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Improvements in insulin sensitivity are blunted by subclinical hypothyroidism

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ABSTRACT

Purpose: Exercise and weight loss induced improvements in insulin resistance (IR) are variable; some individuals experience robust enhancements in insulin sensitivity, while others do not. Thyroid hormone status is related to IR, but it is not clear whether subclinical hypothyroidism may help to explain the variability in improvements in IR with diet and exercise. The purpose of this study was to examine whether thyroid hormone status is related to the improvement in insulin sensitivity and physical fitness following weight loss and exercise training.

Methods: By retrospective nested case control analysis, 8 subclinical hypothyroid (sHT) subjects and 8 matched euthyroid controls underwent a euglycemic hyperinsulinemic clamp and peak oxygen uptake test, before and after a 16-week program of moderate aerobic exercise combined with diet induced weight loss. All subjects were middle aged (57.3±3.3years), overweight to obese (BMI 33.1±0.8kg/m^2) and impaired glucose tolerant.

Results: The improvement in insulin sensitivity was significantly lower (p<.05) in the sHT group than in the euthyroid group. Both groups performed similar amounts of regular exercise and lost a significant amount of body weight during the intervention. VO_2peak tended to improve in the euthyroid group but not in the sHT group.

Conclusion*:* Subclinical hypothyroidism may interfere with beneficial adaptations on muscle metabolism and physical fitness that typically occur with weight loss and increased physical activity. These results may have significant clinical implications due to the high prevalence of both hypothyroidism and insulin resistance in the aging population.

KEY WORDS

Exercise, obesity, physical activity, type 2 diabetes, thyroid function

INTRODUCTION

Paragraph 1 Insulin resistance(IR), known as a characteristic trait of type 2 diseases (24), is associated with obesity (19) and aging (13).Weight loss and increased regular physical activity is currently the first line of standard care. The combination of a moderate weight loss with physical activity has been shown to be effective in reducing the incidence of type 2 diabetes (11, 18) and to improve insulin sensitivity (16) . However, weight loss and exercise-induced improvements in IR are variable; some individuals experience robust enhancements in insulin sensitivity, while others do not. In a previous study (16), we found that 8% of subjects did not improveinsulin sensitivity following a weight loss and exercise program.

Paragraph 2 Subclinical hypothyroidism (sHT) is essentially a biochemical diagnosis with an elevation in serum thyroid stimulating hormone (TSH) with normal levels of thyroid hormones (10). The world-wide prevalence of subclinical hypothyroidism ranges from 1 to 20% depending on age, sex and iodine intake. In a large cross-sectional study in Colorado (7), the mean prevalence was reported as 9%, but was higher in women. Aging is also associated with an increased prevalence of subclinical hypothyroidism (5, 7, 14). In subjects over 60 years old, the prevalence was about 15% for women and 8 % for men (7). Although the exact cut off point for the definition of subclinical hypothyroidism and its management are still controversial among endocrinologists (21, 26-28), many adverse associations between subclinical hypothyroidism or a TSH level in the upper part of the reference range and components of the metabolic syndrome have been found. These include an association with dyslipidemia (4, 8, 23), with systolic and diastolic high blood pressure (3), and with increased insulin resistance measured by the HOMA index (23). Altered muscle metabolism, in terms of pattern of substrate utilization in sHT patients has also been described during an incremental bout of exercise (9).

Paragraph 3 Although thyroid hormone status is related to IR, it is not clear whether a TSH in the upper part of the reference range may help to explain the variability in weight loss- or exercise-induced improvements in IR. The purpose of this study was to examine whether thyroid hormone status was associated with the improvement in insulin sensitivity and physical fitness following four months of weight loss and exercise training in impaired glucose tolerant (IGT) obese subjects. We hypothesized that subclinical hypothyroidism may undermine the beneficial adaptations to lifestyle modifications, blunting the improvement of insulin sensitivity by weight loss and exercise training.

