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Original article

A comprehensive metabolic evaluation reveals impaired glucose metabolism and dyslipidemia in breast cancer patients early in the disease trajectory☆

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SUMMARY

Background & aims: Weight gain in breast cancer patients during treatment is prevalent; the metabolic implications of this weight gain are poorly understood. We aimed to characterize glucose metabolism in breast cancer patients near the initiation of chemotherapy.

Methods: Stage I–II breast cancer patients ($n = 8$) were evaluated near the initiation of chemotherapy and compared with a group of age- and body mass index-matched, as well as a group of young healthy, non-malignant females. Fasting blood samples (analyzed for lipids and cytokines) were taken and an oral glucose tolerance test was performed. Body composition, waist circumference, diet, cardiovascular fitness and muscle strength were evaluated.

Results: Breast cancer patients were abdominally obese (mean ± SD: 94.6 ± 14.0 cm), overweight (28.8 ± 6.0 kg/m^2) and dyslipidemic (triacylglycerides: 1.84 ± 1.17 mM; high-density lipoprotein cholesterol: 1.08 ± 0.23 mM). Compared to non-malignant matched females, fasting glucose and insulin concentrations were similar but fasting c-peptide was greater in patients (2.6 ± 1.2 ng/mL vs. 1.9 ± 0.8 ng/mL, $p = 0.005$). Glucose was elevated to a greater extent in patients during the oral glucose tolerance test compared with all non-malignant females. During the glucose tolerance test, c-peptide, but not insulin, remained elevated in patients compared with all non-malignant females. No differences in body composition, serum cytokines, nutrition or exercise capacity between patients and matched, non-malignant females emerged.

Conclusions: Breast cancer patients present with unhealthy metabolic features early in the disease trajectory. Future investigations need to examine the underlying mechanisms and the potential longitudinal changes following chemotherapy.

1. Introduction

Although breast cancer is the most prevalent form of cancer among Canadian females, 89% of patients achieve 5-year survival.[1] Breast cancer is associated with unhealthy body composition at diagnosis,[2] as well as weight gain and abdominal obesity[3] during treatment[4] and in survivorship,[5] which tend to lead to the development of secondary diseases, like diabetes and cardiovascular disease.[2]

The consequences of unhealthy body composition are well-described in non-malignant populations, where reduced energy expenditure due to decreased physical activity and excess energy

Abbreviations: BMI, body mass index; OGTT, oral glucose tolerance test; AUC, area under the curve; PAQ, physical activity questionnaire; NEFA, non-esterified fatty acid; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; TAG, triacylglycerol; TNF-α, tumor necrosis factor-α; IL, interleukin; CRP, c-reactive protein; EDTA, ethylenediaminetetraacetic acid; VO_{2peak}, peak oxygen uptake; IDF, International Diabetes Federation; NCEP-ATPIII, National Cholesterol Education Program – Third Adult Treatment Panel; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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intake due to overnutrition contribute to the development of high fat mass. Consequently, high fat mass is associated with glucose and lipid dysregulation,[6] as well as with increased systemic inflammation.[7] Pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α)[7] and interleukin-6 (IL-6),[7] have been shown to contribute to insulin resistance. When present in high concentrations, these cytokines may impede insulin signaling in skeletal muscle. These characteristics have been poorly described in breast cancer patients and tumor presence may further exacerbate the effects of systemic inflammation on glucose metabolism.

Epidemiological studies have related breast cancer incidence with metabolic disorders.[8,9] Few studies have critically examined fasting lipids and glucose metabolism during an oral glucose tolerance test (OGTT) in breast cancer populations.[10] Most studies have focused on fasting glucose or insulin concentrations in relation to breast cancer survivor outcomes.[11,12] However, impairments in glucose metabolism are often identified with a glucose challenge. Moreover, a comparison group is important in identifying whether systemic inflammation, as a consequence of current or recent tumor presence, associates with potential dyslipidemia or impaired glucose metabolism. Moreover, age[13] and body mass index (BMI)[14] should be controlled since they positively relate to impairments in glucose metabolism.

