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Physical Inactivity and Obesity Underlie the Insulin Resistance of Aging

Running title: Exercise, age, obesity and insulin resistance

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ABSTRACT

Objective: Age-associated insulin resistance may underlie the higher prevalence of type 2 diabetes in older adults. We examined a corollary hypothesis that obesity and level of chronic physical inactivity are the true causes for this ostensible effect of aging on insulin resistance.

Research Design and Methods: We compared insulin sensitivity in seven younger endurance-trained athletes (YA), 12 older athletes (OA), 11 younger normal weight (YN), 10 older normal weight (ON), 15 younger obese (YO) and 15 older obese (OO) subjects using a glucose clamp. The non-athletes were sedentary.

Results: Insulin sensitivity was not different in YA vs. OA, in YN vs. ON or in YO vs. OO. Regardless of age, athletes were more insulin sensitive than normal weight sedentary subjects, who in turn were more insulin sensitive than obese subjects.

Conclusions: Insulin resistance may not be characteristic of aging, but rather associated with obesity and physical inactivity.

There is a widespread assertion that aging leads to insulin resistance (1-3), which is in turn fundamental to the etiology and higher prevalence of type 2 diabetes in older adults (4-6). The evidence supporting the concept of age-associated insulin resistance, however, is contradicted by reports demonstrating that insulin resistance may not be associated with aging per se but rather with lifestyle patterns linked with aging, such as a reduced physical activity (7) and obesity (8). Thus it is not clear whether insulin resistance is characteristic of aging, or alternatively, whether obesity and/or physical inactivity underlie this 'aging' effect. The purpose of this study was to help detangle the effects of aging, obesity and chronic exercise on insulin resistance by comparing younger and older subjects matched for level of obesity and chronic physical activity.

Research design and Methods

Men (M) and women (W) aged 35.4 ± 1.1 (range 24 to 47 years old) ('younger') and 66.9 ± 0.8 (range 60 to 75 years old) ('older') were recruited through advertisement in the Pittsburgh, PA, area. We studied seven younger endurance-trained athletes (YA, 6M/1W), 12 older athletes (OA, 10M/2W), 11 younger normal weight sedentary (YN, 6M/5W), 10 older normal weight sedentary (ON, 5M/5W), 15 younger obese sedentary (YO, 7M/8W) and 15 older obese sedentary (OO, 7M/8W) subjects. The athletes were currently performing endurance exercise ≥ 5 days/week. Sedentary was defined as exercise ≤ 1 day/week. All subjects were weight stable for at least 6 months, were nonsmokers and in general good health. Subjects were excluded if they had type 2 diabetes, cardiovascular disease, uncontrolled hypertension, and if they were taking any chronic medications known to affect glucose homeostasis. All volunteers gave their

informed written consent and the protocol was approved by the University of Pittsburgh Institutional Review Board.

Insulin sensitivity was measured as rate of insulin-stimulated glucose disposal (Rd) during a 4-hour hyperinsulinemic ($40 \text{ mU}\cdot\text{m}^{-2}\cdot\text{min}^{-1}$) euglycemic clamp performed during standardized conditions (i.e. after an overnight fast and period of no exercise i.e. in the 36-48 hours before the clamp) as described elsewhere (9). We employed stable isotope dilution methods [$6, 6\text{-}^2\text{H}_2$] glucose ($0.22 \mu\text{mol}\cdot\text{kg}^{-1}$, $17.6 \mu\text{mol}\cdot\text{kg}^{-1}$ prime) to account for residual hepatic glucose production. Fat free mass (FFM) and fat mass (FM) were assessed by dual-energy X-ray absorptiometry (GE Lunar Prodigy and Encore 2005 software version 9.30, GE Healthcare, Milwaukee,MI). Peak aerobic capacity (VO_2peak) was measured using a graded exercise protocol as described previously (10).

Differences among the six study groups were analyzed with a between-subject one-way ANOVA. Post hoc tests were performed with the Tukey-Kramer HS adjustment. All analyses were done using JMP version 5.0.1.2 for Macintosh (SAS, Cary, NC) with an alpha level of 0.05.

