Impaired Sensitivity to Thyroid Hormones Is Associated With Diabetes and Metabolic Syndrome

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OBJECTIVE

Diabetes prevalence and incidence increase among individuals with hypothyroidism but also among those with hyperthyroxinemia, which seems contradictory. Both high free thyroxine (fT4) and high thyroid-stimulating hormone (TSH) are present in the resistance to thyroid hormone syndrome. A mild acquired resistance to thyroid hormone might occur in the general population and be associated with diabetes. We aimed to analyze the association of resistance to thyroid hormone indices (the Thyroid Feedback Quantile-based Index [TFQI], proposed in this work, and the previously used Thyrotroph T4 Resistance Index and TSH Index) with diabetes.

RESEARCH DESIGN AND METHODS

We calculated the aforementioned resistance to thyroid hormone indices based on a U.S. representative sample of 5,129 individuals ≥20 years of age participating in the 2007–2008 National Health and Nutrition Examination Survey (NHANES). Also, to approximate TFQI, a U.S.-referenced Parametric TFQI (PTFQI) can be calculated with the spreadsheet formula =NORM.DIST(fT4_cell_in_pmol_per_L,10.075, 2.155,TRUE)+NORM.DIST(LN(TSH_cell_in_mIU_per_L),0.4654,0.7744,TRUE)−1. Outcomes of interest were glycohemoglobin ≥6.5%, diabetes medication, diabetes-related deaths (diabetes as contributing cause of death), and additionally, in a fasting subsample, diabetes and metabolic syndrome. Logistic and Poisson regressions were adjusted for sex, age, and race/ethnicity.

RESULTS

Odd ratios for the fourth versus the first quartile of TFQI were 1.73 (95% CI 1.32, 2.27) (P_{trend} = 0.002) for positive glycohemoglobin and 1.66 (95% CI 1.31, 2.10) (P_{trend} = 0.001) for medication. Diabetes-related death rate ratio for TFQI being above versus below the median was 4.81 (95% CI 1.01, 22.94) (P_{trend} = 0.015). Further adjustment for BMI and restriction to normothyroid individuals yielded similar results. Per 1 SD in TFQI, odds increased 1.13 (95% CI 1.02, 1.25) for diabetes and 1.16 (95% CI 1.02, 1.31) for metabolic syndrome. The other resistance to thyroid hormone indices showed similar associations for diabetes-related deaths and metabolic syndrome.

CONCLUSIONS

Higher values in resistance to thyroid hormone indices are associated with obesity, metabolic syndrome, diabetes, and diabetes-related mortality. Resistance to thyroid hormone may reflect energy balance problems driving type 2 diabetes. These indices may facilitate monitoring treatments focused on energy balance.

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Recent evidence suggests that hyperthyroxinemia may be cross-sectionally and prospectively associated with type 2 diabetes (1). This is at odds with the physiological metabolism-activating action of thyroid hormones, which is considered capable of ameliorating obesity-related morbidities (2). It is also in conflict with the increased incidence of diabetes reported among patients with hypothyroidism (3) and with the increased prevalence of metabolic syndrome described in the upper-normal range of the pituitary thyroid-stimulating hormone (TSH) (also known as thyrotropin) (4), a range associated with lower thyroid activity. Previous evidence is inconsistent (4): some studies find diabetes or metabolic syndrome to be associated with TSH but not with thyroid hormones, whereas others find an association only with thyroid hormones, occasionally linking opposite ends of the thyroid hormone concentration range with diabetes. The effect of thyroid hormones on insulin sensitivity differs by tissue; it enhances glucose uptake in the muscle but reduces it in the liver (5). The overall net effect in hypothyroidism favors insulin resistance, but in hyperthyroidism it may also occasionally favor glucose intolerance (5). These metabolic mechanisms described in clinical thyroid diseases may not be enough to explain the associations found within the normothyroid range.

Physiologically, thyroid hormones and TSH are inversely correlated owing to a negative feedback loop. However, high thyroid hormones coexist with high TSH in individuals with resistance to thyroid hormone syndrome, an inherited autosomal recessive trait (6–8). Yet, a possibly reversible acquired resistance to thyroid hormone, due to homeostatic compensation, has been hypothesized (9). Prolonged fasting produces drops in TSH and increases in pituitary sensitivity to thyroid hormones (10,11). In contrast, morbidly obese individuals tend to have higher levels of both thyroid hormones and TSH (12). Resistance to thyroid hormone manifestations can be systematized into central resistance phenomena, which affect the feedback loop set point in the central nervous system, and peripheral resistance phenomena, which decrease hormones' metabolic effects. The former are easier to evaluate than the latter because they can be quantified just observing thyroid hormones and TSH concentrations or indices derived from them (13,14), although suppression tests have also been described (15).

Thus, given the thyroid feedback loop, the aforementioned reports showing association of high thyroid hormones or high TSH with the prevalence and incidence of metabolic syndrome and diabetes provide apparently contradicting results. In this work, we hypothesized that these conflicting results might be conciliated if high thyroid hormones and high TSH co-occurrence in diabetes reflected a central resistance to thyroid hormone. If that were the case, this central resistance would probably be the expression of a general reduced sensitivity to thyroid hormones, i.e., not only central but also peripheral. This resistance to thyroid hormone could be one additional characteristic of the cardiometabolic traits predicting diabetes. We analyzed continuous National Health and Nutrition Examination Survey (NHANES) (16) data to gain insight into this issue and propose the Thyroid Feedback Quantile-based Index (TFQI), a new resistance to thyroid hormone index focused on deviations close to normality.

