The Association Between Weight Gain and Thyroid Function in an Older Population

A recent article\(^1\) and editorial\(^2\) in the Archives investigated the relationship between thyroid function, within the normal reference range and body weight gain. Fox et al\(^3\) observed that change in serum thyrotropin concentration (ΔTSH) was strongly and linearly associated with weight gain. The authors, however, did not account for diet and physical activity, covariates known to be strongly associated with weight change. We also examined the relationship between ΔTSH within the reference range and weight change over a 5-year period, accounting also for baseline dietary parameters and reported physical activity.

Methods. The Blue Mountains Eye Study (BMES) is a population-based cohort study of age-related eye diseases and other health outcomes. Methods used to ascertain and survey this population were previously described.\(^3\) During 1992 though 1994, 3654 participants 49 years or older were examined (82.4% participation; BMES-1). Surviving baseline participants were invited to attend follow-up examinations after 5 years (1997-1999, BMES-2) and 10 years (2002-2004, BMES-3), at which 2334 (75.1% of survivors) and 1952 (75.6% of survivors) participants were reexamined, respectively. Of these, 926 participants were available for final analyses after exclusions (ie, data on missing covariates, use of thyroid hormone, or abnormal TSH level). Serum TSH concentration was measured in these subjects as previously described.\(^4\) and we used the same TSH reference range of 0.5 to 5.0 mIU/L as Fox et al.\(^3\) Change in serum TSH concentration was analyzed as a continuous variable or as quartiles.

Dietary data were assessed using a 145-item food frequency questionnaire.\(^5\) The physical activity questionnaire was based on the International Physical Activity Questionnaire.\(^6\) Total metabolic equivalents were calculated for each individual, based on their report of time spent performing moderate and/or vigorous activities.

Results. At follow-up, ΔTSH ranged from –2.05 to 3.29 mIU/L in men and from –2.50 to 3.22 mIU/L in women. In women, weight increased by 0.8 kg for every 1-unit increase in TSH during the 5-year period (\(P=.01\)) after adjusting for age, baseline body weight (at BMES-2), and current smoking (Table). This association became stronger after further step-wise adjustment for physical activity and dietary covariates such as fat (\(P<.001\)) and carbohydrates (\(P=.002\)). Increasing TSH level (modeled as a continuous variable) during follow-up was associated with a 50% higher likelihood of weight gain of greater than 2 kg after adjusting for age, baseline body weight, and smoking in women (odds ratio, 1.50; 95% confidence interval, 1.10-2.05). This association persisted after further adjustment for physical activity and dietary covariates.

Weight change at follow-up, however, was not associated with ΔTSH in men (\(P=.92\)), either before or after adjusting for physical activity and diet (Table). Analyses by quartiles of ΔTSH were also unrelated to weight change at follow-up either before or after multivariate adjustment.

Comment. We observed, in women but not in men, a strong positive association between ΔTSH over time (within the reference range) and incident weight gain, which is in agreement with the findings of Fox et al\(^3\) but of a lower magnitude. This association actually strengthened after we further adjusted for diet and physical activity. Since Fox et al\(^3\) observed a smaller effect size in men compared with women, it is likely that we had insufficient study power to detect this association in men. We have shown that obesity was a significant predictor of incident overt hypothyroidism (unpublished data, 2008). Our study supports the findings of Fox et al\(^3\) in providing evidence that the physiological mechanism of obesity may exert some influence on thyroid function and vice versa, as suggested by the editorial.\(^2\)

In conclusion, our study provides additional support for the concept that modest changes in thyroid function

### Table. Five-Year Weight Change in Relation to ΔTSH and Sex in BMES Participants

<table>
<thead>
<tr>
<th>ΔTSH</th>
<th>Weight Change in Women (in kg) ((n=589))</th>
<th>Weight Change in Men (in kg) ((n=417))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\beta^a) (95% Confidence Interval)</td>
<td>(P) Value</td>
</tr>
<tr>
<td>Adjusted for age, baseline body weight, and smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per-unit increase in TSH (in mIU/L)</td>
<td>0.80 (0.17 to 1.43)</td>
<td>.01</td>
</tr>
<tr>
<td>Adjusted for age, baseline body weight, smoking, and physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per-unit increase in TSH (in mIU/L)</td>
<td>1.14 (0.47 to 1.81)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted for age, baseline body weight, smoking, physical activity, and mean energy intake(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per-unit increase in TSH (in mIU/L)</td>
<td>1.11 (0.44 to 1.78)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations: BMES, Blue Mountains Eye Study; ΔTSH, change in serum thyrotropin concentration.

\(^a\) \(\beta\)-Adjusted \(\beta\) coefficient.

\(^b\) Weight-adjusted energy.
may be a potential risk factor for the development of obesity, particularly in women.

