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THYROID STATUS, INSULIN SENSITIVITY AND GLUCOSE TOLERANCE IN OVERWEIGHT AND OBESE ADULTS BEFORE AND AFTER 36 WEEKS OF WHEY PROTEIN SUPPLEMENTATION AND EXERCISE TRAINING

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Abstract

Research suggests that subclinical hypothyroidism influences insulin sensitivity and glucose tolerance. Reductions in thyroid stimulating hormone concentrations are associated with exercise training, which improves insulin sensitivity and glucose uptake.

Purpose—A secondary analysis of a previously published data was conducted to examine the relationship between subclinical hypothyroidism, thyroid stimulating hormone, and glucose homeostatic control at baseline and to assess the impact of exercise training on thyroid status and how subclinical hypothyroidism affects changes in insulin sensitivity after exercise training.

Materials and Methods—Data were obtained from a 36-week exercise training and whey protein supplementation intervention trial. Subjects ($n = 304$, 48 ± 7 years, females = 186) were randomized to a specific whey protein group (0g, 20g, 40g, or 60g per day) and all subjects participated in a resistance (2 d/wk) and aerobic (1 d/wk) training program. Testing was conducted at baseline and post-intervention.

Results—At baseline, 36% ($n=110$) and 12% ($n=35$) of subjects were classified with subclinical hypothyroidism based on the thyroid stimulating hormone $3\mu\text{IU/L}$ or thyroid stimulating hormone $4.5\mu\text{IU/L}$ cut-offs, respectively. No association was found between baseline thyroid stimulating hormone and baseline measures of glucose homeostatic control. Whey protein

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The trial was registered at clinicaltrials.gov as NCT00812409.

DECLARATION OF INTERESTS

WWC was a member of the National Dairy Council Whey Protein Advisory Panel while the current research was being conducted. None of the other authors had any personal or financial conflicts of interest.

supplementation did not influence intervention outcomes. Post-intervention (n=164), no change was observed in thyroid stimulating hormone. Subclinical hypothyroidism did not affect changes in insulin sensitivity following exercise training.

Conclusion—These results support that the health benefits of exercise training for the management of insulin resistance are not blunted by subclinical hypothyroidism.

Keywords

Subclinical hypothyroidism; insulin sensitivity; insulin resistance; thyroid stimulating hormone; glucose tolerance

INTRODUCTION

Though overt hypothyroidism is associated with insulin resistance (IR) (1), associations between subclinical hypothyroidism (SHT) and IR are still unclear. SHT is a grade of primary hypothyroidism described as an elevation in thyroid stimulating hormone (TSH) concentrations in the presence of normal serum thyroxine (T4) concentrations (4.5–12.0 µg/dL) (2). The exact definition of SHT, however, is still an area of debate. Different recommendations for the TSH upper limit are proposed, either based upon NHANES data which shows a population TSH range (2.5th–97.5th percentile) of 0.45–4.12 µIU/L (Upper-limit: 4.5 µIU/L (3)) or the normalization of this non-Gaussian distributed NHANES data (97.5th percentile: 2.5 µIU/L) and additional longitudinal data showing higher incidents of clinical thyroid disease with TSH concentrations > 3.0 µIU/L (4). This difference of ±1.5 µIU/L has resulted in a positive association between SHT and IR, specifically a positive relationship between IR and TSH, in some studies (5, 6) but not others (7, 8).

Current recommendations for the treatment of IR include daily physical activity and exercise training (ExTr) (9), which were also shown to reduce TSH in healthy adults (10, 11). However, not all studies have shown a reduction in TSH following ExTr (12). Additionally, limited research suggests that SHT, versus a normal range, may blunt improvements in insulin sensitivity during ExTr (13).

Given the inconsistencies in the data concerning the relationship between SHT, IR, and the potential beneficial effect of ExTr on TSH in relation to markers of glucose tolerance and insulin sensitivity, a secondary analysis of data from a randomized control trial was conducted. The aims were to assess 1) the relationships between TSH, T4, and glucose homeostatic-control at baseline, 2) the effects of ExTr on TSH and T4, and 3) the effects of baseline TSH and T4 on changes in insulin sensitivity and glucose tolerance following ExTr. We hypothesise that elevated TSH and normal T4 will be associated with IR at baseline, ExTr will reduce baseline TSH, and improvements in insulin sensitivity following ExTr will be blunted by higher TSH.