RESEARCH DESIGN AND METHODS

Design and Participants

Thyroid hormones and TSH were measured in serum in 5,222 (N_1) adults 20 years of age and older in the continuous NHANES (16) performed in 2007 and 2008, which recruited a representative sample of the noninstitutionalized U.S. population. Data on mortality up to 2011 from the National Death Index are available for all but six individuals. The current study estimates cross-sectional associations between resistance to thyroid hormone indices and diabetes-related conditions as well as longitudinal associations between the indices and the diabetes-related mortality rate. Analyses were performed using the entire NHANES data set (N_1) and several subsets (main complete case sample, N_2 = 5,129; normothyroid sample, N_3 = 4,750; and fasting normothyroid sample, N_4 = 1,997) (see flowchart in Supplementary Data). NHANES participants provided written informed consent to participate in the survey, which was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (Continuation of Protocol no. 2005-06).

Thyroxine, TSH, and Resistance to Thyroid Hormone Indices

Free thyroxine (fT4) was quantified with the Access Free T4 assay, a two-step enzyme immunoassay, and TSH was quantified with the Access HYPERsensitive hTSH Assay, a two-site immunoenzymatic ("sandwich") assay. Measurements were performed at the University of Washington (Seattle, WA). The laboratory normality reference ranges were 7.74–20.64 pmol/L for fT4 and 0.34–5.60 mIU/L for TSH.

Thyrotroph T4 Resistance Index (TT4RI) was calculated as fT4 (pmol/L) · TSH (mIU/L) (13). TSH index (TSHI) was calculated as ln TSH (mIU/L) + 0.1345 · fT4 (pmol/L) (14).

TFQI, a New Resistance to Thyroid Hormone Index

Given encouraging preliminary results from the description of participants who were simultaneously in the extreme quartiles of fT4 and TSH (see STATISTICAL ANALYSES and RESULTS sections), we developed a new index to quantify, in a continuous manner, deviations from the median pituitary response (inhibition) to thyroid hormones: the TFQI, which stands for thyroid feedback quantile-based index.

Ranks (order position from minimum to maximum value) of fT4 and TSH were converted to quantiles between 0 and 1, taking into account sampling weights. Fractional quantiles are a generalization that summarizes in a single fraction the ordering number of each part in the sequence and the number of parts, e.g., the upper limit of the second tertile is the value of the quantile 0.66 and the upper limit of the third quartile is the value of the quantile 0.75. That conversion is achieved by applying the population empirical cumulative distribution function (cdf) to hormone concentration. TFQI was calculated as cdf fT4 − (1 − cdf TSH), i.e., the difference between fT4 quantile and the reversed TSH quantile, because they are inversely correlated in the negative feedback loop. This index ranges between −1 and 1. Negative values indicate lower TSH (higher inhibition by fT4) than that expected for the actual fT4 (which means higher sensitivity to fT4). Similarly,

positive values indicate higher TSH (lower inhibition by fT4) than that expected for the actual fT4 (lower sensitivity to fT4). Median TSH response to fT4 is represented by the value 0. This index is more stable than TT4RI and TSHI at abnormal ranges of the thyroid gland responsiveness to TSH. That is, TFQI does not reach extreme values in individuals with thyroid gland–caused (primary) clinical hyper- or hypothyroidism (see data points in the top-left and bottom-right areas of TSH versus fT4 scatterplots in Supplementary Fig. 1).

In order to provide an index that can be calculated for any new value or adapted to other populations, an approximation with the same range and interpretation, the Parametric Thyroid Feedback Quantile-based Index (PTFQI) can be obtained from fT4 in pmol/L and TSH in mIU/L using the standard normal cumulative distribution function as follows: $\Phi((\text{fT4} - \mu_{\text{fT4}})/\sigma_{\text{fT4}}) - (1 - \Phi((\ln \text{TSH} - \mu_{\ln\ \text{TSH}})/\sigma_{ln\ TSH}))$, where $\mu_{\text{fT4}} = 10.075$, $\sigma_{\text{fT4}} = 2.155$, $\mu_{\ln \text{TSH}} = 0.4654$, and $\sigma_{\ln \text{TSH}} = 0.7744$ for the U.S. population. This can be easily achieved with the Excel or LibreOffice spreadsheet formula =NORM.DIST(*fT4_cell*,10.075,2.155,TRUE)+ NORM.DIST(LN(*TSH_cell*),0.4654,0.7744, TRUE)−1.

Other Variables

Demographic (including race/ethnicity as nonhispanic white, nonhispanic black, and other), clinical interview, physical examination, and other laboratory variables were obtained following protocols available in NHANES operation manuals (16). Briefly, glucose was measured with the glucose oxidase method and glycohemoglobin (HbA_{1c}) on the A1c G7 HPLC Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco, CA). Blood was drawn from participants who were visited at any time throughout the day, except for a subsample of participants appointed for a morning visit and requested to fast. In the main sample data set (which includes nonfasting data), high HbA_{1c} (≥6.5%, i.e., ≥48 mmol/mol) and use of diabetes medication were analyzed, as they can be interpreted as proxies for diabetes. In the fasting subsample, diabetes was defined as fasting (≥8 h) glycemia ≥126 mg/dL or presenting the previously mentioned proxies. Obesity was defined as a BMI ≥30 kg/m^2. Metabolic syndrome diagnosis was established using the harmonized criteria (17); i.e., diagnosis was issued when meeting three of the following criteria: *1*) waist circumference ≥102 cm in men or ≥88 cm in women; *2*) triglycerides ≥150 mg/dL; *3*) HDL cholesterol <40 mg/dL in men or <50 mg/dL in women; *4*) systolic or diastolic blood pressure ≥130 mmHg or ≥85 mmHg, respectively (or receiving medication for hypertension); and *5*) glucose ≥100 mg/dL (or receiving medication for diabetes).

