Serum Molecular Signatures of Weight Change during Early Breast Cancer Chemotherapy

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Abstract

Purpose: Weight gain in women receiving chemotherapy for breast cancer is associated with a higher risk of recurrence but its mechanisms are poorly understood.

Experimental Design: To investigate this, we assessed the metabolic, cytokine, and appetite-related peptide alterations during adjuvant chemotherapy for early breast cancer in postmenopausal women, and correlated these with body mass measurements. Specifically, we performed global metabolic profiling using 1H-nuclear magnetic resonance spectroscopy of sequential sera, examined ghrelin immunoreactivity, RIAs for GLP-1 and peptide YY, and electrochemiluminescent cytokine analyses (tumor necrosis factor-α and interleukin-6) on sequential samples.

Results: In those who gained >1.5 kg, several metabolite levels were positively associated with weight gain, specifically lactate, which was 63.5% greater in patients with increased body weight during chemotherapy compared with those with no weight gain (P < 0.01; the prespecified primary end point). A strong correlation (r = 0.7, P < 0.001) was detected between the rate of weight change and serum lactate levels, and on average, lactate levels exhibited the greatest metabolic response to chemotherapy, increasing by up to 75%. Normalized levels of peptide YY were also observed to be elevated in patients not gaining weight posttreatment (+30% compared with -7% for the weight gain group; P < 10^-4). Baseline lactate, alanine, and body fat were all prognostic for weight gain (area under the receiver operator characteristic curves, >0.77; P < 0.05). No associations were observed between any other parameter and weight gain, including cytokine levels.

Conclusions: Metabonomics identifies excess energy expenditure pathways perturbed during chemotherapy for breast cancer, and establishes a significant association between serum lactate, body fat, and substantive weight gain during chemotherapy.

Weight gain remains a common problem among patients with early breast cancer who receive chemotherapy (1, 2). However, three decades since the original reports (3–5), we are no closer to understanding the mechanisms involved, although its detrimental effects have been increasingly noted. Weight gain adversely affects quality of life, is “distressing,” and leads to cardiovascular disorders, hypertension, diabetes, and orthopedic problems, and interestingly, those individuals who gain the most weight seem to have an increased incidence of local and/or distant recurrence of breast cancer and possibly a decreased overall survival (6–9). In addition, there is strong evidence for reduced response to neoadjuvant chemotherapy and poorer survival in overweight and obese breast cancer patients (10). Despite this, most studies focus almost exclusively on the epidemiologic aspects of weight gain (6–8), whereas other research has detailed issues surrounding only cancer-related cachexia (for example, at our institution, we have performed a study infusing the appetite stimulant ghrelin in patients with...
Translational Relevance

Weight gain during breast cancer chemotherapy is a commonly reported problem, associated with early tumor relapse, decreased survival, and poor quality of life, but its mechanism has remained elusive. To investigate this, we have used the new technology of metabolomic profiling (metabolomics) along with measurement of cytokines and appetite stimulatory and inhibitory peptides in sequential samples from postmenopausal women receiving standard chemotherapy for early breast cancer. We found that a number of factors were associated with weight gain, including lactate and alanine levels which were prognostic. Several metabolites associated with excess energy expenditure were also positively associated with weight gain. These data establish a significant association between serum lactate, body fat, and substantive weight gain during chemotherapy. Our study provides further evidence that drug response could be predicted in the clinic using this approach, helping to target patients for intervention to reduce body fat and thereby potentially influencing prognosis.

Materials and Methods

Patients and sample collection. Serum samples were obtained from 21 postmenopausal women before and during chemotherapy for breast cancer in either the adjuvant or neoadjuvant settings. All patients received 5-fluorouracil–based (500 mg/m²), cyclophosphamide-based (500 mg/m²), and epirubicin-based (75 mg/m²) i.v. chemotherapy every 3 wk. Standard antiemetics with ondansetron and domperidone were administered.