METHODS

Study Design, Subjects and Intervention

Paragraph 4 All subjects included in this nested case control analysis were enrolled in our ongoing clinical trial, which is a 16-week pre/post intervention that includes exercise and weight loss. Volunteers were included if they were in good health, without recent illnesses, currently not engaged in a regular program (one or less days per week of continuous physical activity), 30 to 75 years old, impaired glucose tolerant (2h OGTT>140mg/dl but<200 mg/dl), overweight or obese (BMI 25-38 kg/m^2) and weight stable (±3 kg) for at least 6 months before the study. Subjects were excluded if they had a history of type 2 diabetes, coronary heart disease, peripheral vascular disease, uncontrolled hypertension and if they were taking chronic medications known to affect glucose homeostasis. Thyroid Stimulating Hormone (TSH) was measured among other screening tests and volunteers were excluded if they had overt hypothyroidism (TSH>8uIU/ml). The protocol was approved by the University of Pittsburgh Institutional Review Board. All volunteers gave written informed consent.

Paragraph 5 The exercise training protocol consisted of 16 weeks of moderate intensity supervised aerobic exercise. Subjects were asked to engage in 3 to 5 sessions per week with at least 3 sessions supervised in our facility. Each session was 30 to 45 minutes in duration. Subjects could walk, bike or row. The intensity of their workout was monitored by the use of heart rate (HR) monitors (Polar Electro Oy, Finland). Moderate intensity was defined as 75% of their peak HR. The exercise prescription was based on the subject's individual peak HR achieved during graded exercise tests conducted at baseline and adapted at the mid-point of the intervention with a submaximal ergometer test. Exercise logs and HR monitors were also used for the unsupervised sessions to quantify exercise. Adherence to the exercise program was evaluated using the average duration of the exercise sessions, average HR per session and average sessions per week. These measures allowed us to estimate average energy expended per session during the 16 weeks of intervention as previously described (22).

Paragraph 6 The weight loss program consisted in a deficit of 500Kcal/day of their habitual diet with less then 30% of calories from fat. Subjects met weekly with our registered dietitian. All subjects were maintained weight stable for the last 2 weeks before the post-intervention measurements.

Definition of Cases and Controls

Paragraph 7 Cases and controls were defined by transforming the baseline Thyroid Stimulating Hormone (TSH) level in a dichotomous variable as follows: sHT cases >3-8 uIU/ml and controls 0.5-3 uIU/ml. Cases were found, then controls were matched on gender, BMI (±2.5 kg/m^2) and age. This process was performed by the first author who was blinded to the outcome data until the selection of cases and controls was complete.

Paragraph 8 The cut off point for the transformation of baseline TSH was chosen based on a recent cross-sectional population based study (3) and on the National Academy of Clinical

Biochemistry Guidelines (21). Due to the ongoing controversy in clinical endocrinology (27), we acknowledge the different opinions regarding the cut off points and decided to opt for 3 uIU/ml, thus choosing the more statistically conservative approach. If a difference was to be seen with a lower cut off, then indeed the difference would be robust. Also, for the clarity of the text, we named the cases as "subclinical hypothyroidism" and the controls as "euthyroid". However, we understand that the subclinical hypothyroidism group could be seen as a group with serum TSH in the upper level of the reference range.

Outcome Measures

Paragraph 9 Insulin sensitivity was determined by the glucose infusion rate (GIR) of the last 30 minutes of steady state of a 4 hours hyperinsulinemic (40 mU/m^2/min) euglycemic clamp as previously described (16). On the evening before the clamp, subjects were admitted in the Clinical & Translational Research Center. They received a standard dinner (7.5 Kcal/kg of body weight; 50% carbohydrate, 30% fat, 20% protein) and then fasted until completion of the glucose and insulin infusion. For the post intervention assessment, the clamp was performed 36-48 hours following the last exercise session to avoid the acute effects of exercise on insulin sensitivity.The GIR reflects mostly skeletal muscle insulin sensitivity as it is assumed that hepatic glucose production is nearly completely suppressed at this insulin infusion rate.

Paragraph 10 Weight was measured on a calibrated medical digital scale (BWB-800, Tanita Corporation, Japan) in undergarments. Height was measured at the same time with a wall-mounted stadiometer. *Body mass index (BMI)* was calculated as weight (kg) divided by square height (m). *Body composition*, including fat mass (FM), fat free mass (FFM) and percent of body fat (BF), was assessed by dual-energy X-ray absorptiometry (Lunar, GE Lunar Prodigy and Encore 2005 software version 9.30). Fat free mass (FFM) was used to express physical fitness and insulin sensitivity in relative units.

Paragraph 11 Physical fitness was determined by the peak aerobic capacity (VO_2 peak) measured using a graded exercise protocol on an electronically braked cycle ergometer (Ergoline 800S, Sensormedics, Yorba Linda, CA) as described previously (22). Heart rate, blood pressure and electrocardiogram were recorded before, during and after the exercise test. Oxygen consumption was computed via indirect calorimetry (Moxus, AEI Technologies, Pittsburgh).

