunostaining was 3+. Ki-67 index was considered

positive when greater than or equal to 14% of neoplastic cells were immunostained.

Serum levels of total cholesterol, HDL, LDL, triglycerides and fasting glucose, weight, BMI, blood pressure, staging, lymph node involvement, histological grade and immunohistochemical panel (estrogen and progesterone receptors, ki-67 and HER-2/neu) were recorded.

GraphPad InStat software (GraphPad, San Diego, CA, USA) was utilized. According to the distribution (Kolmogorov-Smirnov test), data were expressed as the mean ± standard deviation (SD), and the values were compared by using Student's t-test. P-values less than 0.05 were considered statistically significant.

Results

Mean weight was 66.9±13.67 kg. Mean height was 1.57±0.07 m. Mean cholesterol, LDL, HDL, triglycerides and fasting glucose were respectively 205.13±47.15 mg/dL, 125.13±42.45 mg/dL, 50.67±14.48 mg/dL, 158.93±77.95 mg/dL and 99.58±37.52 mg/dL.

Table 1 shows the metabolic parameters related to clinical and pathological prognostic factors. Histological grades 1 and 2 were significantly correlated with higher HDL serum levels (p=0.02), compared with grade 3. Higher levels of triglycerides were found more frequently in grade 3, and highest weight was related to Ki-67 positive, but only with a trend towards significance (p=0.07). There was no statistical significance in relation to

other parameters, or in relation to systolic and diastolic pressure (data not shown in Table 1).

Discussion

There is an increase in senescent population in the Western world, and an increase in the number of people with chronic diseases. The most common comorbidity among these is diabetes mellitus, which can also be a possible risk factor for breast cancer and prognostic factor. One study showed that patients with diabetes and breast cancer with negative estrogen receptor had more than 2-fold higher risk for distant metastasis than patients without diabetes. Diabetes has also been associated with an almost 2-fold increase in mortality within five years follow-up period[6]. The presence of the metabolic syndrome can be considered an important prognostic factor for recurrence of breast cancer[2].

An association of low plasma HDL-cholesterol with risk of breast cancer has been demonstrated[7]. Studies suggest that patients with breast cancer are exposed to oxidative stress conditions caused by excess generation of reactive oxygen species and reduced antioxidant levels in target cells and tissues, and it is closely related to all aspects of cancer treatment carcinogenesis and prevention. Reactive oxygen species are able to change all major classes of biomolecules such as lipids, proteins and nucleic

Table 1. Metabolic parameters related to clinical and pathological prognostic factors in patients with breast cancer (n=100)

	Weight Mean±SD	BMI Mean±SD	Fasting glucose Mean±SD	Cholesterol Mean±SD	HDL Mean±SD	LDL Mean±SD	Triglycerides Mean±SD
Grade							
1 / 2	66.5±13.2	27.5±4.9	100.5±41.1	209.1±48.8	52.7±14.3*	127.3±44.5	150.1±73.4**
3	68.4±15.3	28.3±5.2	96.1±17.2	187.9±36.2	39.2±9.8	112.9±27.4	206.5±90.5
Stage							
0-II	67.8±13.6	27.9±5	102.2±41.1	205.9±48.5	48.8±13	127.1±44.2	162.5±78.6
III / IV	62.8±13.3	26.2±4.5	88.7±12.3	200.5±40.9	60.8±18.9	115.7±33.3	142.5±77.4
Lymph nodes							
Negative	67.6±13.4	27.8±4.9	101.3±44.2	210.4±49.3	51.6±15.9	129.4±44.1	159.8±69.2
Positive	65.3±14.1	27.2±4.8	96±17.1	189.2±37.2	47.8±9.1	114.2±37.1	156.3±101.8
ER							
Negative	68.3±13.6	39.5±3.1	90.6±11.5	204.9±46.6	52.1±11	128.8±37.1	149.2±44.5
Positive	66.3±13.7	39.7±4.2	103.5±44	205.1±47.9	50.2±15.5	124.1±44.2	162.1±86.3
PR							
Negative	66.1±13.9	27.4±4.9	99.3±41.3	202.2±42.4	50.4±15.5	125.6±35.6	149.6±69.5
Positive	68.1±13.3	27.9±4.9	100.6±31.1	208.5±53	51±13.4	124.5±50.2	170.5±87.7
Ki-67							
Negative	64.4±12.7***	27.2±4.7	94.8±24.2	214.6±50.9	53.5±17.2	136.5±43.1	145.4±60
Positive	69.4±14.3	28.1±5.1	105.3±48,8	198.3±44.9	42.5±11.1	113.7±40.3	170.7±92.4
Her2-neu							
Negative	67.3±14.1	27.7±5.1	95±20.2	207.6±50	51±14.9	127.8±45	160.2±78.3
Positive	64.1±10.1	26.9±4	127.5±84.1	192.3±27.6	49±12.4	110.2±18.9	152.8±81