MATERIALS AND METHODS

Study Design

Data were used from a double-blind, placebo-controlled, community-based, randomized 36-week intent-to-treat whey protein intervention study conducted from 2007–2010 (14). Subjects were 304 overweight and obese middle-aged males and females (35–65 years old; 115 males, 189 females) randomized to consume a daily whey protein supplement of different protein quantity while engaging in resistance (2 d/wk) and aerobic (1d/wk) ExTr for 9 months. Details of inclusion criteria, randomization scheme, resistance and aerobic training protocols, baseline and post anthropometric and biomedical measurements, and compliance records are published elsewhere (14). Blood samples were collected after a 12-h overnight fast in tubes containing sodium heparin to obtain plasma (BD Vacutainer Brand; Becton, Dickinson and Co). Following 3-h oral-glucose-tolerance test (OGTT) where blood samples were collected every 30 min, plasma glucose and insulin concentrations were measured and homeostatic model assessment of insulin resistance (HOMA-IR) (15) and whole-body (composite) insulin sensitivity index (ISI) (16) were calculated. Plasma glucose concentrations were measured via enzymatic colorimetry using an oxidase method on a COBAS Integra 400 analyzer (Roche Diagnostic Systems). Plasma insulin concentrations were measured by an electrochemiluminescence immunoassay method on the Elecsys 2010 analyzer (Roche Diagnostic Systems). Serum thyroid stimulating hormone (TSH) and total thyroxine (T4) concentrations were measured using an electrochemiluminescence immunoassay (“ECLIA”) on an Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, IN). Participants taking medications for elevated blood pressure, reduced high density lipoprotein cholesterol (HDL-C), or elevated triacylglycerol, including statins, were included. Participants with abnormal thyroxine concentrations (<4.5 or >12.0 $\mu\text{g/dL}$), taking anti-thyroid medications or thyroid replacement hormones such as levothyroxine were excluded from this analysis. The total numbers of subjects included in the analysis for this study are 304 and 164 at baseline (pre-intervention) and week 36 (post-intervention), respectively. The Purdue University Institutional Review Board approved the study protocol, which complied with the Helsinki Declaration as revised in 1983.

Statistical Analyses

TSH and T4 were both treated as continuous and categorical variables, which allowed for the comparison of the absolute amount of TSH and T4 to outcome variables and the comparison of outcome variables between SHT and normal TSH subjects. Serum TSH was categorised as ≤ 3 $\mu\text{IU/L}$ and > 4.5 $\mu\text{IU/L}$ to classify SHT, according to the variations in the TSH upper limit recommendation (3, 4). Whey protein supplementation did not influence the current study’s outcome variables; therefore data from the four supplementation groups were combined for the current analysis. Sensitivity analysis revealed total fat mass and body fat percent at baseline were different in those who completed the study ($n=164$) then those with baseline data only ($n=140$). Baseline fat mass and body fat percent were then controlled for in all analyses. Analysis of covariance with baseline TSH and T4 as factors was used to assess baseline fasting plasma glucose and insulin, HOMA-IR, plasma glucose and insulin 2 hours post oral glucose tolerance test (OGTT), and insulin sensitivity index (ISI), controlling for the significant covariates: age,

gender, menopausal status, hormone replacement therapy, baseline body mass index, total fat mass, and body fat percent. Partial eta squared (η^2) were computed to address effect size of each factor or covariate. Log transformations were performed on dependent variables (plasma glucose and insulin 2hr OGTT) that were not normally distributed prior to performing analysis of covariance. Pearson's and partial correlations were run for pre and post-intervention and change over time. Partial correlations were computed controlling for covariates for glucose and insulin parameters. Additional correlations were computed controlling for age and gender for markers of adiposity.

RESULTS

Outcomes from Parent Study

The body composition and glucose tolerance results from the 36-week whey protein and exercise intervention trial (14) were as follows: body mass was unchanged, lean body mass and fasting glucose increased, while BMI, fat mass, and 2h plasma insulin decreased over time (i.e. with ExTr; Table 1). At baseline, 52% of the study population was obese ($n=157$, >30 BMI), 58% displayed elevated waist circumference measurements ($n=176$, Men: >102 cm, Women: >88 cm), and 21% showed signs of insulin resistance ($n=63$, <2.5 ISI). Whey protein supplementation did not influence these responses or the current study's outcomes of interest; therefore data from the four supplementation groups were combined for the current analyses. Figure 1 describes the flow of participants from baseline assessment to post-intervention.