In all cases, samples were obtained immediately prior to each three weekly cycles of chemotherapy (thus the baseline sample was taken at cycle 1, and the final sample 18 wk later at cycle 6). Venous blood (7.5 mL) was obtained at room temperature in standard serum bottles containing 100 μL of aprotinin (Trasylol, Bayer AG), a peptidase inhibitor. These were immediately centrifuged using a desktop machine in the clinic at 4°C, 12,000 × g for 10 min. The serum was then aliquoted into 2 mL Eppendorf tubes and immediately frozen in a -20°C freezer for 24 h prior to transfer to a -80°C freezer.

Patients’ weights were obtained using a Tanita BC-418 pro-segmental body fat analyzer, which was kindly loaned to us for this study (Tanita UK, Ltd.). This analyzer measures body composition with a validated four-compartment model as recently described (16). Height was measured to the nearest 5 mm using a wall-mounted stadiometer and the body mass index was calculated. Weight changes over the course of early chemotherapy of >1.5 kg were classified as the “gained weight group”, those with weight change of <1.5 kg as having “no gain” i.e., stable or decreasing weight. Appropriate ethical approval was obtained.

1H-Nuclear magnetic resonance spectroscopy of sera and spectral processing. Serum samples were defrosted at room temperature for no longer than 20 min and 200 μL aliquots combined with 400 μL of saline (0.9% NaCl in 10% D₂O/90% H₂O) were centrifuged at 12,000 × g for 5 min. A 550 μL aliquot of this solution was pipetted into a 5-mm nuclear magnetic resonance (NMR) tube and samples were frozen at -40°C until NMR analysis. 1H-NMR spectra for all serum samples were collected on a Bruker DRX600 spectrometer (Bruker Biospin), at a frequency of 600.29 MHz and temperature of 300 K. Samples were automatically inserted into a 5 mm TXI probe and gradient shimming was performed prior to the acquisition of each spectrum.

Multivariate pattern recognition (partial least squares-discriminant analysis). NMR spectra were divided into ∼0.01 ppm wide regions which were then integrated (“binning”). After removal of regions containing the residual water signal (4.18-5.2 ppm) and extremes of the spectrum (≤0 and ≥10 ppm) this produced a data table of 898 spectral variables. Partial least squares-discriminant analysis (PLS-DA) was conducted using SIMCA 11 (Umetrics) in which the single class variable was 1 if the sample was from a patient gaining weight or 0 for any other sample. Each variable was centered to a mean of 0 prior to analysis.

Cytokine and peptide measurements. Chrelin-like, GLP-1-like, and peptide YY (PYY)–like immunoreactivity was measured with specific and sensitive RIAs as we have previously established and described (17, 18).

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Cytokine levels were determined using a Human Pro-inflammatory 7-plex kit (Meso Scale Discovery). The method uses a sandwich immunoassay, whereby the cytokine binds to a capture antibody and is then labeled with an electrochemiluminescent compound (MSD SULFO-TAG). Cytokines were "activated" by adding 25 μL of human serum cytokine assay diluent to each well and allowed to incubate for 30 min at room temperature with shaking. Data acquisition and subsequent analysis used Meso Scale Discovery Workbench software.

Statistical analysis. All statistical analyses were conducted using SPSS v16. Unless stated otherwise, group means were compared by Dunnett's t test, and for serum molecules, all measurements for each individual were averaged prior to the calculation of group means and statistical analysis. Area under the receiver operator characteristic curves (ROC-AUC) were calculated for the average and initial (pretreatment) parameter values using membership of the weight gain group as the positive case.

