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Lower dipeptidyl peptidase-4 following exercise training plus weight loss is related to increased insulin sensitivity in adults with metabolic syndrome

Steven K. Malin[a,b], Hazel Huang[a], Anny Mulya[a], Sangeeta R. Kashyap[c,d], John P. Kirwan[a,b,d,*]

[a] Department of Pathobiology, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, United States
[b] Department of Nutrition, School of Medicine, Case Western Reserve University, Cleveland, OH, United States
[c] Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic, Cleveland, OH, United States
[d] Metabolic Translational Research Center, Endocrine and Metabolism Institute, Cleveland Clinic, Cleveland, OH, United States

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ABSTRACT

Dipeptidyl peptidase-4 (DPP-4) is a circulating glycoprotein that impairs insulin-stimulated glucose uptake and is linked to obesity and metabolic syndrome. However, the effect of exercise on plasma DPP-4 in adults with metabolic syndrome is unknown. Therefore, we determined the effect of exercise on DPP-4 and its role in explaining exercise-induced improvements in insulin sensitivity. Fourteen obese adults (67.9 ± 1.2 years, BMI: 34.2 ± 1.1 kg/m^2) with metabolic syndrome (ATP III criteria) underwent a 12-week supervised exercise intervention (60 min/day for 5 days/week at ~85% HR_{max}). Plasma DPP-4 was analyzed using an enzyme-linked immunosorbent assay. Insulin sensitivity was measured using the euglycemic-hyperinsulinemic clamp (40 mU/m^2/min) and estimated by HOMA-IR. Visceral fat (computerized tomography), 2-h glucose levels (75 g oral glucose tolerance), and basal fat oxidation as well as aerobic fitness (indirect calorimetry) were also determined before and after exercise. The intervention reduced visceral fat, lowered blood pressure, glucose and lipids, and increased aerobic fitness ($P < 0.05$). Exercise improved clamp-derived insulin sensitivity by 75% ($P < 0.001$) and decreased HOMA-IR by 15% ($P < 0.05$). Training decreased plasma DPP-4 by 10% (421.8 ± 30.1 vs. 378.3 ± 32.5 ng/ml; $P < 0.04$), and the decrease in DPP-4 was associated with clamp-derived insulin sensitivity ($r = -0.59$; $P < 0.04$), HOMA-IR ($r = 0.59$; $P < 0.04$) and fat oxidation ($r = -0.54$; $P < 0.05$). Increased fat oxidation also correlated with lower 2-h glucose levels ($r = -0.64$; $P < 0.02$). Exercise training reduces plasma DPP-4, which may be linked to elevated insulin sensitivity and fat oxidation. Maintaining low plasma DPP-4 concentrations is a potential mechanism whereby exercise plus weight loss prevents/delays the onset of type 2 diabetes in adults with metabolic syndrome.

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1. Introduction

Dipeptidyl peptidase-4 (DPP-4) is an important cytokine that has been implicated in the development of metabolic syndrome and type 2 diabetes [21]. DPP-4 is a glycoprotein membrane bound enzyme that also exists in soluble form and is ubiquitously expressed throughout the body, including: skeletal muscle, kidney, liver, and adipose tissue [27]. DPP-4 was initially associated with immune and inflammatory processes, but the endocrine role of DPP-4 has gained more attention recently since DPP-4 reduces pancreatic insulin secretion through decreased action of glucagon-like peptide-1 and glucose-dependent insulinotrophic polypeptide [6,9]. Clinically, the use of pharmacological DPP-4 inhibitors improves glycemic control and cardiometabolic health [9,19,25,31,34]. However, our understanding of *in vivo* DPP-4 in relation to insulin sensitivity is limited, and the effect of DPP-4 on insulin action may be a potential mechanism whereby inflammatory-related cytokines raise cardiometabolic disease risk [2,7,21]. Indeed, recent work suggests that DPP-4 impairs insulin signaling at the level of Akt in skeletal muscle thereby impairing glucose tolerance and raising metabolic syndrome risk [21]. In addition, DPP-4 deficient rodents have increased expression of PPAR-α, which in turn, contributes to higher fat oxidation and insulin sensitivity compared to normal controls [7].

Abbreviations: Akt, protein kinase B; PPAR-α, peroxisome proliferator-activated receptor alpha; TNF-α, tumor necrosis factor alpha; SREBP-1c, sterol retinol-element binding protein one c.

* Corresponding author at: Department of Pathobiology, Lerner Research Institute, Cleveland Clinic Foundation, 9500 Euclid Ave (NE40), Cleveland, OH 44195, United States. Tel.: +1 216 444 3412; fax: +1 216 636 1496.
E-mail address: kirwanj@ccf.org (J.P. Kirwan).

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Exercise and weight loss interventions reduce metabolic syndrome criteria in part by reducing cytokines (e.g. TNF-α and leptin) that impair insulin sensitivity [4,16,17,22,35–37]. In fact, work from our lab shows that exercise-induced weight loss reduces cytokines in parallel with improved glucose tolerance and insulin sensitivity [15,18]. Since leptin has been associated with higher DPP-4 concentrations, and leptin is known to decrease following exercise and weight loss interventions, it would seem reasonable to hypothesize that DPP-4 would also decrease following exercise. Indeed, a study recently reported that a low-fat diet combined with increased physical activity led to a lowering of plasma DPP-4 in overweight children [29]. The generalizability of these findings, however, is limited, as adults with metabolic syndrome were not studied. Moreover, the use of self-reports to characterize physical activity and surrogate measures of insulin sensitivity (fasting glucose and insulin) rather than the use of supervised exercise programs and the euglycemic-clamp to directly measure insulin sensitivity, limits our understanding of the role of exercise in regulating DPP-4. Therefore, the objective of this study was to determine the effects of exercise on DPP-4 in adults with metabolic syndrome. We hypothesized that exercise would decrease DPP-4, and that the change in DPP-4 would correlate with increased insulin sensitivity, elevated fat oxidation, and a reduction in cardiometabolic risk factors.