Results

Within each age group, age was similar among athletes, normal weight and obese groups. Body mass index (BMI) was higher in the obese groups (33.8 ± 0.6 and $33.7\pm 0.54 \text{ kg/m}^2$ for YO and OO, respectively) compared to normal weight (23.5 ± 0.6 and $24.4\pm 0.7 \text{ kg/m}^2$ for YN and ON, respectively) and the athletes (24.7 ± 0.8 and $23.6\pm 0.6 \text{ kg/m}^2$ for YA and OA, respectively). Similar patterns were observed for the

relative proportion of body fat, except that the ON had a higher ($P<0.05$) proportion of body fat than YN. Cardiorespiratory fitness (VO_{2peak}) was higher in YA (72.8 ± 3.7 $ml\cdot min^{-1}\cdot kg_{FFM}^{-1}$) than OA (54.0 ± 1.9 $ml\cdot min^{-1}\cdot kg_{FFM}^{-1}$), who were both higher than normal weight sedentary (43.4 ± 1.92 for YN and 40.3 ± 2.0 $ml\cdot min^{-1}\cdot kg_{FFM}^{-1}$ for ON) and obese sedentary (39.6 ± 1.7 for YO and 30.7 ± 1.7 $ml\cdot min^{-1}\cdot kg_{FFM}^{-1}$ for OO) subjects.

Within athletes, normal weight or obese subjects, insulin sensitivity (Rd) was not different according to age (Figure 1). Regardless of age, athletes were more insulin sensitive than normal weight sedentary subjects, who in turn were more insulin sensitive than obese subjects, even after adjusting for fat mass or the proportion of body fat. Similar to peripheral insulin sensitivity, hepatic insulin sensitivity, that is, residual hepatic glucose production during the clamp was similar in older and younger subjects within athlete, normal weight and obese groups (data not shown). Both younger and older obese subjects, however, had greater ($P<0.01$) residual hepatic glucose production.

Conclusions

The key finding was that insulin resistance is not an inherent feature of older age, but that obesity and physical inactivity underlie the purported insulin resistance of aging. While previous studies have examined whether or not insulin resistance is associated with older age (11,12), they either limited their observations to only normal weight subjects, or they did not objectively account for physical fitness or physical activity. Therefore, our results significantly expand upon these studies by comparing, for the first time, insulin resistance in younger and older subjects across groups of normal weight,

obese and athletic subjects, who were expected to have a wide range of insulin sensitivity.

We clearly demonstrate that after accounting for both obesity and high level of chronic physical activity, aging per se is not associated with insulin resistance. Moreover, hepatic insulin resistance, measured by residual hepatic glucose production during the clamp, was also similar between younger and older subjects. Thus the similar peripheral insulin sensitivity between older and younger subjects was not confounded by residual hepatic glucose production.

Our study was not designed to determine potential mechanisms for insulin resistance associated with age, obesity or physical inactivity, nor does it rule out possible differences in the etiology of insulin resistance between older and younger persons. While the study of highly trained athletes is useful to compare younger and older subjects at very high levels of both physical activity and insulin sensitivity, it does not allow us to extrapolate these findings to subjects with more moderate physical activity levels that correspond to current physical activity recommendations (13). However, these data are consistent with studies demonstrating significant improvements in insulin sensitivity induced by moderate exercise in older subjects (7). Therefore, although more modest levels of physical activity can improve insulin sensitivity in this population, further investigations are needed to determine whether older and younger obese adults experience similar improvements in insulin sensitivity with weight loss and moderate exercise programs.

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Figure legends

Figure 1

Insulin sensitivity in athletes and sedentary normal weight and obese, young and old, individuals

Bars are mean rates of insulin-stimulated glucose disposal (Rd), error bars are SEM.

One way ANOVA with Tukey-Kramer HS adjustment: * denotes

difference ($P < 0.05$) between athletes and either normal weight or obese, ** denotes

significant difference ($P < 0.05$) between normal weight and obese.