Results

Weight and body fat changes during chemotherapy. Patients were assigned to groups depending on their weight change between the first (prechemotherapy) and last sample collected. Those individuals gaining ≥1.5 kg were categorized as "weight gain" individuals, the remainder were categorized as "no gain" individuals. According to these criteria, 10 of 21 patients (48%) gained weight, whereas 11 of 21 individuals (52%) exhibited stable or decreasing weight during their evaluation period.
(Supplementary Table S1). Initial group differences and changes during the study in terms of body weight, body mass index, and total body fat are summarized in Supplementary Table S2. On average, the weight gain group was 18.2% heavier at the start of the study with a higher percentage of body fat (+8.2%; \( P < 0.05 \)) compared with the no gain group. During treatment, this group showed a 4.8% (\( P < 0.001 \)) increase in body weight at an average rate of at least 0.1 kg/wk, and a 6.4% (\( P < 0.05 \)) increase in body fat relative to initial measurements (Fig. 1). The remaining patients lost an average of 1.7% weight and 5.4% (\( P < 0.05 \)) of their body fat during chemotherapy, all at an average rate of <0.1 kg/wk comparing baseline with final measurements.

**Determination of a metabolite signature associated with weight change.** Untargeted metabolic profiling of sera from all patients was conducted using \(^1\)H-NMR spectroscopy to establish which metabolic pathways were perturbed during chemotherapy. Visual comparison of the average spectra from the weight gain group with the average of the remaining spectra indicated that there were systematic differences in particular metabolites (Fig. 2A). To identify objectively which signals (resonances) were associated with weight change, we constructed a PLS-DA model of the NMR data trained to differentiate the weight gain group (Fig. 2B; \( Q^2 \) was 0.235 for a two-component model with 7-fold cross-validation; \( P < 0.002 \) by random permutation of the groups). The regression weights of the first model component indicated which spectral regions were responsible for this discrimination (Fig. 2C) and were tested for significance using a \( t \) test with the aim of defining a subset for univariate statistical analysis within the Gaussian distribution.

To minimize the selection of artificial signals, only where two neighboring spectral regions produced a significant (\( P < 0.01 \)) regression weight was a metabolite resonance considered for further analysis (i.e., expectation value of <1 false-positive selections). This procedure identified 70 spectral variables corresponding to \( \sim 20 \) resonances from up to 12 metabolites potentially associated with weight change during chemotherapy. One resonance was integrated for each metabolite and the average intensity values for all samples from each patient during treatment were subject to further analysis to determine the relationship between these metabolites and weight change (Table 1A).

Individual patient averages were subject to Dunnett’s test to compare weight gain and no gain groups (Table 1A), as well as adjuvant/neoadjuvant (tumor) groups (data not shown). In addition, the ROC-AUC for detection of the weight gain group was calculated. Of the metabolites tested, only lactate exhibited a clear difference in the weight gain group average, exhibiting 63.5% higher levels in weight gain patients (\( P = 0.008 \), Fig. 3A). Mean levels of alanine (31.3%, \( P = 0.093 \)), tyrosine (16.2%, \( P = 0.071 \)) and valine (14.8%, \( P = 0.059 \)) showed no statistically significant differences between weight change groups. When used to detect weight gain, patients mean lactate levels gave an ROC-AUC of 0.945 (\( P = 0.001 \)), and the Pearson correlation between mean lactate levels and the rate of weight change across all patients measured \( r = 0.70 \) (\( P < 0.001 \); Fig. 3B). No metabolite from the tested panel was

