Serum molecular signatures that predict weight gain during early breast cancer chemotherapy

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Weight gain in women receiving chemotherapy following breast cancer diagnosis has negative implications on quality of life and those who gain weight during treatment appear to be at higher risk of disease recurrence. The mechanism(s) implicated in these phenomena are poorly understood. To investigate this further, we assessed the metabolic, cytokine and appetite related peptide alterations before and during adjuvant FEC chemotherapy for early breast cancer in post-menopausal women, and correlated these with body mass measurements. Specifically, we performed global metabolic profiling (metabonomics/metabolomics) using $^1$H nuclear magnetic resonance spectroscopy of sequential sera, examined ghrelin immunoreactivity, performed radioimmunoassays for glucagon like peptide-1 (GLP-1) and peptide YY (PYY) and electrochemiluminescent cytokine analyses (tumor necrosis factor-α; and interleukin-6; TNF−α, IL-6) on the sequential samples. In those who gained > 1.5kg (on average ~5% of initial body weight), several metabolite levels were positively associated with weight change, in particular lactate which was 55% greater in patients with increased body weight during chemotherapy compared to those with stable weight during chemotherapy (p<0.01; the pre-specified primary end-point). A significant inverse relationship was also observed between levels of TNF-α and weight gain (ρ 0.476, p<0.05). Baseline lactate, alanine and body fat were all prognostic for weight gain (ROC AUC >0.77, p<0.05). No significant associations were observed between any other parameter and weight gain, including other cytokine and appetite-regulating peptide levels. Using a metabonomic approach we identify pathways perturbed during early chemotherapy for breast cancer, and establish a significant association between serum lactate, body fat, inflammation and substantive weight changes during chemotherapy. Higher systemic levels of lactate may confer higher growth potential and protection for tumours against anti-proliferative chemotherapy. Our study provides further evidence that drug response could be predicted in the clinic using pharmaco-metabonomics, helping to target patients for intervention to reduce body fat, and thereby potentially influencing prognosis.