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Original research

Cardiorespiratory fitness is positively associated with increased pancreatic beta cell function independent of fatness in individuals with the metabolic syndrome: Fitness versus fatness☆

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ABSTRACT

Objectives: The vulnerability of individuals with the metabolic syndrome (MetS) to cardiovascular events (CVEs) is attenuated by increased cardiorespiratory fitness (CRF), despite the presence of obesity as a usual component of MetS. To better understand the importance of CRF and body fat in treating this condition, we investigated the relationship between fitness and fatness with pancreatic beta cell function (BCF) indices that are known independent predictors of CVEs.
Design: Cross sectional study.
Methods: This study included 84 individuals with MetS. BCF indices were derived from a fasted steady state (basal disposition index [DI], proinsulin, proinsulin:insulin, and proinsulin:C-peptide) and dynamic conditions via an oral glucose tolerance test (1st and 2nd phase DI). CRF and body fat percentage (BF%) were assessed via indirect calorimetry (during a maximal exercise test) and dual energy X-ray absorptiometry, respectively.
Results: CRF was positively associated with basal DI ($r = 0.40$, $p < 0.001$), 1st phase DI ($r = 0.49$, $p < 0.005$), and 2nd phase DI ($r = 0.38$, $p = 0.02$). Hierarchical multiple regression analysis showed CRF was associated with basal DI ($\beta = 0.18$, $p = 0.04$), 1st phase DI ($\beta = 0.36$, $p = 0.04$), and 2nd phase DI ($\beta = 0.33$, $p = 0.03$), independent of BF% and other confounding factors including age, sex, diabetic status, anthropometric measures, lipid profile, and insulin sensitivity. No significant associations were found between CRF and proinsulin measures. BF% was not significantly correlated with BCF indices.
Conclusions: Increased CRF was independently associated with enhanced BCF. This study provides evidence that equal, if not more attention should be dedicated to CRF improvement relative to fat-loss for favorable pancreatic BCF and thus possible reduction in CV risk in individuals with MetS.

1. Introduction

Individuals with metabolic syndrome (MetS) have a 3-fold increased risk of cardiovascular events (CVEs) compared to healthy counterparts.[1] However, people with MetS and high cardiorespiratory fitness (CRF), which refers to the ability of different organ systems to deliver and utilize oxygen for energy production, have less risk of CVEs compared to less fit counterparts, despite the presence of obesity as a usual component of this syndrome.[2]

Recently, impaired pancreatic beta-cell function (BCF) has been linked with increased severity of MetS.[3] The preserved ability of beta cells to continuously secrete insulin to compensate for increasing blood glucose levels in insulin-resistant individuals could prevent further exacerbation of insulin resistance (IR) in different tissues.[4] BCF improvement is therefore important in this cohort, given that IR has been postulated to play a central role in the emergence of other MetS components, such as hyperglycemia, hypertriglyceridemia, depressed high-density lipoprotein cholesterol (HDL-C), and hypertension.[5] Several surrogate markers of BCF from fasted steady-state [SS] (basal disposition index [DI]) and

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dynamic conditions (1st and 2nd phase DI derived from an oral glucose tolerance test [OGTT]) have been well established,[6] and have shown to be independent risk factors of coronary artery disease (CAD).[7] DI reflects the beta cell's ability to respond to a change in insulin sensitivity, calculated as the product of insulin secretion and insulin sensitivity (DI = insulin secretion × insulin sensitivity), and thus the state of an individual's glucose tolerance. Normal glucose tolerance is maintained if there is no change in DI, reflecting the beta cell's ability to secrete adequate insulin in response to reduced insulin sensitivity. Whereas the failure of the beta cells to up-regulate insulin secretion to compensate for reduced insulin sensitivity could reflect development of glucose intolerance. In essence, a higher absolute DI value reflects better BCF.[6] Recently, fasting proinsulin levels have also been recognized as a marker of BCF. Increased proinsulin concentration reflects the reduced ability of the beta cells to process and excise C-peptide from the proinsulin molecule to produce insulin.[8] Similar with CRF,[9] intact proinsulin level indices have been shown to be an independent predictor of all-cause and CV mortality,[10] yet its associations with fitness and fatness to our knowledge are presently unknown.

There is evidence that higher CRF is associated with better BCF in obese and overweight adults[11] and adolescents.[12,13] However, the relative contributions of CRF and adiposity toward BCF in MetS individuals are presently unknown. MetS individuals are inevitably more susceptible to glucolipotoxicity that is linked to mechanisms underlying beta-cell failure,[14] compared to cohorts included in the previous studies.[11–13] Moreover, an exercise-induced increase in CRF has been shown to be inversely related to traditional and novel cardiovascular disease (CVD) risk factors[9,15] that are significant contributors to a 'glucolipotoxic' environment. It is therefore of interest to investigate the independent associations of CRF and fatness with BCF specifically in MetS individuals. This may enable health professionals to better target treatment of decreased BCF, which has shown to be more pronounced in these individuals compared to their healthy counterparts.[3]

The aim of this study was to therefore investigate the independent associations of CRF and body fat percentage (BF%) with different BCF indices in MetS individuals. We hypothesized that higher CRF would correlate with BCF independent of BF% in MetS individuals.