Mortality

Survey data were linked with the National Death Index by the NCHS. Besides the leading cause of death, records also include contributing causes of death in a 20 entity axis set of codes for multiple causes of death. The public use linked mortality data set provided by the NCHS includes a flag variable for diabetes when ICD-10 codes E10–E14 appear as one of the 20 contributing or multiple causes of death. We used this flag, i.e., diabetes-related death, as our end point.

Statistical Analyses

Mean and SD of thyroid parameters were calculated for population sex, age, and race strata. TSH and TT4RI were processed in the logarithmic scale given their skewed distributions. We created scatterplots of TSH versus fT4 and plotted population-based percentiles of the indices.

The interesting results observed when we compared participants who were either at the lowest or at the highest quartiles of fT4 and TSH simultaneously (see Supplementary Data and RESULTS) led us to develop TFQI and PTFQI (described above). These indices enabled us to study pituitary feedback response with a continuous variable.

We created population-based quartiles for each resistance to thyroid hormone index (TFQI, PTFQI, TT4RI, and TSHI). Differences, odds ratios (ORs), and rate ratios (RRs) across quartiles, using the lowest as reference, were estimated with generalized linear, logistic, and Poisson regression models, respectively. Model 1 adjusted for sex, age, and race. Model 2 further adjusted for BMI. Model 3 further adjusted for initially presenting HbA_{1c} ≥6.5% and diabetes medication use. For each trend, significance was tested with each index quartile ordinal as a continuous variable. Given that there were no diabetes-related deaths within the first quartile of three indices, this outcome was compared between values above and below the median, and trend was tested with each index as a continuous variable.

In the main sample and the normothyroid sample, interquartile comparisons were performed for BMI, obesity, HbA_{1c} ≥6.5%, diabetes medication use, and diabetes-related mortality. BMI was modeled with linear regression; obesity, HbA_{1c} ≥6.5%, and diabetes medication were modeled with logistic regression, and death was modeled with Poisson regression.

In the fasting subsample, ORs for diabetes, metabolic syndrome, and metabolic syndrome criteria were calculated for 1-SD increase of resistance to thyroid hormone indices except for TT4RI. This index was analyzed using the logarithmic scale, and its OR was calculated for a TT4RI multiplicative increase by an SD equivalent ($\times\ 2^{\text{SD log2 TT4RI}}$). Diabetes, metabolic syndrome, and metabolic syndrome criteria were modeled with logistic regression.

As part of sensitivity analyses, we further adjusted models for education level, physical activity performed at work or during leisure time, and daily sedentary time. All analyses were performed with statistical computing software R (18), version 3.4.4, with the package "survey" (19) to account for the NHANES complex survey design.

RESULTS

The 5,222 participants in the sample represented the U.S. population 20 years of age and older, and they had a mean (SD) age of 46.9 (16.6) years (Table 1). Indices of resistance to thyroid hormone were higher among older people and lower among black individuals (Table 1).

In a preliminary analysis, obesity prevalence and, especially, HbA_{1c} ≥6.5% and use of diabetes medication showed a tendency to be higher among participants whose fT4 and TSH were simultaneously above their 75th percentiles (Supplementary Data).

A scatterplot of TSH versus fT4 shows the negative correlation of these variables, while the contour lines show selected percentiles for each one of the resistance to thyroid hormone indices (Fig. 1 and Supplementary Fig. 1). TT4RI and TSHI (Supplementary Fig. 1) take extreme values (>95th and <5th

Table 1—Characteristics and thyroid parameters of the U.S. population represented in the NHANES sample (N_1 = 5,222)

	%	fT4	*P*	TSH*	*P*	TFQI	*P*	TT4RI*	*P*	TSHI	*P*
All		10.08 (2.15)		1.59		0.00 (0.37)		15.73		1.82 (0.74)	
Male	48.3	10.04	0.431	1.62	0.220	0.00	0.403	16.02	0.147	1.83	0.299
Female	51.7	10.11		1.57		−0.01		15.47		1.81	
≥20 years and <40 years	37.0	10.00	<0.001	1.47	<0.001	−0.05	<0.001	14.41	<0.001	1.73	<0.001
≥40 years and <60 years	39.3	9.80		1.64		−0.03		15.79		1.81	
≥60 years	23.7	10.67		1.72		0.13		17.96		1.98	
White	70.7	10.06	0.234	1.69	<0.001	0.02	<0.001	16.68	<0.001	1.88	<0.001
Black	10.0	9.91		1.19		−0.17		11.51		1.51	
Other	19.3	10.22		1.49		−0.01		14.95		1.77	

Data are percentages or means (SD) unless otherwise indicated. *P* values are for differences between groups and were calculated from linear regression models. *Calculated as geometric means.

percentile) for almost all patients diagnosed with clinical hypo- and hyperthyroidism. This seemingly inappropriate result together with our observation that a quantile-based approach (Supplementary Data) uncovered the above-mentioned associations and provided more moderate values among patients with clinical thyroid gland–caused (primary) disease is what led us to develop TFQI.

