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Original article

Glucose metabolism during the acute prostate cancer treatment trajectory: The influence of age and obesity

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SUMMARY

Background & aims: Obesity and age, key risk factors for aggressive prostate cancer, are associated with insulin resistance. Glucose-related parameters in patients with aggressive prostate cancer were compared with 2 reference groups: men of similar age and body mass index (BMI) without cancer, and healthy young men. Acute changes in these parameters following radiation treatment were also evaluated.

Methods: Nine patients with aggressive prostate cancer underwent metabolic assessments prior to treatment (baseline), 7 and 33 weeks post-baseline (post-treatment initiation). Baseline measures were compared with the 2 reference groups. Evaluations included: 1) fasting and oral glucose tolerance test (OGTT) blood samples for glucose, C-peptide, and insulin, 2) fasting blood samples for triglycerides, cholesterols, leptin, adiponectin, IL-6, and TNF-α, 3) body composition, 4) nutrition, and 5) physical activity.

Results: At baseline, patients had normal fasting glucose concentrations (<5.6 mM; 4.9 ± 1.2 mM) but impaired 2-h OGTT glucose concentrations (>7.8 mM; 8.7 ± 2.9 mM). Both reference groups had normal fasting (matched males: 4.2 ± 0.5 mM; young males: 3.7 ± 0.4 mM) and 2-h OGTT glucose concentrations (matched males: 5.6 ± 1.8 mM; young males: 3.1 ± 0.1 mM) that were significantly lower than patient values. During the OGTT, patients had higher insulin (120 min) and C-peptide (45, 60, 90, 120 min) concentrations compared to the matched males. At 7 weeks, 2-h OGTT glucose concentrations in patients improved to healthy ranges without changes in insulin, C-peptide, IGF-1, IGFBP-3 or other metabolic parameters.

Conclusions: At baseline patients with aggressive prostate cancer demonstrated impaired glucose tolerance compared with men of similar age and body size. Following treatment, glucose tolerance improved in the absence of changes in expected modifiers of glucose metabolism. These improvements may be related to treatment.

Abbreviations: 1-RM, 1 Repetition Maximum; ADT, Androgen Deprivation Therapy; AUC, Area Under the Curve; BMI, Body Mass Index; CRP, C-reactive Protein; CVD, Cardiovascular Disease; DBP, Diastolic Blood Pressure; FFM, Fat Free Mass; FM, Fat Mass; HDL, High-Density Lipoprotein; HOMA-IR, Homeostatic Model of Insulin Resistance; IGF, Insulin-like Growth Factor; IGFBP, Insulin-like Growth Factor Binding Protein; IL, Interleukin; LDL, Low-Density Lipoprotein; MM, Matched Males; OGTT, Oral Glucose Tolerance Test; PC, Prostate Cancer; PSA, Prostate Specific Antigen; QUICKI, Quantitative Insulin Sensitivity Check Index; RIA, Radioimmunoassay; RT, Radiation Therapy; SBP, Systolic Blood Pressure; SF-BIA, Single Frequency-Bioelectrical Impedance Analysis; SMI, Skeletal Muscle Index; SMM, Skeletal Muscle Mass; TG, Triglycerides; TNF, Tumor Necrosis Factor; YM, Young Males.

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1. Introduction

Prostate cancer (PC) development has been associated with age [1], obesity [2] and metabolic syndrome [3]. However, non-cancer populations commonly develop impaired insulin and adipokine signalling with aging [4] and obesity [5]. PC patients typically exhibit hyperinsulinemia [6], elevated C-peptide concentrations [6], dyslipidemia [6], adipokine perturbations [6], and/or pro-inflammation [7] that contribute to tumour development and influence the presence of various comorbidities, including insulin resistance. Given the prevalence of insulin resistance and PC in older men, it is important to distinguish whether impairments in glucose metabolism are related to PC or are a consequence of obesity and aging.

PC treatment may incite unique metabolic disturbances contributing to the development of CVD and diabetes or exacerbate existing metabolic conditions. Androgen deprivation therapy (ADT) has been associated with increased risk of diabetes and cardiovascular disease (CVD) in PC survivors [8,9], which may relate to muscle loss and adipose tissue gains during ADT. However, in PC patients who developed diabetes after diagnosis, only 12.1% received hormonal therapy their primary treatment [10]. Radiation therapy (RT) is often used in conjunction with prostatectomy and ADT, yet the specific metabolic consequences (i.e. glucose, insulin, C-peptide, adipokine metabolism) of each of these treatments are largely unknown.

The purpose of this study was to examine the metabolic deviations associated with PC diagnosis and potential changes during the acute treatment trajectory (primarily RT with secondary ADT). Our objectives were to: 1) characterize differences in glucose metabolism as well as lipids, body composition, cytokines, dietary intake, and physical activity between newly diagnosed PC patients, men of the same age and body size (matched males (MM)), and a young comparison group (young males (YM)) and 2) describe potential changes in these measures during the acute treatment trajectory (~33 weeks post-treatment initiation).