### Table 1. Relationships between levels of serum molecules and weight change

<table>
<thead>
<tr>
<th>Weight group mean (±SE)</th>
<th>( \Delta ) (vs. No gain)</th>
<th>%</th>
<th>( P ) (t test)</th>
<th>AUC</th>
<th>( P )</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(A) Metabolites (relative intensity)</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lactate</td>
<td>1.31-1.34 ppm</td>
<td>77.5 ± 8.9</td>
<td>47.4 ± 1.9</td>
<td>63.5%</td>
<td>0.008*</td>
<td>0.945</td>
</tr>
<tr>
<td>Alanine</td>
<td>1.45-1.5 ppm</td>
<td>19.3 ± 23</td>
<td>14.7 ± 0.8</td>
<td>31.3%</td>
<td>0.093</td>
<td>0.709</td>
</tr>
<tr>
<td>Proline</td>
<td>2.324-2.372 ppm</td>
<td>7.4 ± 0.8</td>
<td>6.8 ± 0.7</td>
<td>8.8%</td>
<td>0.591</td>
<td>0.555</td>
</tr>
<tr>
<td>Choline</td>
<td>3.19-3.224 ppm</td>
<td>35.0 ± 1.4</td>
<td>31.8 ± 1.7</td>
<td>10.1%</td>
<td>0.164</td>
<td>0.673</td>
</tr>
<tr>
<td>Valine</td>
<td>1.02-1.05 ppm</td>
<td>7.0 ± 0.3</td>
<td>6.1 ± 0.3</td>
<td>14.8%</td>
<td>0.059</td>
<td>0.745</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>7.165-7.205 ppm</td>
<td>1.3 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>16.2%</td>
<td>0.071</td>
<td>0.700</td>
</tr>
<tr>
<td>BCAl</td>
<td>0.938-0.994 ppm</td>
<td>22.2 ± 1.1</td>
<td>20.1 ± 0.1</td>
<td>10.4%</td>
<td>0.146</td>
<td>0.709</td>
</tr>
<tr>
<td>Unknown 1</td>
<td>1.055-1.06 ppm</td>
<td>0.8 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>33.3%</td>
<td>0.197</td>
<td>0.627</td>
</tr>
<tr>
<td>Glutamine</td>
<td>2.405-2.468 ppm</td>
<td>11.1 ± 0.4</td>
<td>10.9 ± 1.0</td>
<td>1.8%</td>
<td>0.871</td>
<td>0.409</td>
</tr>
<tr>
<td>Glucose</td>
<td>3.683-3.8 ppm</td>
<td>126.5 ± 11.7</td>
<td>115.0 ± 5.6</td>
<td>10.0%</td>
<td>0.377</td>
<td>0.555</td>
</tr>
<tr>
<td>Unknown 2</td>
<td>4.057-4.075 ppm</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>-0.1%</td>
<td>0.995</td>
<td>0.527</td>
</tr>
<tr>
<td><strong>(B) Appetite peptides (pmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GLP-1</td>
<td>27.0 ± 1.5</td>
<td>27.5 ± 1.2</td>
<td>-1.8%</td>
<td>0.878</td>
<td>0.491</td>
<td>0.944</td>
</tr>
<tr>
<td>PYY</td>
<td>16.8 ± 0.9</td>
<td>18.5 ± 1.2</td>
<td>-9.2%</td>
<td>0.364</td>
<td>0.373</td>
<td>0.324</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>596.2 ± 74.8</td>
<td>701.2 ± 79.8</td>
<td>-15.0%</td>
<td>0.446</td>
<td>0.409</td>
<td>0.481</td>
</tr>
<tr>
<td><strong>(C) Cytokines (pg/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor necrosis factor-( \alpha )</td>
<td>0.98 ± 0.13</td>
<td>1.34 ± 0.15</td>
<td>-26.9%</td>
<td>0.158</td>
<td>0.263</td>
<td>0.074</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.43 ± 0.07</td>
<td>0.47 ± 0.08</td>
<td>-8.5%</td>
<td>0.765</td>
<td>0.434</td>
<td>0.621</td>
</tr>
</tbody>
</table>

Note: All measurements for each individual were averaged prior to calculation of group means and statistical analysis. Values are presented as means +/- s.e.m or percentage difference (D) from mean value for no weight gain group. Statistical analysis used Dunnett’s t-test or area under the receiver operator characteristic curves (AUC) for detection of weight gain patients CI - 95% confidence interval calculated using a non-parametric assumption.

* \( P < 0.05 \).
† \( P < 0.01 \).
significantly associated to the presence of palpable tumor (i.e., adjuvant/neoadjuvant status).