Relationships Among Thyroid Status, Insulin Sensitivity and Glucose Tolerance

At baseline, 36% ($n=110$) and 12% ($n=35$) of subjects were classified with SHT based upon the TSH ≤ 3.0 μ IU/L or >4.5 μ IU/L cut-off, respectively (Table 1). No differences in measures of glucose and insulin parameters at baseline were observed between TSH groups ≤ 3.0 μ IU/L and >4.5 μ IU/L (Table 2). TSH was also not correlated with any of the glucose and insulin parameters at baseline with or without controlling for significant covariates: age, gender, menopausal status, hormone replacement therapy, baseline body mass index, total fat mass, and body fat percent (Table 3).

The Effects of Exercise on Thyroid Status

Serum TSH was not changed following ExTr ($P=0.65$).

The Effects of Thyroid Status on Changes in Insulin and Glucose Parameters with Exercise

TSH was not correlated with any glucose or insulin parameter post-intervention with or without controlling for covariates (Table 3). No differences in the glucose and insulin parameters after ExTr were observed between TSH groups ≤ 3.0 μ IU/L and >4.5 μ IU/L.

Baseline TSH did not correlate with changes in glucose or insulin parameters over the 36-week intervention (Table 4). Analysis of covariance revealed no effect of age, gender, baseline BMI or TSH (as independent variables) on changes in glucose and insulin parameters (as dependent variables).

DISCUSSION

Due to their metabolically influential interactions (1, 9–11) and associations to cardiovascular disease, type 2 diabetes, and cancer (17), it is important to assess the relationship between markers of IR, TSH, and the effect of ExTr. At baseline, 12–36% of subjects had SHT based on cut-off points for TSH of $3.0 \mu\text{IU/L}$ (4) or $4.5 \mu\text{IU/L}$ (3). These estimates of prevalence exceed those of other studies reporting a prevalence of 4.6% using the $4.5 \mu\text{IU/L}$ cut-off (18) and 8.6% using the $3.0 \mu\text{IU/L}$ cut-off (19). The higher prevalence of SHT in the current study may be due to our focus on overweight and obese individuals who often have elevated TSH as a result of greater fat mass versus thyroid dysfunction (8), whereas previous studies showcased a broader population base.

A decrease in the production and utilization of glucose is often observed in hypothyroid states (20), thus it is hypothesized that similar effects may be seen in SHT. In contrast to other studies (21, 22), when TSH was analysed as a continuous variable, no significant interaction was found between baseline thyroid status and markers of IR. Previous findings were predominately in severely obese adults, with a mean BMI 40 kg/m^2 , versus the current study's overweight and obese population (mean BMI $\approx 30 \text{ kg/m}^2$). Similar non-significant findings were shown in more comparable populations of overweight and obese women (23).

Previous research documents associations between energy balance, thyroid function and total body mass, as weight loss or weight gain decreased or increased TSH, respectively (24, 25). In contrast to these findings changes in TSH over time were not observed in the current study. Though participants experienced changes in body composition following ExTr, the weight stability and moderate intensity of ExTr may account for the unaltered TSH. Similar changes in body composition failed to affect thyroid concentrations during a modest (-0.7% BW per week) versus intense (-1.4% BW per week) weight loss intervention period (26). Furthermore, though TSH decreased in young athletic college rowers during a 10-week intense exercise phase, TSH returned to baseline upon entering the study's 10-week moderate exercise phase (10). Details of the study's exercise regimen were not entirely specified; however it is likely the current study's ExTr closely resembles the moderate exercise phase of Baylor and Hackney (2013). Additionally, it is important to note the vast differences between the two study's populations (20 ± 0.8 years old, 23.8 BMI vs. 49 ± 8 years old, 30.0 BMI), as they are not only metabolically different (27) but also differ in their responses to ExTr (28).

To our knowledge, this is one of only two studies to assess the effects of thyroid status on changes in glucose and insulin parameters following ExTr. In contrast to the current study, Amati et al. (2009) showed that participants with serum TSH $< 3 \mu\text{IU/L}$ had greater improvements in insulin sensitivity following ExTr than those with serum TSH $\geq 3 \mu\text{IU/L}$, whom they defined as SHT. Amati et al. (2009) questioned whether the improvements in insulin sensitivity were due in part to changes in regional adiposity, particularly of the abdominal region. In the current study, waist circumference and body composition did not significantly affect the relationship between TSH and glucose homeostatic-control.