BMI, obesity prevalence, $HbA_{1c} \geq 6.5\%$, and use of diabetes medication were progressively higher across TFQI quartiles after adjustment for sex, age, and race (all $P < 0.01$). ORs of the fourth versus the first TFQI quartile for $HbA_{1c} \geq 6.5\%$ and use of diabetes medication were 1.73 (95% CI 1.32, 2.27) and

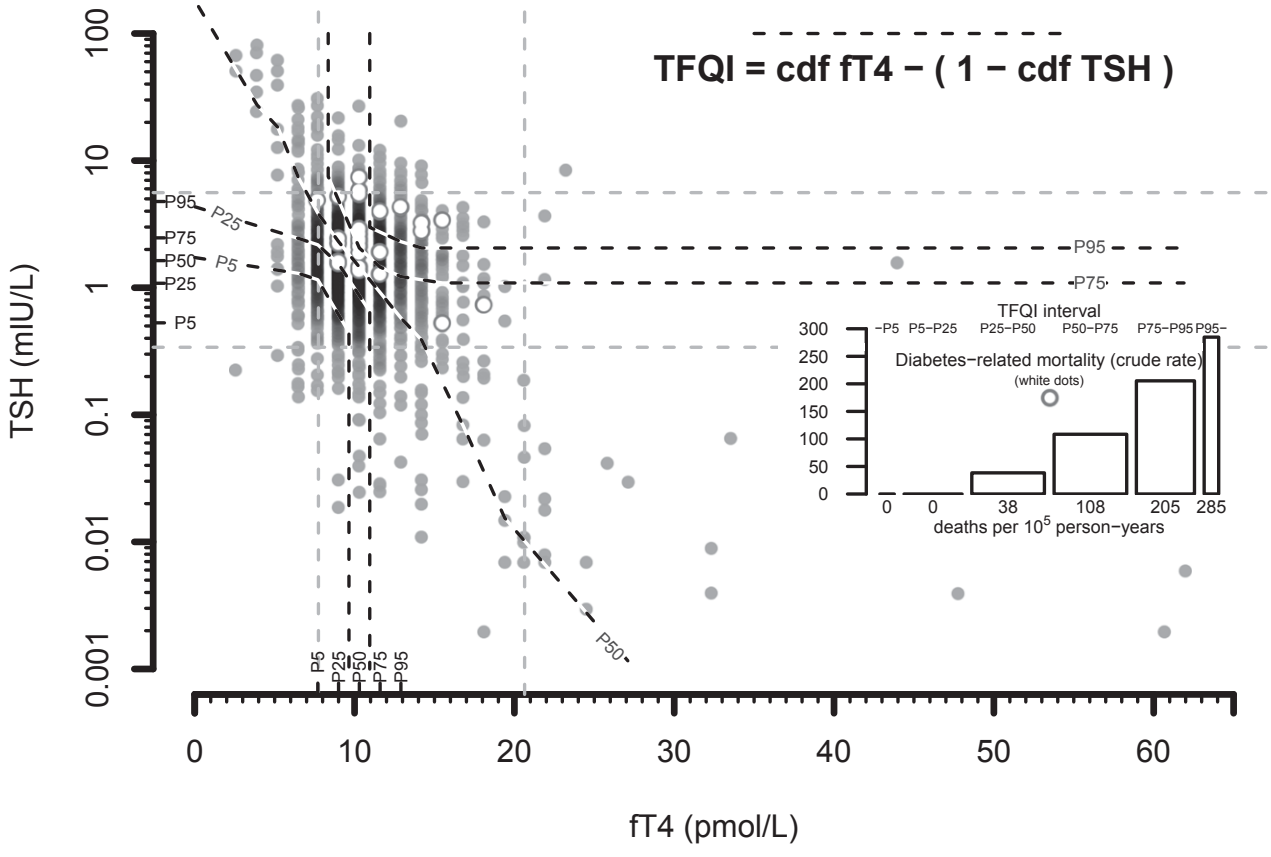

Figure 1—Scatterplot of TSH versus fT4 and bar plot of crude diabetes-related death rates across intervals of TFQI in the NHANES sample (N_1 = 5,222). Scatterplot: dots represent observations. White dots represent participants who died during follow-up and whose deaths were diabetes related. Gray dashed vertical and horizontal straight lines mark fT4 and TSH normality ranges. Inner marks in the axes represent the 5th, 25th, 50th, 75th, and 95th percentiles of fT4 and TSH. TFQI was calculated for each observation, and its value grows gradually across the plot area, from the lower-left corner to the upper-right corner. Black dashed curves represent the 5th, 25th, 50th, 75th, and 95th percentiles of TFQI. Inner plot: the bars and the number at the base show crude death rates for each TFQI interval (percentile <5, 5–25, 25–50, 50–75, 75–95, and ≥95) in deaths per 10^5 person-years. The widths of the bars are proportional to the fraction of the population at risk in each bar so that the area of the bar is proportional to the absolute number of deaths (i.e., the count of white dots in the scatterplot). cdf, empirical cumulative distribution function; fT4, free thyroxine; TFQI, Thyroid Feedback Quantile-based Index; TSH, thyroid-stimulating hormone.