Serum lactate levels exhibit the greatest response during chemotherapy. Normalizing levels of serum molecules to the pretreatment (cycle 1) measurement for each individual, serum lactate showed the greatest response to chemotherapy, exhibiting up to 75% higher values just prior to the fourth cycle of treatment (Fig. 4A). The molecules showing the next largest responses were also metabolites that had been earlier identified as having the largest differences between the weight change groups on average, specifically alanine (+54%), valine (+38%) and one unknown metabolite (+61%). No statistically significant differences were observed in normalized metabolite levels between the weight change groups, but differences in absolute levels of lactate were maintained throughout treatment.

Increased serum PYY is associated with weight loss. We determined serum levels of three gut peptides known to regulate food intake and energy balance, ghrelin (an orexigenic “appetite-stimulating” peptide; ref. 19), PYY (an anorexigenic peptide; ref. 20), and GLP-1 (an anorexigenic peptide analogues of which are used to treat diabetes; ref. 21) for which the relationship to weight change during chemotherapy was unknown, as we have recently described (refs. 19–22; Table 1B). Using the same statistical analyses used for selected metabolite levels, no associations with absolute peptide levels were detected; however, after normalization to pretreatment values, PYY levels exhibited significant differences between weight change groups, specifically elevated by 30% in patients not gaining weight posttreatment compared with a minor decrease of 7% for the weight gain group ($P < 10^{-4}$; Fig. 4B). Average pretreatment PYY was near identical for both weight groups ($\sim183$ pmol/L; $P > 0.5$).

Inflammatory cytokines are not associated with weight gain. Multiple inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-$\alpha$ (previously referred to as cachectin) are also thought to contribute to the development of anorexia and cachexia and historical descriptions of their associations are well documented by ourselves (23) and others (24, 25). A decrease of 26.9% in tumor necrosis factor-$\alpha$ was observed in patients gaining weight without reaching statistical significance ($P = 0.158$). Detection of weight gain individuals by ROC analysis also suggested a negative association that approached statistical significance (AUC, 0.264; $P = 0.074$). IL-6 levels were not significantly associated with weight gain showing only minor differences (data were characterized by wide confidence intervals for IL-6; Table 1C).

Pretreatment serum lactate levels predict weight gain during chemotherapy. To investigate the hypothesis that a pre-existing metabolic phenotype was associated with weight gain during chemotherapy, we examined the prognostic ability of pretreatment serum molecules and body weight parameters to predict weight gain for each patient. The ROC-AUC values for the detection of weight gain in individuals was calculated for each parameter (Table 2). Of the measurements tested, pretreatment levels of lactate (AUC, 0.782; $P < 0.029$), alanine (AUC 0.782, $P < 0.029$), and percentage of body fat (AUC, 0.791; $P < 0.024$) were significantly predictive of weight gain in patients not gaining weight posttreatment without reaching statistical significance ($P = 0.9$). Values were averaged across all samples for each individual prior to analysis.
individuals. In the same analysis, total body fat and body mass index did not reach statistical significance ($P = 0.057$). This indicated that a metabolic state, as defined by high body fat and systemic lactate and alanine levels, is prognostic for weight gain in response to early breast cancer chemotherapy, irrespective of neoadjuvant/adjuvant (tumor) status.

**Discussion**

There are few data elucidating the molecular basis for weight gain in breast cancer chemotherapy. Using a combination of untargeted metabolic profiling and specific peptide and cytokine assays, we have measured (to the best of our knowledge, for the first time) a number of parameters in sera related to metabolism and appetite regulation in women during chemotherapy for early breast cancer, and determined their relationship to weight change (comparing women who gained weight with others). We show that systemic levels of several metabolites are potentially associated with weight change and that the metabolite most significantly associated with weight gain, lactate, is also prognostic for increased body weight. Patients gaining weight during chemotherapy were also significantly heavier initially and had a higher percentage of body fat, the latter factor also being prognostic for subsequent weight gain. No specific associations were detected between weight gain and the appetite regulating and cachexic factors examined in our study.