Blood Analyses

Paragraph 12 TSH was obtained in the morning after an overnight fast and was processed through standard hospital certified laboratory protocols at the Special Chemistry Lab (Department of Pathology) with an automated platform using the chemoluminescence technique (Centaur, Siemens Medical Solutions, Tarrytown, NY). Plasma glucose during the screening OGTT and the glucose clamp were measured using an automated glucose oxidase reaction (YSI, 2300 Glucose Analyzer, Yellow Springs, OH).

Statistical Analysis

Paragraph 13 Although nested case control studies are considered strong observational studies (15) due to the fact that selection biases are reduced, we first explored the data with statistical tests specific for small sample sizes (non parametric test). These include the Wilcoxon signed rank test (within group comparison) and the Mann-Whitney test (between group comparison). After assessing the normality of the data (Lilliefors test of normality) and possible outliers, we carried out parametric tests. These included independent t tests to assess baseline differences between groups and exercise adherence parameters. A 2x2 repeated measures ANOVA was performed on the dependent variables as a function of group (2 levels: sHT and controls) and time (2 levels: pre and post intervention). The assumptions of compound symmetry were checked with the Box's M and the Mauchly's test.

Data are presented as mean and standard error of the mean (SE). The P values reported in the results are those of the parametric tests. Nonparametric tests are detailed in Figure 1. The alpha level was set a priori at .05. All the analyses were performed in a 2-tails approach using Stata for Windows, version 9.2 (StataCorp, Colege Station, TX) and SPSS for Windows, version 13.0 (SPSS inc., Chicago, IL).

RESULTS

Baseline characteristics

Paragraph 14 Among the subjects that adhered to the exercise intervention (>2 supervised exercise sessions per week), 8 cases were found, 5 females and 3 males. Their mean TSH was 3.96±.56 uIU/ml, with a range from 3.06 to 7.66. Controls (1:1) were matched as described above. Controls mean TSH was 1.75±.31 uIU/ml, with a range from .71 to 2.79. The baseline characteristics for the cases and controls can be found in Table 1. No significant differences were found between groups at baseline for any of the variables (weight, BMI, FM, FFM, BF, physical fitness and insulin sensitivity).

Improvements with intervention

Paragraph 15 No significant differences were found between groups on the average duration of exercise performed per session, the average intensity performed per session (% of maximal HR), the average number of sessions per week and the average calories expended per session (Table 2).

Paragraph 16 Percent changes in insulin sensitivity, weight and VO_2 peak are presented in figure 1. The improvement in insulin sensitivity was significantly greater in the controls compared to the cases (Interaction effect, p=.037). Both the cases and the controls lost a similar and significant amount of BMI (and weight) with intervention (Main effect of time, p<.001)

without a significant difference between the 2 groups. Physical fitness tended to increase in the controls but not in the cases (Interaction effect, p=.07).

DISCUSSION

Paragraph 17 Physical activity and moderate weight loss are advocated for the treatment of obesity and insulin resistance in subjects with impaired glucose tolerance at risk for type 2 diabetes. Unfortunately, improvements in insulin resistance are variable; while most individuals experience robust enhancements in insulin sensitivity, some do not. In our study, insulin sensitivity significantly improved in the euthyroid group but not in the subclinical hypothyroid subjects. Physical fitness determined by VO_2 peak tended to improve in the euthyroid group but not in the hypothyroid subjects. This was despite the fact that both groups lost a significant amount of weight with the intervention. The findings of this nested case control study support the hypothesis that subclinical hypothyroidism may in part explain the variability in improvements in insulin resistance and physical fitness that typically occur with weight loss and increased physical activity.

Paragraph 18 The differential response in the improvement in insulin sensitivity was not explained by the degree of weight loss or fat mass. Although not measured in this study, the possibility remains that changes in regional fat distribution, particularly changes in abdominal adipose tissue, could explain part of this difference. Subjects exercised at a similar intensity, with a similar duration of exercise per session and similar number of sessions per week. The estimated energy expenditure per exercise session was similar in both groups. Therefore, exercise adherence was similar, and we do not have evidence that thyroid status influenced the overall energy expenditure during exercise. The lack of significance in the improvement in physical fitness (VO_2 peak) is likely due to the rather large variability in this response to moderate

increases in physical activity. Although in the larger study we did not observe a relationship between the change in physical fitness and the change in insulin sensitivity, in this small nested case control sample a significant positive relationship was found R^2=0.30 P=0.03. Thus, it is possible that the blunted response in VO_2 peak may be one factor for the blunted response in insulin sensitivity.