Table 2—Association of TFQI with BMI, obesity, high HbA_{1c}, use of diabetes medication, and diabetes-related deaths in the main sample (N_2 = 5,129)

	Thyroid Feedback Quantile-based Index (TFQI)				
	Quartile 1 [≥−1 and <−0.25)	Quartile 2 [≥−0.25 and <0)	Quartile 3 [≥0 and <0.25)	Quartile 4 [≥0.25 and ≤1)	P_{trend}
N	1,319	1,259	1,270	1,281	
BMI (kg/m^2)	28.1	28.0	29.0	28.8	
Model 1, difference (95% CI)	0.0 (Reference)	0.1 (−0.6, 0.7)	1.1 (0.7, 1.5)	0.9 (0.1, 1.6)	0.006
Obesity (%)	31.0	29.0	36.7	35.8	
Model 1, OR (95% CI)	1.00 (Reference)	0.93 (0.76, 1.14)	1.34 (1.17, 1.54)	1.29 (1.11, 1.50)	0.001
HbA_{1c} ≥6.5% (%)	5.0	6.4	8.9	10.0	
Model 1, OR (95% CI)	1.00 (Reference)	1.28 (0.96, 1.71)	1.70 (1.37, 2.12)	1.73 (1.32, 2.27)	0.002
Model 2, OR (95% CI)	1.00 (Reference)	1.19 (0.91, 1.54)	1.38 (1.06, 1.78)	1.43 (1.07, 1.92)	0.034
Diabetes medication (%)	4.8	7.2	9.2	9.9	
Model 1, OR (95% CI)	1.00 (Reference)	1.46 (1.00, 2.13)	1.72 (1.21, 2.44)	1.66 (1.31, 2.10)	0.001
Model 2, OR (95% CI)	1.00 (Reference)	1.36 (0.96, 1.94)	1.41 (1.00, 1.98)	1.39 (1.10, 1.75)	0.028
Diabetes-related deaths (*n*)	0	4	7	16	
Crude rate (per 100,000 person-years)	0.0	38.9	108.9	211.3	
Crude rate (per 100,000 person-years)	19.5		159.2		
Model 1, RR (95% CI)	1.00 (Reference)		4.81 (1.01, 22.94)		0.015#
Model 2, RR (95% CI)	1.00 (Reference)		3.92 (0.88, 17.51)		0.035#
Model 3, RR (95% CI)	1.00 (Reference)		3.51 (0.78, 15.85)		0.099#

Differences, ORs, and RRs (rate ratios) are estimated with generalized linear, logistic, and Poisson regression models, respectively. Model 1 is adjusted for sex, age, and race. Model 2 is further adjusted for BMI. Model 3 is further adjusted for initially presenting HbA_{1c} ≥6.5% and using diabetes medication. P_{trend} is calculated with the TFQI quartile ordinal as a continuous variable except in the models with only two categories in which it is calculated with TFQI as a continuous variable. #P_{trend} for TFQI as a continuous variable.

1.66 (1.31, 2.10), respectively, and the association was independent of BMI, given that after adjustment, OR estimations were only partially reduced to 1.43 (1.07, 1.92) and 1.39 (1.10, 1.75), respectively (P_{trend} <0.05) (Table 2). Participants had a median follow-up of 3 years and 11 months, during which there were 27 deaths with diabetes listed within the entity axis codes for multiple causes of death. In nine of these cases, diabetes was the leading cause of death. For participants with TFQI above the median (versus below it), sex-, age-, and race-adjusted RR for diabetes-related death was 4.81 (95% CI 1.01, 22.94). TFQI was linearly associated with the rate for diabetes-related death (P = 0.015), and the association remained statistically significant even after adjustment for BMI (P = 0.035). One-fourth of

Table 3—ORs (95% CI) of diabetes, metabolic syndrome, and metabolic syndrome criteria for 1-SD increase of TFQI, PTFQI, and TSHI or multiplication by an SD equivalent of TT4RI in the fasting normothyroid sample (N_4 = 1,997)

	TFQI (+1 SD)	PTFQI (+1 SD)	TT4RI (× $2^{SD\ log2\ TT4RI}$)	TSHI (+1 SD)
Diabetes	1.13 (1.02, 1.25)	1.13 (1.02, 1.25)	1.09 (0.89, 1.33)	1.10 (0.93, 1.31)
P	0.041	0.036	0.420	0.299
Metabolic syndrome	1.16 (1.02, 1.31)	1.16 (1.03, 1.31)	1.30 (1.09, 1.56)	1.28 (1.09, 1.50)
P	0.040	0.031	0.014	0.013
Waist criterion	0.99 (0.88, 1.11)	0.99 (0.89, 1.11)	1.06 (0.91, 1.24)	1.05 (0.91, 1.21)
P	0.814	0.870	0.439	0.536
Triglyceride criterion	1.07 (0.88, 1.30)	1.07 (0.88, 1.29)	1.40 (1.16, 1.69)	1.33 (1.10, 1.61)
P	0.510	0.506	0.005	0.013
HDL criterion	1.21 (1.05, 1.39)	1.21 (1.06, 1.38)	1.21 (1.04, 1.40)	1.22 (1.06, 1.41)
P	0.024	0.018	0.034	0.021
Blood pressure criterion	1.18 (1.04, 1.34)	1.19 (1.06, 1.35)	1.22 (1.07, 1.38)	1.21 (1.08, 1.37)
P	0.023	0.016	0.013	0.008
Glycemia criterion	1.06 (0.94, 1.20)	1.06 (0.94, 1.19)	1.08 (0.88, 1.32)	1.07 (0.90, 1.28)
P	0.364	0.371	0.472	0.461

ORs are estimated with generalized logistic regression models adjusted for sex, age, and race (model 1) for the increase of 0.37 units TFQI, 0.33 units PTFQI, and 0.74 units TSHI (1 SD) and for the multiplication of TT4RI by 2.1 (1 SD equivalent). Indices enter the models as continuous variables. TT4RI enters the model as base 2 log so that the regression coefficient is for each duplication of its value. ORs are comparable across columns in terms of influence of the index variation on the outcome prevalences.

deaths occurred among participants without initial presence of proxies for diabetes. However, in spite of a similar magnitude of association for being above the median, RR 3.51 (0.78, 15.85), such a small number of events made it impossible to detect a statistically significant association after adjustment for the initial condition. All results were similar in examination of PTFQI instead of TFQI (Supplementary Data). Adjustment for education, physical activity, and sedentary time did not substantially change these results (Supplementary Data).