_Bamini Gopinath, PhD_
_Gerald Liew, MBBS_
_Victoria M. Flood, PhD_
_Jie Jin Wang, PhD_
_Annette Kifley, PhD_
_Stephen R. Leeder, MD, PhD_
_Paul Mitchell, MD, PhD_

**Correspondence:** Dr Mitchell, Centre for Vision Research, University of Sydney, Westmead Hospital, Hawkesbury Road, Westmead, NSW 2145, Australia (paul_mitchell@wmi.usyd.edu.au).

**Author Contributions:** Study concept and design: Gopinath, Liew, and Mitchell. Acquisition of data: Mitchell. Analysis and interpretation of data: Gopinath, Flood, Wang, Killey, and Leeder. Drafting of the manuscript: Gopinath. Critical revision of the manuscript for important intellectual content: Liew, Flood, Wang, Killey, Leeder, and Mitchell. Statistical analysis: Killey. Obtained funding: Mitchell. Administrative, technical, and material support: Gopinath, Liew, and Flood. Study supervision: Wang and Mitchell.

**Financial Disclosure:** None reported.


**COMMENTS AND OPINIONS**

**Thyroid Function and Body Weight: Should We Also Consider the Interplay With Insulin Resistance and Fat Distribution?**

We read with great interest the article “Relations of thyroid function to body weight” by Fox et al.1 As stated by the authors, some evidence suggests that modest increases in serum thyrotropin (TSH) concentration, within the reference range, may be associated with weight gain, but no causality can be inferred.1

On the basis of our experience, we would like to make some comments about this interesting issue. Overt thyroid dysfunction is well recognized to affect body weight, and this may have important clinical significance when obesity, as well as associated metabolic complications (eg, insulin resistance, chronic low-grade inflammation), are the undesirable counterparts. Along with this, the influence of obesity perse on thyroid function remains unclear, but recent observations suggest a relationship through adipocytokines release (eg, leptin) or visceral fat metabolism.2-4

From the overall series of overweight and obese patients admitted to our institutions for weight concern, only 580 euthyroid (TSH reference range, 0.26-5.00 mIU/L) patients were considered (435 female and 145 male patients; age range, 14-70 years; and body mass index range, 25.5-65.8 [median, 35.7] [calculated as weight in kilograms divided by height in meters squared]). According to the BMI classes, mean (SD) TSH levels slightly rose (from 1.48 [0.83] to 1.99 [1.05] mIU/L), while free thyroxine (FT4) levels did not change. Serum TSH levels, but not FT4 levels, were strongly associated with BMI (weight-, sex-, and age-adjusted multiple regression, P < .001).

Furthermore, TSH and FT4 levels showed a positive and negative, respectively, association with waist circumference (P < .001) and with Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) (P < .001), even after correcting for weight, waist circumference, and obesity degree (BMI classes). Moreover, insulin-resistant patients (HOMA-IR ≥ 2.7; 60.6%) had higher mean (SD) TSH levels (1.87 [1.0] vs 1.67 [0.9] mIU/L; P = .02) and lower mean (SD) FT4 levels (0.900 [0.008] vs 0.803 [0.008] ng/dL [to convert to picomoles per liter, multiply by 12.871]; P < .001) than the 39.4% with normal insulin sensitivity.

On the whole, our results again suggest the existence of a relationship between thyroid function and overweight and obesity status.5,6 In addition, it seems likely that the hypothalamic-pituitary-thyroid axis is altered in obesity as a consequence of insulin resistance,7 which reflects both intra-abdominal fat deposition and obesity duration.8 In agreement with Fox et al,1 we cannot state whether variations in TSH and/or thyroid hormone level, within a normal range, can influence body weight or if obesity can alter thyroid function. However, it is hoped that future studies aimed to evaluate the interplay between thyroid function and body weight would better consider not only changes in thyroid hormone levels1,2 but also body fat distribution,1 insulin resistance,1 obesity duration, and low-grade inflammation.5,6 In this regard, it would be of interest to perform further adjustments for both baseline and follow-up changes in BMI and indexes of fat distribution and not only for weight, which may scarcely account for the relationship suggested herein.

Alexis Elias Malavazos, MD
Emanuele Cereda, MD
Alessandra Delneo, MD
Elena Passeri, MD
Antonietta Tufano, MD
Laura Shurlati, MD
Emanuela Orsi, MD
Lelio Morricone, MD
Bruno Ambrosi, MD

**Correspondence:** Dr Malavazos, Endocrinology Unit, Department of Medical and Surgical Sciences, University of Milan, IRCCS Policlinico San Donato, Via Morandi 30, 1-20097, San Donato Milanese (MI), Italy (alexis.malavazos@libero.it).