ER: Estrogen Receptor. PR: Progesterone Receptor. *p=0.02 compared to grade 3; **p=0.07 compared to grade 3; ***p=0.07 compared to positive Ki-67.

acids. These changes may not only change the structure of these molecules but also can change the function. Moreover, there is an increasing evidence for an involvement of lipids, lipid metabolism and lipid peroxidation in the development of breast cancer[8,9].

Another study examined laboratory parameters in premenopausal women with a family history of breast cancer, and demonstrated significant increase in fasting and postprandial glucose, in fasting and postprandial insulin, insulin resistance and serum triglycerides, when compared with women with no family history of breast cancer. So, there may be an association between family history of breast cancer and insulin resistance syndrome. The study also showed a significant decrease in HDL among women with a family history of breast cancer[10]. Studies have shown that HDL changes that may occur in patients with breast cancer can accelerate metastasis and progression of breast cancer. These results suggest an additional route for the search for therapeutic strategies for patients with breast cancer based on the oxidized HDL adverse effects on the breast cancer metastasis, which is the leading cause of increased mortality. Changes in HDL (such as glycation, oxidation, diabetic HDL) can lead to accelerated progression, proliferation, migration and invasion of breast cancer[8,9].

In our study, higher HDL levels significantly related with well and moderately-differentiated tumors. This result may reflect a better prognosis in patients with a better lipid profile. Moreover, high serum levels of triglycerides were related to higher histological tumor grade, therefore reflecting a worse prognosis. However, there was only a tendency to statistical significance, perhaps because of small sample size.

A randomized study selected women for ten years, grouping them into two groups: usual diet and diet with reduction of lipids, demonstrating that small reductions in lipid consumption reduced serum concentrations of estradiol, estradiol binding globulin, estrone, and estrone sulfate in the follicular phase, and increased testosterone in the luteal phase of the menstrual cycle. These results indicate that small reductions in the consumption of lipids in adolescence reduce hormone levels related to increased risk for breast cancer[11].

In a study performed in Norway, there were evaluated 1,364 women with breast cancer. Women with a BMI 30 kg/m² had higher mortality compared with women with a BMI between 18.5 and 25 kg/m². Among women with a BMI up to 25 kg/m², improved survival was observed in those who regularly engaged in physical activity compared to sedentary women[12]. A cohort study showed that menopausal women with metabolic syndrome have higher risk of breast cancer. Obesity is a known risk factor for breast cancer recurrence and metastasis, both before and after menopause[3]. In our study, Ki67 positivity was related to greater weight, indicating a worse prognosis, but there was only a tendency to statistical significance, perhaps because of small sample size. The positivity

for estrogen receptors, progesterone and HER2 showed no relevance in the present study.

A prospective study demonstrated the importance of serum LDL in patients with breast cancer as a prognostic factor. Thus, the metabolism of cholesterol can be an important therapeutic target for patients with breast cancer. LDL serum levels above 117 mg/dL were associated with a worse prognosis characteristics, such as high histological grade, higher proliferative rate and more advanced clinical stage. Patients with LDL cholesterol >144 mg/dL were also more likely to have lymph node metastasis. In addition, there was a relationship of elevated serum LDL with Her2/neu (ErbB2) positive[13]. Simvastatin can modulate estrone sulfate concentrations, and new investigations could show a potential chemopreventive activity in breast cancer[14,15].

One limitation of this study is the small sample size. However, it was able to demonstrate the relationship between HDL levels with the degree of tumor differentiation, and may be targeted by new future studies.

Conclusion

Serum levels of HDL, triglycerides and weight may be related to prognosis in malignant neoplasm of the breast. To our knowledge, this is the first study in the literature that found a positive relation between high levels of HDL and lower tumor grade. Further studies with a larger number of patients are required to elucidate the role of metabolic disorders and prognosis in patients with breast cancer, which may be new target for these disease management strategies.

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