2. Methods

2.1. Study design

High-risk PC patients receiving either conventional RT with upfront ADT (n = 4) or hypofractionated RT with salvage ADT (n = 5) were recruited for this study and were compared with a group of non-cancer, age- and BMI-matched males (MM) and a young healthy group of males with normal BMI (YM).

Clinical and metabolic assessments were conducted over 2 separate days (2–7 days apart). PC patients underwent assessments at: 0 weeks (baseline, pre-treatment), ~7 weeks (post-RT), and ~33 weeks (6 months post-RT). Assessments included: 1) fasting and OGTT blood samples, 2) body composition analysis (weight, BMI, Single Frequency-Bioelectrical Impedance Analysis (SF-BIA)), 3) resting heart rate, systolic (SBP) and diastolic blood pressure (DBP), 4) physical activity measures (VO_{2peak}, repeated 1-RM, physical activity questionnaire), and 5) 3-day food diary. This study was reviewed and received clearance from University of Waterloo Office of Research Ethics (all groups) and by Tri-Hospital Research Ethics Board (PC patients only).

2.2. Participants

2.2.1. Prostate cancer patients

Nine high-risk (Gleason score >8, PSA >20 ng/dL, or Stage >T3A) PC patients were recruited from the Grand River Regional Cancer Centre (Kitchener, ON) following diagnosis, but prior to treatment initiation. Patients were of any age (≥18 years old), BMI, and fitness level; however, patients were excluded for hyperglycemia (fasting glucose >7.0 mM) or any diagnosis of metabolic disease (cardiovascular disease, diabetes). Treatment regimes included: 1) conventional RT (whole pelvis followed by prostate specific) with upfront ADT including 6 months of bicalutamide and an LHRH agonist, beginning concurrently with RT, or 2) escalated dose hypofractionated RT (single phase to the prostate and regional lymph nodes) and salvage ADT consisting of an intermittent androgen blockade and was discontinued when PSA levels reached undetectable levels and restated if PSA increased beyond 3 ng/mL. It is important to note that the amount of radiation received in both RT regimes was equal.

2.2.2. Non-malignant reference groups

We sought to individually match community-dwelling men without cancer to each PC patient by age (±5 years) and BMI (±3 kg/m^2). MM were required to be weight stable, have a fasting blood glucose <7.0 mM, and no history of metabolic disease. To evaluate the effects of aging, PC patients and MM were compared with the YM who were between 20 and 30 years old, weight stable with normal BMI (18.5–24.9 kg/m^2), active (VO_{2peak} > 45 mL/kg/min), without metabolic disease and fasting blood glucose <5.6 mM.

2.3. Blood sampling and analysis

Blood was sampled following an overnight fast (8–12 h with no food or drink except for water), with a sterile catheter inserted into an antecubital vein and 25 mL of blood drawn (Timepoint: −30). Following 30 min (Timepoint: 0), a second fasting sample of 5 mL was drawn. Participants consumed a 75 g glucose drink (Trutol Glucose Tolerance Beverage, ThermoFisher Scientific; East Providence, RI) within 10 min for the OGTT. Post-prandial blood samples (5 mL) were drawn at 15, 30, 45, 60, 90, and 120 min following consumption of the drink (total time = 150 min). Blood samples were obtained from 8 of 9 PC patients due to sampling difficulties; thus, n = 8 for all blood measures.

Fasting blood samples were analyzed for glucose, insulin, C-peptide, total cholesterol, LDL cholesterol, HDL cholesterol, TG, leptin, adiponectin, IL-1β, IL-4, IL-6, IL-8, IL-10, TNF-α, C-reactive protein (CRP), testosterone, IGF-1, and IGFBP-3. Post-prandial blood sample were analyzed for glucose, insulin, and C-peptide.

Glucose was analyzed using spectrofluorometric methods [11]. Insulin and C-peptide were analyzed using commercially available kits (Insulin: Human Insulin Specific RIA kit, EDM Millipore, St. Charles, MO; C-Peptide Double Antibody RIA Kit, Siemans Healthcare Diagnostics; Deerfield, IL). Triglycerides and cholesterols were analyzed spectrofluorophotometricly (Pointe Scientific; Canton, MI). Cytokines were analyzed using BD Cytometric Bead Array and BD FACSCalibur flow cytometer (BD Biosciences; Mississauga, ON). Leptin, adiponectin, IGF-1, IGFBP-3, and CRP were measured using ELISAs and testosterone using a Parameter assay (R&D Systems Inc, Minneapolis, MN).

2.4. Body composition

Weight was determined using a balance beam scale and height by stadiometer. These values were used to calculate BMI. SF-BIA was used for body composition. Fat free mass (FFM) was calculated as previously described [12] and was used to estimate fat mass (FM) and percent body fat. Skeletal muscle mass (SMM), calculated as previously described [13], was used to estimate skeletal muscle index (SMI; kg/m^2) to identify individuals who were sarcopenic (Cutpoint in Men: ≤8.5 kg/m^2) [14].

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