The current study is valuable as it measures TSH in a group of middle-aged, overweight and obese adults who are at high risk for cardiovascular diseases, type 2 diabetes, and other illnesses linked to IR (29). Multiple indices of insulin sensitivity and glucose tolerance were assessed, including fasting plasma glucose and insulin, HOMA-IR, plasma glucose and insulin 2 hours following a 75g standard glucose dose. There are admittedly some limitations to our study. As a secondary assessment, our data analysis cannot provide causality but only reveal associations. Even though our small effect sizes for TSH and T4 support our conclusions, the current sample size was not specifically calculated for the study's hypotheses. Participants included in our analysis also may not be representative of the entire population because of their higher risk of metabolic syndrome, given the specific age and weight inclusion criteria.

In conclusion, there was no indication that middle-aged, overweight/obese adults with SHT had a higher prevalence of IR than those with normal thyroid status before or after 36 weeks of ExTr. ExTr did not influence serum TSH concentrations, consistent with a null effect on thyroid status. Likewise, thyroid and SHT status did not influence the metabolic or physiological responses to ExTr such as changes in body composition and glucose tolerance. These results indicate that SHT does not blunt or limit the health benefits of exercise in the management of IR.

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Fig 1.
CONSORT Diagram
Flow diagram of participants through study

Table 1

Subject characteristics at baseline and after a 36-week period of exercise training

Variable	Baseline (<i>n</i> = 304)	Post-intervention (<i>n</i> = 164)	Delta (<i>n</i> = 164)	* <i>p</i>
Age (y)	48 ± 8	49 ± 8		NA
Body mass (kg)	86.5 ± 16.0	87.8 ± 13.1	0.03 ± 13.1	0.920
BMI (kg/m ²)	30.3 ± 2.6	30.0 ± 2.8	−0.4 ± 2.8	0.021
Fat mass (kg)	35.2 ± 6.2	33.6 ± 7.3	−0.9 ± 3.1	<0.001
Fat mass (%)	40.5 ± 6.4	38.5 ± 7.0	−1.4 ± 4.1	<0.001
Lean body mass (kg)	49.6 ± 10.4	51.3 ± 10.6	0.9 ± 1.2	<0.001
Serum TSH (μIU/L)	2.9 ± 1.6	3.0 ± 1.8	0.04 ± 1.3	0.632
T4 (μg/dL)	7.3 ± 1.2	7.3 ± 1.2	−0.07 ± 0.8	0.264
Fasting plasma glucose (mmol/L)	5.3 ± 0.5	5.4 ± 0.5	0.08 ± 0.5	0.033
Fasting plasma insulin (pmol/L)	80.7 ± 49.3	78.8 ± 45.6	1.1 ± 32.6	0.663
HOMA-IR (μU/mL)	2.8 ± 2.1	2.8 ± 1.7	0.08 ± 1.2	0.321
2h plasma glucose (mmol/L)	6.7 ± 1.9	6.5 ± 1.9	−0.08 ± 1.9	0.624
2h plasma insulin (pmol/L)	523.8 ± 441.9	371.8 ± 281.2	−111.5 ± 281.9	<0.001
Composite ISI	5.0 ± 3.1	5.5 ± 4.1	0.3 ± 3.1	0.145

Values are means ± SD. Delta values (post-baseline) are reported for subjects who completed the intervention.

* Paired t test was performed for subjects who completed the intervention.

Abbreviations: TSH, thyroid stimulating hormone; HOMA-IR, homeostatic model assessment of insulin resistance; 2-h insulin and 2-h glucose refer to measurements taken at hour 2 of the oral glucose tolerance test; ISI, whole body (composite) insulin sensitivity index

Table 2

F test for serum TSH $</ 3\mu\text{IU/L}$ and $</ 4.5\mu\text{IU/L}$ at baseline against glucose and insulin parameters as dependent variables