2. Materials and methods

2.1. Subjects

Fourteen older (67.9 ± 1.2 years; range: 61–77 years) obese adults were included in this prospective study, and some of the clamp-derived insulin sensitivity data were reported for a different study [33]. Subjects were recruited from the Cleveland area via newspaper advertisements and community flyers. All subjects met at least 3 of 5 the National Cholesterol Education Program Adult Treatment Panel (ATP) III criteria for metabolic syndrome [13]. Subjects were only included if between the ages of 60–80 years of age, were weight stable (<2 kg in previous 6 months), sedentary (less than < 60 min/week of aerobic exercise and/or weight training), and free of chronic disease (i.e. hematological, renal, hepatic, cardiovascular). Women were post-menopausal and not on hormone replacement therapy. Subjects were excluded if they smoked or took diabetic or cholesterol lowering medications. Subjects were verbally briefed about the study and signed consent documents approved by the Cleveland Clinic Institutional Review Board.

2.2. Aerobic fitness

Subjects were screened with a resting electrocardiogram as well as an incremental graded exercise stress test before participation in the intervention to exclude individuals with underlying cardiovascular abnormalities. Maximum oxygen consumption (VO_2max) was determined by using a continuous incremental treadmill exercise test (Jaeger Oxygcon Pro; Viasys, Yorba Linda, CA) as previously described [33]. Maximum heart rate (HR_{max}) obtained during this test was used to prescribe exercise intensity. VO_2max was repeated at weeks 4 and 8 to directly measure HR_{max} so that the appropriate exercise intensity could be maintained throughout training.

2.3. Exercise training intervention

Participants underwent a 12-week aerobic exercise intervention. During the first 4 weeks, subjects underwent a fully supervised aerobic exercise program 5 days per week at 60–85% of maximal heart rate (HR_{max}). Thereafter, the exercise intensity was increased and maintained at 80–85% HR_{max} for the duration of the intervention. Appropriate exercise intensity was managed using heart rate monitors (Polar Electro, Inc. Woodbury, NY). Exercise adherence was defined as a percent of completed exercise sessions over the intervention. Subjects met weekly with a dietitian to review 3-day diet logs to ensure maintenance of their pre-intervention macronutrient intake, such that weight loss was primarily the result of exercise energy expenditure. Food records were averaged over a 3-day period for analysis before and after the intervention to assess dietary intake.

2.4. Control period

Metabolic assessments were conducted during a 3-day inpatient stay at the Clinical Research Unit. Resting metabolic rate was determined after subjects rested in the supine position for 30 min. Expired air (i.e. VO_2 and VCO_2) was collected for 20 min using a ventilated hood and indirect calorimetry, and the last 10 min were used to calculate energy expenditure (Vmax Encore, Viasys, Yorba Linda, CA) [12]. Subjects were then provided weight-maintenance meals (resting metabolic rate × 1.2 activity factor; 55% CHO, 30% fat, 15% protein). All post-intervention outcome measures were obtained 16–18 h after the last exercise session.

2.5. Cardiometabolic risk factors

After an overnight fast, height was measured without shoes using a wall-mounted stadiometer and weight was recorded on a digital platform scale with minimal clothing. Dual-X-ray absorptiometry (iDXA; Lunar Prodigy, Madison, WI) was used to quantify total fat and fat free-mass. Computerized tomography (Siemens Medical Solutions, Malvern, PA) was used to determine visceral adipose tissue mass without contrast at the fourth lumbar vertebrae (L_4) as previously described [26]. Waist circumference was measured up to 3 times using a plastic Gulick tape measure approximately 2 cm above the umbilicus. Blood pressure was recorded after 10 min of rest in the seated position. An intravenous catheter was placed in an antecubital vein. Fasting samples were obtained for DPP-4, TNF-α, leptin, glucose, triglyceride, cholesterol and high-density lipoprotein (HDL). A 75 g oral glucose load was then conducted for assessment of impaired glucose tolerance. An ATP III score was calculated from the sum of risk factors meeting metabolic syndrome criteria before and after the intervention.

2.6. Insulin sensitivity

After an overnight fast, a 2-h euglycemic-hyperinsulinemic clamp was performed according to DeFronzo et al. [8]. Prior to insulin infusion, expired air was collected for 20 min using a ventilated hood and indirect calorimetry to determine basal substrate oxidation. A constant infusion (40 mU/m^2/min) of insulin was then administered via an indwelling catheter placed in an antecubital vein. Glucose was infused at a variable rate to maintain plasma glucose at 90 mg/dl. A retrograde hand catheter was also placed and the hand was warmed to 60 °C for collection of arterialized blood. Plasma glucose was collected every 5 min to determine the appropriate glucose infusion rate (GIR). Insulin sensitivity was defined as the average GIR divided by the ambient insulin concentrations during the final 30 min of the clamp. Expired air was also collected during the last 30 min to determine insulin-stimulated substrate oxidation. Non-oxidative glucose disposal was calculated as: GIR – total rates of carbohydrate oxidation. Homeostatic model assessment (HOMA-IR) was also calculated as fasting glucose x fasting insulin/405. Insulin-stimulated suppression of free fatty acids (FFA) was calculated as: $[1 - (FFA_{clamp}/FFA_{fast}) \times 100\%]$.

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