2. Methods

Eighty-four individuals who met the International Diabetes Federation criteria of the MetS were included in this study.[16] This was a sub-study from participants recruited for the 'Exercise in the prevention of MetS (EX-MET)' Trial (registration number: NCT01676870), a randomized controlled multi-center international trial investigating the impact of high-intensity interval training on MetS risk factors. This sub-study presents data collected at the Brisbane site where participants were asked to undertake an OGTT. This measure is not being performed at other EX-MET study sites. Individuals were excluded if they met any of the following: unstable angina, recent myocardial infarction (4 weeks), severe valvular heart disease, uncompensated heart failure, pulmonary disease, uncontrolled hypertension, kidney failure, and cardiomyopathy. Oral and written informed consents were obtained from all participants. Participants were instructed to refrain from stimulants (caffeine and alcohol) for at least 24 h, and strenuous activities for at least 48 h before each of the following tests conducted on separate days: (i) CRF; (ii) body composition; (iii) BCF and IS indices; (iv) MetS risk factors. This study was approved by the Medical Research Ethics Committee, University of Queensland, Brisbane, Australia (2012000627).

Participants' eligibility for this sub-study was determined through a series of tests following a 12-h overnight fast: (i) lipid profile (see below) and fasting glucose (FG) level; (ii) resting brachial systolic (SBP) and diastolic blood pressures (DBP); and (iii) anthropometric measures (height, body mass index [BMI], waist circumference [WC], and hip circumference [HC]). Blood pressure measurements were collected after 15 min of seated quiet rest. Mean arterial pressure (MAP) was calculated as: MAP = 2/3DBP + 1/3SBP. A Cholestech LDX system was used to measure participants' fasting lipid profile (HDL-C, triglyceride [TG], total cholesterol [TC], low-density lipoprotein-cholesterol [LDL-C]) and glucose levels. MetS severity was presented by the sex-specific MetS z-scores calculated as: MetS $z\text{-score}_{men}$ = [(40 − HDL-C)/8.9] + [(TG − 150/69)] + [(FG − 100)/17.8] + [(WC − 102)/11.5] + [(MAP − 100)/10.1]; MetS $z\text{-score}_{women}$ = [(50 − HDL-C)/14.5] + [(TG − 150/69)] + [FG − 100)/17.8] + [WC − 88)/12.5] + [(MAP − 100)/10.1].[17]

CRF was measured as the peak oxygen uptake ($\dot{V}O_2$ peak) via indirect calorimetry (Metamax II system, Cortex, Leipzig, Germany or Parvo Medics TrueOne 2400, UT, USA) during an incremental exercise test using a treadmill (n = 69) or cycling (n = 15) protocol. $\dot{V}O_2$ peak was determined as the highest 15-sec time averaged $\dot{V}O_2$. The treadmill was the preferred exercise test and exercise training mode of the EX-MET trial. However, participants who were unable to exercise on a treadmill due to physical limitations (n = 10), or for those preferring to train on a bike (n = 5), a cycling protocol was used for testing. The physical limitations were poor balance (n = 2), previous knee injury/knee instability (n = 1), and exercise physiologist perceived-inability of participants to bear their own weight for prolonged periods (n = 7).

A sustagen drink (250 mL, Dutch Chocolate, Nestle, Gympie QLD, Australia) was consumed 2 h before the test in attempt to standardize nutrition across all participants. The pre-exercise beverage consisted of the following primary macronutrients, with additional nutritional information found in the company's website[18]: (i) carbohydrate = 42.3 g; (ii) protein = 12.5 g; and (iii) fat = 3.3 g. An 8-min warm-up that consisted of two 4-min warm-up stages (warm-up stage 1: 4 km/h at 0% incline or 50–60 rpm at 0 W; warm-up stage 2: 4 km/h at 4% or 50–60 rpm at 25 W) preceded all tests to familiarize the participants to the test protocol and selected ergometers. The test started at a slightly higher workload and intensity than warm-up stage 2 (treadmill: speed individualized [4–6 km/h]; intensity: ~6% incline or 50 W). Thereafter, the speed (individualized: set at 6–9 km/h or 60–70 rpm) and load (2% incline or 25 W) increased each minute until exhaustion. Standardized verbal cues were provided throughout the tests to ensure participants reached maximal effort. $\dot{V}O_2$ peak was expressed relative to fat free mass ($mL/kg_{FFM}/min$) to eliminate adiposity as a confounding factor, and thus allow a better understanding of the associations between CRF and BCF indices.

Total BF%, trunk fat percentage (TF%), and lean body mass (LBM, kg) were measured using dual-energy X-ray absorptiometry (DEXA, hologic QDR4500A version12.5, MA, USA). BF% was calculated as the percentage of fat mass from total mass. TF% is the percentage of fat mass from total trunk mass.

Blood samples were withdrawn from the participants' antecubital vein following a 12-h overnight fast. Serum samples were obtained by collecting whole blood (WB) into tubes without anticoagulants. These tubes were left in room temperature for 30 min to allow WB to clot before centrifugation at 2500 rpm for 10 min at 4 °C. Serum aliquots were stored at −80 °C for later analysis of basal insulin, C-peptide (Electrochemiluminescence immunoassay [ECLIA], Cobas e411 immunoassay analyzer, Roche Diagnostics USA), and intact proinsulin (Human intact proinsulin enzyme-linked immunosorbent assay, EZHIPI-17K, Merck Millipore, Darmstadt, Germany). When the proinsulin values are below detection limit (0.5–100 pM), a value of 0.1 pM was assigned

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