Variable (df = 1)	Fasting Insulin($n = 304$)			Fasting Glucose($n = 304$)			HOMA-IR($n = 304$)			2-h Insulin ^a ($n = 302$)			2-h Glucose ^a ($n = 302$)			ISI($n = 301$)		
	F	P	Partial η^2	F	P	Partial η^2	F	P	Partial η^2	F	P	Partial η^2	F	P	Partial η^2	F	P	Partial η^2
TSH $3\mu\text{IU/L}$	0.20	.659	.001	0.01	.940	<.001	0.14	.706	.001	0.40	.526	.003	0.03	.853	<.001	0.05	.819	<.001
T4	1.14	.323	.015	0.62	.542	.008	1.28	.281	.017	0.74	.478	.010	1.78	.171	.023	0.88	.416	.012
TSH $4.5\mu\text{IU/L}$	1.98	.161	.007	0.27	.606	.001	1.21	.273	.004	1.05	.307	.004	0.14	.707	.001	1.96	.163	.007
T4	0.78	.460	.006	2.46	.087	.017	0.97	.382	.007	2.25	.107	.016	2.65	.073	.019	1.95	.145	.014

Analysis of covariates was performed with TSH and T4 as factors and age, gender, menopausal status, hormone replacement therapy, baseline BMI, total fat mass, and body fat percent for covariates.

^a Responses were transformed using natural logarithm to satisfy normality assumption of residuals.

* $p < .05$

Abbreviations: TSH, thyroid stimulating hormone; T4, thyroxine; η^2 , partial eta squared; HOMA-IR, homeostatic model assessment of insulin resistance; 2-h insulin and 2-h glucose refer to measurements taken at hour 2 of the oral glucose tolerance test; ISI, whole body (composite) insulin sensitivity index.

Table 3
Pearson's and Partial Correlation between Serum TSH and Glucose and Insulin Parameters

		Baseline			
Serum TSH		Fasting Insulin	Fasting Glucose	HOMA-IR	ISI
<i>Pearson's Correlation</i>					
<i>r</i>	−0.006	−0.061	−0.017	0.030	0.005
<i>p-value</i>	.915	.289	.766	.601	.932
<i>N</i>	304	304	304	302	301
<i>Partial Correlation</i>					
<i>ρ</i>	0.005	−0.044	0.008	0.026	−0.014
<i>p-value</i>	.930	.464	.898	.667	.814
<i>N</i>	283	283	283	283	283

		Post-Intervention			
Serum TSH		Fasting Insulin	Fasting Glucose	HOMA-IR	ISI
<i>Pearson's Correlation</i>					
<i>r</i>	0.116	−0.096	0.092	0.043	−0.045
<i>p-value</i>	.142	.224	.246	.583	.569
<i>N</i>	164	164	164	164	163
<i>Partial Correlation</i>					
<i>ρ</i>	0.125	−0.111	0.100	0.034	−0.044
<i>p-value</i>	.122	.170	.216	.675	.590
<i>N</i>	152	152	152	152	152

Partial correlation was computed controlling for age, gender, menopausal status, hormone replacement therapy, BMI, total fat mass, and body fat percentage at baseline.

Abbreviations: TSH, thyroid stimulating hormone; HOMA-IR, homeostatic model assessment of insulin resistance; 2-h insulin and 2-h glucose refer to measurements taken at hour 2 of the oral glucose tolerance test; ISI, whole body (composite) insulin sensitivity index

Pearson’s and Partial Correlation between Baseline Serum TSH and Change in Glucose and Insulin Parameters after Intervention

Table 4

	Baseline Serum TSH	Change in					ISI
		Fasting Insulin	Fasting Glucose	HOMA-IR	2-h Insulin	2-h Glucose	
<i>Pearson's Correlation</i>							
<i>r</i>		0.089	0.001	0.079	0.129	0.117	−0.151
<i>P</i>		.256	.987	.312	.100	.135	.053
<i>n</i>		164	164	164	164	164	164
<i>Partial Correlation</i>							
<i>ρ</i>		0.070	−0.018	0.065	0.112	0.086	−0.145
<i>P</i>		.387	.827	.424	.162	.283	.071
<i>n</i>		154	154	154	154	154	154

Partial correlation was computed controlling for age, gender, menopausal status, hormone replacement therapy, BMI, total fat mass, and body fat percentage at baseline.

Abbreviations: TSH, thyroid stimulating hormone; HOMA-IR, homeostatic model assessment of insulin resistance; 2-h insulin and 2-h glucose refer to measurements taken at hour 2 of the oral glucose tolerance test; ISI, whole body (composite) insulin sensitivity index