TT4RI and TSHI were cross-sectionally associated with obesity, although not with diabetes proxies. Nonetheless, both were prospectively associated with diabetes-related mortality independently of initial presence of diabetes proxies (Supplementary Data). All of these results persisted in the normothyroid subsample (Supplementary Data) with the exception of RR for mortality. Although the magnitudes for its indicators were very similar, they failed to reach statistical significance, probably due to the statistical loss of power caused by excluding two deceased participants who had marginally subclinical hypothyroidism (Fig. 1 and Supplementary Data).

We tested cross-sectional associations of the indices with diabetes and metabolic syndrome in the fasting subsample of normothyroid participants. Only TFQI (and its approximation, PTFQI) was associated with diabetes based on glycemia, HbA_{1c}, and medication. All resistance to thyroid hormone indices were associated with metabolic syndrome in general and with HDL and blood pressure metabolic syndrome criteria. Lastly, TT4RI and TSHI were also associated with triglyceride criterion (Table 3).

CONCLUSIONS

Based on a sample representative of the U.S. population, we provide evidence of the association between indices measuring resistance to thyroid hormone and prevalence of obesity, diabetes, and metabolic syndrome as well as between these indices and the incidence of diabetes-related deaths. These associations were also identified within the normal fT4 and TSH ranges. These results not only reconcile previous reports linking diabetes to hypothyroidism (3) and to hyperthyroxinemia (1) but also call for a new interpretation of thyroid hormone changes associated with diabetes.

As far as we are aware, this is the first time that indices of resistance to thyroid hormone have been evaluated in the general population and associated with cardiometabolic health characteristics. Our analyses showed that TT4RI and TSHI indices seemed to systematically classify thyroid gland–caused (primary) hypothyroidism and hyperthyroidism (clinical and subclinical) as resistant or very sensitive to thyroid hormones, respectively. Thus, we proposed a new index, TFQI. TFQI is based on the empirical joint distribution of fT4 and TSH with the advantage of not yielding extreme values in cases of thyroid gland dysfunction. Its parametric version (PTFQI) can readily be used as a formula to calculate the index for any particular individual with reference to the U.S. population, or it can be adapted to other reference populations.

All these resistance to thyroid hormone indices measure central sensitivity/resistance, i.e., the grade of pituitary gland inhibition by fT4 levels. Thus, they evaluate the set point of the central regulation of thyroid hormone concentration. Among participants with high values, peripheral resistance could also be present because, despite higher fT4, we find in this group higher prevalence of obesity, diabetes, and metabolic syndrome, phenotypes usually associated with hypothyroidism.

Thyroid hormones increase energy expenditure and thermogenesis (20), increase glucose and fatty acid oxidation in muscle (21) and the liver (22), increase adipose tissue lipolysis (23), and promote lower body weight (24). In sum, they have an overall effect on metabolism that would prevent diabetes development. Interestingly, thyroid hormones also sensitize to catecholamines, which increase liver hepatic glycogenolysis, neoglucogenesis, and glucose output (25); reduce insulin anabolic actions in the liver; and increase glucose intestinal absorption (5), though the latter effect plays a minor role in glucose level derangement. In overt hyperthyroidism, these changes could be responsible for decompensation of preexisting diabetes and even trigger ketoacidosis (25), but they may be less important within the normal range of thyroid hormones and unlikely to cause diabetes onset in a previously metabolically normal individual.

Besides secretion regulation by the hypothalamic-pituitary-thyroid axis, thyroid hormone action is modulated (6,26) at cell membrane transport, enzymatic modification into active and inactive species by deiodinases, and nuclear receptors. Nutritional signals can modulate the thyroid system during some of the regulation, secretion, and action steps. Hypothalamic neurons inhibit secretion when leptin levels fall, providing a system to protect against starvation (27). Meanwhile, an increase in leptin derived from adipose tissue accumulation may indicate availability of energetic substrates, and, thus, the subsequent activation of the thyroid axis could also be interpreted as a homeostatic regulation. Accordingly, high TSH—within normal levels—is associated with increased adiposity (28) and consistent with near-hypothyroidism hormonal end effects. This can be interpreted as a deficient thyroid hormone production in relative terms, unable to meet the metabolic increase required to compensate and avoid more fat accumulation. Interestingly, in morbidly obese individuals thyroid hormones are also elevated (12), hinting at a downstream signal problem. Activity of deiodinases (29), epigenetic modification of histones, and interaction with signaling of other transcription factors (30) also regulate, at the cellular level, thyroid hormone actions on metabolism. In addition, in obesity a steady consumption of high-calorie foods may even overpower the thyroid stimulus that increases resting metabolic rate (31), leading to a biochemical phenotype compatible with an apparent resistance to thyroid hormone. We previously proposed a similar interpretation for the origin of insulin resistance in obesity (32).