**Lactate and obesity.** Given the long-established tendency for tumors to exhibit high levels of glucose uptake and glycolysis to lactate (the Warburg effect; refs. 26–28), our initial expectation was that lactate levels would be dependent on tumor burden; this clearly was not observed. The fact that both total body fat and serum lactate were prognostic for weight gain suggests that these parameters both reflect the same metabolic phenotype. Acutely, higher lactate levels indicate insufficient oxidative capacity to meet energy expenditure, such as during exercise. Higher blood lactate levels have been previously observed with obesity in several studies (29–31), which could be due to either higher energy demand associated with higher free fat mass (32), or associated mitochondrial dysfunction (33, 34), or both. Another metabolite observed to be positively associated with weight change in our study, alanine, also provides a substrate for oxidative metabolism via the Krebs cycle. Alanine (like lactate, a direct metabolite of pyruvate) has further been shown to be an important lipogenic precursor in the obese Zucker rat (35). Hence, the metabolic profile detected in our study in patients gaining weight is consistent with an excess of energy expenditure relative to oxidative capacity, a phenotype likely to be present in obese individuals and may predispose to it.

**Obesity, metabolic regulation and chemosensitivity.** A combination of epidemiologic and laboratory studies have provided evidence that a derangement of insulin signaling via the insulin-like growth factor signaling pathway associated with obesity could play a role in breast cancer etiology and treatment outcome, but without a clear picture emerging (36–38). Although no specific association was observed between weight gain and the appetite regulating and cachexic factors examined in our study (an increase in PYY posttreatment was observed primarily in no gain patients), there are several reports indicating that leptin levels are associated with weight change and obesity in breast cancer patients (39). Leptin is well known to play a role regulating adiposity and can directly affect the function of reproductive organs (40, 41). The primary metabolic phenotype identified by metabolic profiling as indicative of future weight gain, lower oxidative capacity relative to energy expenditure, could also indicate an environment predisposing to recurrent disease and poorer outcome. Loss of the mitochondrial bioenergetic capacity underlies the glucose avidity of carcinomas, and can influence chemosensitivity (42, 43). Global reduction of mitochondrial activity and increased expression of glycolytic enzymes could provide a more favorable environment for tumor growth and reduce the efficacy of drug treatment.

**Lactate and chemosensitivity.** Alternatively, higher systemic lactate levels may directly affect tumor development and responses to chemotherapy. Several studies have made an association between tumor lactate levels and poor prognosis (44, 45). Recent data have also suggested that lactate is selectively used as a substrate by oxygenated tumor cells for energy production via oxidative metabolism (46, 47). This would allow glucose to diffuse more thoroughly to hypoxic tumor cells, where glycolysis to the lactate is the major source of ATP, synergistically providing more substrate for oxygenated tumor cells. Inhibition of the lactate transporter MCT1 selectively kills hypoxic tumor cells in vivo, as oxygenated tumor cells revert back to glucose as a substrate, and sensitizes the rest of the tumor to radiotherapy (46, 47). Further work will be required to establish if higher systemic levels
of lactate confer higher growth potential and protection for tumors against antiproliferative chemotherapy.

**Conclusions**

Studies in larger groups of patients followed prospectively aiming to detail metabolic correlations with response, to time progression, and survival. The data presented herein illustrate the potential value of serum metabolic profiling, in conjunction with other clinical and molecular parameters, as a means to stratify and monitor patients with differing prognoses. Although weight gain was associated with baseline differences in weight and body fat, molecular parameters (in this case, lactate and alanine levels) could improve the accuracy of classification when used in combination with anthropometric parameters, and could correlate better with outcome if they reflect effects to relevant pathways. Serum profiling is rapid and minimally invasive, and metabolic biomarkers thus defined have the potential to translate between clinical and laboratory measurements without altering analytical protocols for species differences (48). The principle of using global metabolic profiles to predict pharmacokinetics and pharmacodynamics is analogous to pharmacogenomics, and has been shown in proof-of-principle experiments in both models and man ("pharmacometabonomics"; ref. 49). Our study provides further evidence that drug response could be predicted in the clinic using this approach, helping to target patients for intervention to reduce body fat, and thereby, potentially influencing prognosis.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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