We studied glucose and lipid metabolism in breast cancer patients near the initiation of chemotherapy (prior to potential treatment-related changes in body composition). We aimed to: 1) comprehensively characterize glucose metabolism in breast cancer patients near the initiation of chemotherapy; and 2) compare patients to non-malignant females of similar age and BMI (HM females). Body composition, inflammation, nutrition and exercise capacity were also assessed to evaluate their role in metabolic syndrome, and specifically in potential glucose impairments of patients and HM females. Our secondary objective was to compare breast cancer patients and HM females to a reference group of non-malignant, healthy young females with normal BMIs (HY females) to measure the extent of potentially impaired glucose metabolism in the patient and matched female group. We hypothesized that breast cancer patients would demonstrate impairments in glucose metabolism, which would be worse in patients compared to HM and HY females. We further hypothesized that these impairments may be explained by the presence of inflammation, hypercaloric intakes and reduced physical activity.

2. Methods

2.1. General study design

This study involved 26 participants: 8 breast cancer patients, 8 HM females (who were individually age- and BMI- matched to each patient), and 10 HY females (who were 18–25 years old, had BMIs in the normal range and were recreationally active). All participants underwent 4 evaluations within a 1 week period: 1) blood sampling after an overnight fast (for glucose- and lipid-related parameters, as well as inflammatory markers) and during an OGTT to measure glucose-related markers; 2) body composition using skinfold and waist circumference measurements; 3) nutrition using 3-day food diaries; and 4) exercise capacity using a cardiovascular test, upper and lower body strength tests, and physical activity questionnaires (PAQs) (for evaluation of habitual activity). Blood sampling and body composition assessments were conducted on the same day following an overnight fast. Exercise assessments were conducted on a separate day, at least 48 h prior to or at least 24 h following the blood sampling and body composition assessment. No more than 1 week elapsed between these 2 assessment days. Participants completed the nutrition assessment at home, using a 3-day food record, during the same week as all other assessments. This study was reviewed and received ethics clearance by the University of Waterloo Office of Research Ethics (for all participants) and by the Tri-Hospital Research Ethics Board (for breast cancer patients).

2.2. Recruitment and screening of participants

Breast cancer patients were recruited from the Grand River Regional Cancer Center in Kitchener, Ontario. Potential patients were initially screened for eligibility by Clinical Trials staff at the Grand River Regional Cancer Center. Prior to consenting, eligibility was confirmed during a second comprehensive screening at the University of Waterloo (refer to Table 1 for eligibility criteria) where patients arrived at the laboratory after an overnight fast (no food or drink except water after midnight). Screening included a finger-prick test for fasting glucose (Aviva Accu-Check; Roche Diagnostics) to confirm that it was <7.0 mM for breast cancer patients (Table 1). Potential participants were also weighed and measured to determine BMI, and completed a Health Status Screening Form to

Table 1
Eligibility criteria for all participant groups.

	Breast cancer patients	HM	HY
Inclusion criteria			
Sex	• Female		
Age (years)	• ≥18	• Within ±3 years of matched patient	• 18–25
BMI (kg/m^2)		• Within ±2 kg/m^2 of matched patient	• 18.5–24.9
Clinical characteristics	• Recent diagnosis of breast cancer and up to 4 weeks following first cycle of chemotherapy • Clinical stages I–II		
Hormonal contraceptive and menstrual status		• Use/no use of hormonal contraception matched to patient; menopausal status also matched to patient	• Not currently using hormonal contraceptives and have not used hormonal contraceptives within the past 6 months
Physical activity levels			• Recreationally active 3–5 days per week
Fasting serum glucose (mM)	• <7.0	• <7.0	• <6.0
Exclusion criteria			
• Previous diagnosis of cancer in the last 5 years (other than carcinoma *in situ*)			
• Cardiovascular disease or thyroid disease that is not currently managed with medication			
• Diabetes or HIV			
• Injuries or health conditions that prevent participants' safe participation in exercise			