From a clinical point of view, there seems to be a gradient of increasing thyroid hormones levels—within the normal range—across early stages of diabetes (33). Furthermore, prospectively, higher levels of thyroid hormones are associated with incident diabetes (1) in spite of the fact that hypothyroidism is the disorder that clearly increases diabetes risk (3). As resistance to thyroid hormone is one of the differential diagnoses when both fT4 and TSH are elevated (34), our results offer an explanation for thyroid profiles commonly

found in patients with diabetes. That is, at the population level, measurements of resistance to thyroid hormone are cross-sectionally associated with diabetes, independently of the degree of obesity as measured with BMI, suggesting that there might be other underlying mechanisms linking diabetes and resistance to thyroid hormone. Furthermore, prospectively, these measurements were also associated with diabetes-related deaths, even independently of the initial diabetes status.

Measurements of resistance to thyroid hormone were also cross-sectionally associated with metabolic syndrome on a consistent basis. Previous attempts to relate metabolic syndrome with the thyroid axis either showed an association with TSH but not with fT4 (35) or yielded inconsistent results. We hypothesized that whereas a metabolic status with excess energy may stimulate the thyroid axis, the thyroid boost to energy expenditure fails to compensate. This results in an expression compatible with resistance to thyroid hormone. Thyroid stimuli still increase, although insufficiently, the uncoupled thermogenic oxidative processes, which can be observed as an increase of oxidative stress in metabolic syndrome (36). A sustained compensatory TSH stimulus could also explain, in part, the recently reported association of metabolic syndrome, insulin resistance, and diabetes with thyroid enlargement, thyroid nodules, and thyroid cancer (37). We cannot exclude that other conditions, like immunity disorders, could also explain a coincidence of elevated thyroid hormones, due to autoimmune thyroid disease, and latent autoimmune diabetes of adults. However, from a population perspective, energy imbalance is much more prevalent.

Type 2 diabetes requires a broad clinical management beyond glucose control, focused on energy balance. Monitoring resistance to thyroid hormone could be used to evaluate the intended reversal of the abnormal energy balance. Interestingly, where traditional interventions of food intake reduction and physical exercise increase seem to fail, new treatments trying to modify the activity of uncoupling proteins have been proposed (2,38,39).

This study is based on a representative sample of the U.S. population with strict data collection protocols. Consistency in results between cross-sectional associations and longitudinal mortality analyses support our conclusions. However, some limitations exist. Indices of resistance to thyroid hormone increase markedly with aging. Whereas all analyses are adjusted for age and other potential confounders, some residual confounding may remain. Given that many factors may be associated with diabetes and metabolic syndrome, it is not possible to adjust for unavailable variables and unknown factors, and the potential residual confounding must be considered when interpreting the study results. One antidiabetes oral agent, metformin, lowers TSH (leaving fT4 unchanged) among patients with hypothyroidism (37), and there is some evidence hinting that it sensitizes the pituitary gland and peripheral tissues to thyroid hormone action (40). Thus, our results may underestimate the true association between resistance to thyroid hormone and diabetes; i.e., the association may be even stronger than the statistically significant association reported here. Because our analysis focused on resistance to thyroid hormone indices, which are all fT4 based, fT3 was intentionally excluded from the models, since it was considered to be downstream in the action pathway. Actually, deiodinases balance may play a role in the modulation of sensitivity to thyroid hormones (29), and future projects should be devoted to specifically study their role in resistance to thyroid hormone in obesity, metabolic syndrome, and diabetes. Diabetes and related outcomes were based on one single measurement of HbA_{1c} or fasting plasma glucose, which is a common limitation in population-based studies. Finally, the small number of observed diabetes-related deaths limits the statistical power needed to find subtle effects as well as to perform subgroup analyses. Notwithstanding, the association was strong enough to bear statistically significant results.

Conclusion

Higher values in indices of resistance to thyroid hormone are associated with obesity, metabolic syndrome, and diabetes for the entire population in general and also for normothyroid individuals in particular. Higher values are also prospectively associated with diabetes-related mortality. These associations with diabetes morbidity and mortality were independent of obesity. We propose the new TFQI to identify mild levels of acquired resistance in the general population. Type 2 diabetes is in part driven by an energy balance problem, and the associated central resistance measured by indices of resistance to thyroid hormone may be the result of the physiologic contraregulation against it. These indices may facilitate the monitoring and evaluation of new therapies that focus on energy expenditure.

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References

1. Ittermann T, Schipf S, Dörr M, et al. Hyperthyroxinemia is positively associated with prevalent and incident type 2 diabetes mellitus in two population-based samples from Northeast Germany and Denmark. Nutr Metab Cardiovasc Dis 2018;28:173–179

2. Vargas-Castillo A, Fuentes-Romero R, Rodriguez-Lopez LA, Torres N, Tovar AR. Understanding the biology of thermogenic fat: is browning a new approach to the treatment of obesity? Arch Med Res 2017;48:401–413

3. Gronich N, Deftereos SN, Lavi I, Persidis AS, Abernethy DR, Rennert G. Hypothyroidism is a risk factor for new-onset diabetes: a cohort study. Diabetes Care 2015;38:1657–1664

4. Laclaustra M, Hurtado-Roca Y, Sendin M, et al. Lower-normal TSH is associated with better metabolic risk factors: a cross-sectional study on Spanish men. Nutr Metab Cardiovasc Dis 2015;25:1095–1103

5. Dimitriadis GD, Raptis SA. Thyroid hormone excess and glucose intolerance. Exp Clin Endocrinol Diabetes 2001;109(Suppl. 2):S225–S239