Paragraph 19 This efficacy-oriented study was not designed to take into account any generalizability element due to relatively small sample sizes. The purpose was only to examine the internal validity of our hypothesis based on physiological markers. Thus, we only included subjects that were adherent to the exercise regimen and defined the cases and the controls using solely the dichotomous transformation of the baseline TSH level without taking into account any prior diagnosis or treatment of thyroid disease. TSH measurement in our healthy and asymptomatic volunteers was performed only for screening purposes (12). In individuals with an intact hypothalamic-pituitary axis, serum TSH is more sensitive than free T4 for detecting sHT (21). Thus we did not measure serum thyroid hormones levels or thyroid antibodies. We acknowledge this as a limitation, as well as the ongoing controversy among endocrinologists regarding the exact definition (serum TSH cut off point) and treatment for subclinical hypothyroidism (2). Our study is not intended to show that a lower cut off point is needed to define subclinical hypothyroidism; it supports the hypothesis of an association between thyroid status and exercise-induced changes in insulin resistance.

Paragraph 20 The potential mechanisms that could explain this blunted effect on muscle metabolism are not yet clearly identified. Prior studies in animal models showed that thyroid hormones play a role in the regulation and activation of signaling pathways, such as AMPK (6) , on insulin receptors (20) and glucose transporter proteins (29) , and impacts the expression of different isoforms of skeletal muscle myosin heavy chains (1). In hypothyroidism, skeletal

muscle structural, biochemical and electromyographic changes have been reported (17) as well as mitochondrial alterations (25). It is not known if these skeletal muscle alterations already exist in subclinical hypothyroidism; if present these may potentially limit exercise-induced changes in skeletal muscle metabolism and peripheral insulin sensitivity. Further investigations are clearly needed to identify mechanisms underlying the attenuation or elimination of improved insulin sensitivity and physical fitness with weight loss and exercise due to thyroid status.

Paragraph 21 In summary, despite similar amounts of exercise and weight loss, insulin sensitivity and physical fitness improved in euthyroid but not in subclinical hypothyroid subjects. Therefore, subclinical hypothyroidism may interfere with beneficial adaptations on metabolic risk factors that typically occur with weight loss and increased physical activity. Due to the important prevalence of this condition particularly in women and in the aging population, this observation may have considerable clinical implications. Thyroid status could explain why some individuals do not seem to respond to traditional lifestyle modification programs that include diet and exercise. Further studies are needed to corroborate this observation, explore potential mechanisms for this effect, and to investigate whether treatment with thyroid hormone replacement may restore the ability to respond to lifestyle modifications.

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CONFLICT OF INTEREST

Paragraph 23 The authors have nothing to disclose. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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FIGURES TITLES AND LEGENDS

Figure 1

Title: Percent changes by group

1a. Change in glucose infusion rate

1b. Change in BMI

1c. Change in VO_2peak

Legend:

Solid bar represents the sublinical hypothyroid group, shaded bar the euthyroid control group.

Bars show mean percent change. Error bars show SE.

# P<.05 and §=.08 between group comparison (Mann-Whitney test)

* P<.05 and †=.09 within group comparison (Wilcoxon signed-rank test).

TABLE 1

Body composition, physical fitness and insulin sensitivity before and after intervention

Variables	Cases N=8		Controls N=8	
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Age (years)	57.8 (4.7)		56.9 (5.0)	
Weight (kg)	88.3 (4.7)	82.5 (4.9)	94.4 (3.8)	87.0 (3.8)
BMI (kg/m^2)	33.2 (1.0)	31.0 (1.2)	33.1 (1.2)	30.5 (1.0)
Fat mass (kg)	36.2 (2.7)	31.8 (2.7)	39.4 (2.4)	33.3 (2.1)
Fat free mass (kg)	50.3 (3.9)	49.0 (3.5)	52.5 (4.4)	51.5 (4.2)
Body fat (%)	41.3 (2.5)	38.6 (2.3)	42.4 (3.0)	38.8 (2.9)
VO_2 peak (l/min)	2.02 (.22)	1.96 (.22)	2.12 (.27)	2.28 (.33)
VO_2 peak ($ml/kg_{FFM}/min$)	39.5 (3.4)	39.5 (4.0)	39.8 (2.5)	43.0 (3.0)
Glucose Infusion Rate (mg/min)	278.1 (27.7)	335.7 (43.9)	276.3 (31.4)	432.2 (44.5)
Glucose Infusion Rate ($mg/kg_{FFM}/min$)	5.71 (.69)	6.91 (.89)	5.81 (1.07)	8.97 (1.27)