6. Dumitrescu AM, Refetoff S. The syndromes of reduced sensitivity to thyroid hormone. Biochim Biophys Acta 2013;1830:3987–4003
7. Onigata K, Szinnai G. Resistance to thyroid hormone. Endocr Dev 2014;26:118–129
8. Ortiga-Carvalho TM, Sidhaye AR, Wondisford FE. Thyroid hormone receptors and resistance to thyroid hormone disorders. Nat Rev Endocrinol 2014;10:582–591
9. Tjørve E, Tjørve KMC, Olsen JO, Senum R, Oftebro H. On commonness and rarity of thyroid hormone resistance: a discussion based on mechanisms of reduced sensitivity in peripheral tissues. Med Hypotheses 2007;69:913–921
10. Azizi F. Effect of dietary composition on fasting-induced changes in serum thyroid hormones and thyrotropin. Metabolism 1978;27:935–942
11. Warren MP. Endocrine manifestations of eating disorders. J Clin Endocrinol Metab 2011;96:333–343
12. Laurberg P, Knudsen N, Andersen S, Carlé A, Pedersen IB, Karmisholt J. Thyroid function and obesity. Eur Thyroid J 2012;1:159–167
13. Yagi H, Pohlenz J, Hayashi Y, Sakurai A, Refetoff S. Resistance to thyroid hormone caused by two mutant thyroid hormone receptors beta, R243Q and R243W, with marked impairment of function that cannot be explained by altered in vitro 3,5,3′-triiodothyroinine binding affinity. J Clin Endocrinol Metab 1997;82:1608–1614
14. Jostel A, Ryder WDJ, Shalet SM. The use of thyroid function tests in the diagnosis of hypopituitarism: definition and evaluation of the TSH Index. Clin Endocrinol (Oxf) 2009;71:529–534
15. Ercan-Fang S, Schwartz HL, Mariash CN, Oppenheimer JH. Quantitative assessment of pituitary resistance to thyroid hormone from plots of the logarithm of thyrotropin versus serum free thyroxine index. J Clin Endocrinol Metab 2000;85:2299–2303
16. Zipf G, Chiappa M, Porter KS, Ostchega Y, Lewis BG, Dostal J. National Health and Nutrition Examination Survey: plan and operations, 1999-2010. Vital Health Stat 1 2013:1–37
17. Alberti KGMM, Eckel RH, Grundy SM, et al.; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–1645
18. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria, R Foundation for Statistical Computing, 2018
19. Lumley T. Analysis of complex survey samples. J Stat Softw 2004;9:1–19
20. Kim B. Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. Thyroid 2008;18:141–144
21. Salvatore D, Simonides WS, Dentice M, Zavacki AM, Larsen PR. Thyroid hormones and skeletal muscle–new insights and potential implications. Nat Rev Endocrinol 2014;10:206–214
22. Sinha RA, Singh BK, Yen PM. Direct effects of thyroid hormones on hepatic lipid metabolism. Nat Rev Endocrinol 2018;14:259–269
23. Carmean CM, Cohen RN, Brady MJ. Systemic regulation of adipose metabolism. Biochim Biophys Acta 2014;1842:424–430
24. Fox CS, Pencina MJ, D'Agostino RB, et al. Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. Arch Intern Med 2008;168:587–592
25. Potenza M, Via MA, Yanagisawa RT. Excess thyroid hormone and carbohydrate metabolism. Endocr Pract 2009;15:254–262
26. Refetoff S, Bassett JHD, Beck-Peccoz P, et al. Classification and proposed nomenclature for inherited defects of thyroid hormone action, cell transport, and metabolism. Thyroid 2014;24:407–409
27. Hollenberg AN. The role of the thyrotropin-releasing hormone (TRH) neuron as a metabolic sensor. Thyroid 2008;18:131–139
28. de Moura Souza A, Sichieri R. Association between serum TSH concentration within the normal range and adiposity. Eur J Endocrinol 2011;165:11–15
29. Gereben B, Zavacki AM, Ribich S, et al. Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. Endocr Rev 2008;29:898–938
30. Mullur R, Liu Y-Y, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev 2014;94:355–382
31. Carneiro IP, Elliott SA, Siervo M, et al. Is obesity associated with altered energy expenditure? Adv Nutr 2016;7:476–487
32. Laclaustra M, Corella D, Ordovas JM. Metabolic syndrome pathophysiology: the role of adipose tissue. Nutr Metab Cardiovasc Dis 2007;17:125–139
33. Lambadiari V, Mitrou P, Maratou E, et al. Thyroid hormones are positively associated with insulin resistance early in the development of type 2 diabetes. Endocrine 2011;39:28–32
34. Koulouri O, Moran C, Halsall D, Chatterjee K, Gurnell M. Pitfalls in the measurement and interpretation of thyroid function tests. Best Pract Res Clin Endocrinol Metab 2013;27:745–762
35. Iwen KA, Schröder E, Brabant G. Thyroid hormones and the metabolic syndrome. Eur Thyroid J 2013;2:83–92
36. Hurtado-Roca Y, Bueno H, Fernandez-Ortiz A, et al. Oxidized LDL is associated with metabolic syndrome traits independently of central obesity and insulin resistance. Diabetes 2017;66:474–482
37. Meng X, Xu S, Chen G, Derwahl M, Liu C. Metformin and thyroid disease. J Endocrinol 2017;233:R43–R51
38. Song N-J, Chang S-H, Li DY, Villanueva CJ, Park KW. Induction of thermogenic adipocytes: molecular targets and thermogenic small molecules. Exp Mol Med 2017;49:e353
39. Tamucci KA, Namwanje M, Fan L, Qiang L. The dark side of browning. Protein Cell 2018;9:152–163
40. Krysiak R, Okopien B. Thyrotropin-lowering effect of metformin in a patient with resistance to thyroid hormone. Clin Endocrinol (Oxf) 2011;75:404–406