Notes:

Data are presented as mean (SE)

TABLE 2

Exercise Adherence

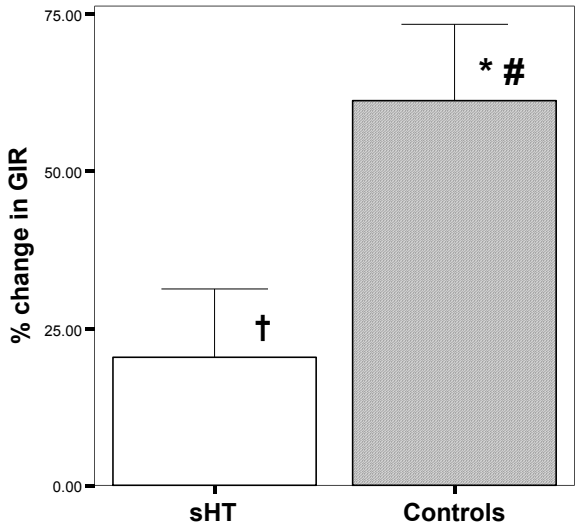
Variables	Cases N=8	Controls N=8	P value
Avg time/session (min)	38.5 (3.3)	39.2 (1.5)	.85
Avg HR/session (% of maximal HR)	77.0 (2.6)	76.6 (2.0)	.89
Avg sessions/week	3.5 (.4)	3.5 (.2)	.94
Avg Energy Expended/session (Kcal)	226.8 (30.0)	277.1 (32.4)	.27

Notes:

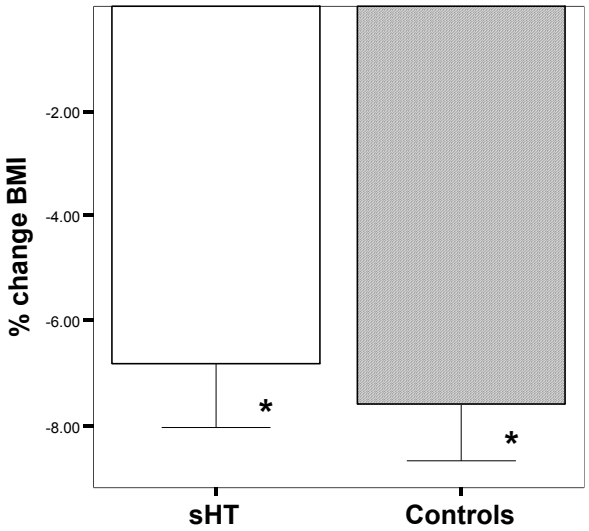
Data are presented as mean (SE)

P values are for 2-sided independent T test

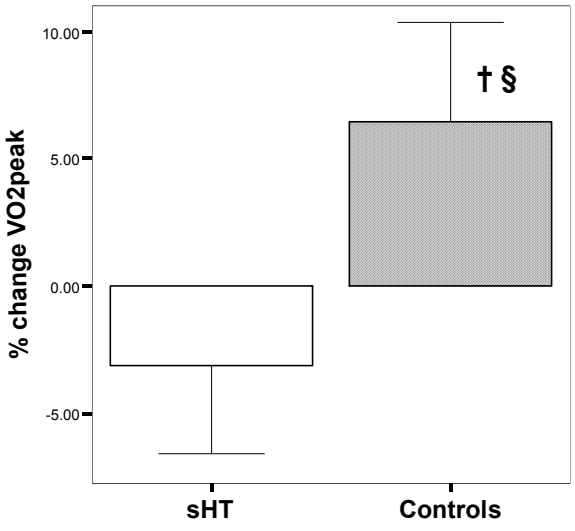
Figure 1: Percent changes by group



1a. Change in glucose infusion rate



1b. Change in BMI



1c. Change in VO_2 peak