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Low-Normal Free Thyroxine Levels in Euthyroid Male Are Associated with Prediabetes

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Abnormal thyroid function is associated with impaired glucose homeostasis. This study aimed to determine whether free thyroxine (FT4) influences the prevalence of prediabetes in euthyroid subjects using a cross-sectional survey derived from the Korea National Health and Nutrition Examination Survey, conducted between 2013 and 2015. We studied 2,399 male participants of >20 years of age who were euthyroid and non-diabetic. Prediabetic participants had lower FT4 concentrations than those without prediabetes, but their thyrotropin concentrations were similar. We stratified the population into tertiles according to FT4 concentration. After adjusting for multiple confounding factors, glycosylated hemoglobin (HbA1c) levels significantly decreased with increasing FT4 tertile, whereas fasting plasma glucose (FPG) levels were not associated with FT4 tertiles (HbA1c, $P<0.01$ in T3 vs. T1; FPG, $P=0.489$ in T3 vs. T1). The prevalence of prediabetes was significantly higher in T1 (odds ratio, 1.426; 95% confidence interval, 1.126 to 1.806; $P<0.01$) than in T3. In conclusion, subjects with low-normal serum FT4 had high HbA1c and were more likely to have prediabetes. These results suggest that low FT4 concentration is a risk factor for prediabetes in male, even when thyroid function is within the normal range.

Keywords: Blood glucose; Glycated hemoglobin A; Prediabetic state; Thyroxine

INTRODUCTION

It is well known that thyroid hormone regulates metabolic processes, including thermogenesis, lipid metabolism, and carbohydrate metabolism [1]. Thyroid hormone is known to increase serum glucose by enhancing hepatic glucose production and insulin degradation [2,3]. However, the contribution of thyroid hormone to glucose homeostasis is more complicated since it has a role in promoting pancreatic proliferation, increasing energy expenditure, and inducing weight loss [4-7].

Although thyroid hormone has well documented effects on carbohydrate metabolism, it is not clear whether thyroid hormone concentrations within the physiological range affect serum glucose concentrations. A few studies have shown that high fasting glucose levels are associated with low-normal thyroid hormone [8], while others have shown that thyroid hormone concentrations within the physiological range do not correlate with blood glucose levels, even though there is an association between thyroid hormone and insulin resistance [9,10]. Thus, there is no consensus regarding whether thyroid hormone concentrations within the physiological range influence glucose metabolism and the risk of diabetes.

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Therefore, we designed a study to evaluate the relationships between thyroid hormone concentrations and fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), and the prevalence of prediabetes in euthyroid subjects.

METHODS

Data source and participants

This study utilized data from the Korea National Health and Nutrition Examination Survey (KNHANES), collected in 2013 to 2015 (IRB no.: 2013-07CON-03-4C and 2013-12EXP-03-5C). In male participants over 20 years of age, subjects with free thyroxine (FT4) or thyrotropin (TSH) concentrations outside the reference range, diabetic values of FPG or HbA1c, or a past history of thyroid disease or diabetes were excluded. Subjects with no or incomplete data for thyroid hormone, fasting glucose, or HbA1c concentrations were also excluded. Following this, 2,399 euthyroid non-diabetic male were enrolled. All the survey participants gave their written informed consent.

Measurements of biochemical and clinical parameters

Serum TSH, FT4, and thyroperoxidase (TPO) antibody concentrations were measured using electrochemiluminescence immunoassays (Roche Diagnostics, Mannheim, Germany). TSH was measured using an E-TSH kit (Roche Diagnostics), for which the reference range was 0.35 to 5.50 mIU/L. FT4 was measured using an E-Free T4 kit (Roche Diagnostics), with a reference range of 0.89 to 1.76 ng/mL. HbA1c concentration was measured using high-performance liquid chromatography (HLC-723G7; Tosoh, Tokyo, Japan), and serum FPG using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). Impaired fasting glucose (IFG) was defined by a FPG of >100 to 125 mg/dL, and a high-risk HbA1c concentration was defined as a HbA1c of 5.7% to 6.4% [11]. Prediabetes was defined by the presence of IFG or a high-risk HbA1c concentration.

Waist circumference (WC) was measured standing with a soft tape-measure placed midway between the lowest rib and the iliac crest. Blood pressure (BP) was measured using a cuff on the right arm attached to a mercury sphygmomanometer (Baumanometer; W. A. Baum, Copiague, NY, USA). Serum total cholesterol, high density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were measured using a Hitachi Automatic Analyzer 7600 (Hitachi). Metabolic syndrome was defined according to the criteria of the American Heart Association [12]. Urine iodine concentrations were measured in random spot urine samples using inductively coupled plasma mass spectrometry (Perkin Elmer, Waltham, MA, USA). Demographic and personal medical data were collected using standardized health questionnaires. These data included any past history of hypertension (HTN) or hyperlipidemia, family history of diabetes or thyroid disease, history of alcohol consumption, and smoking history.

Statistical analyses

All continuous data are presented as mean±standard deviation, and all categorical data as numbers and percentages. The tertiles were compared with regard to baseline characteristics using analysis of variance or chi-square tests. Analysis of covariance was used to estimate the mean FPG and HbA1c values for each tertile, after adjustment for multiple variables. Multivariable logistic regression models were used to estimate the prevalence of prediabetes in each tertile. For all statistical tests, $P<0.05$ was considered to be statistically significant. Statistical analysis was performed using SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

General characteristics of participants stratified tertiles

The general characteristics of the participants are presented in Supplementary Table 1. Of the 2,399 euthyroid male, 1,190 had prediabetes and 1,209 did not. The participants were divided into tertiles on the basis of their serum FT4 concentrations (Table 1). In the tertile with the highest FT4 levels, the participants were significantly younger and had lower body mass index (BMI). The FT4 concentration increased with increasing tertile. TSH concentration also decreased with tertile, but anti-TPO antibody concentration did not show differences. FPG and HbA1c concentrations were significantly lower in tertile 3 than in tertile 1, and the prevalences of IFG and high-risk HbA1c concentration were also lower in tertile 3. WC, systolic and diastolic BP, and TG showed downward trends with increasing tertile, while HDL-C increased with tertile. Consistent with this, the prevalence of metabolic syndrome was significantly lower in tertile 3. I/Cr ratio tended to decrease with tertile. A past history of HTN or hyperlipidemia was significantly less likely in tertile 3 than in tertile 1. However, family histories of diabetes and thyroid disease, and social histories of alcohol consumption and smoking were similar among the tertiles.

Table 1. Baseline clinical characteristics of study participants stratified into tertiles according to levels of free thyroxine

Characteristic	T1 (n=800)	T2 (n=800)	T3 (n=799)	P value
Age, yr	48.1±13.8	43.2±14.3	38.2±14.1	<0.01
BMI, kg/m^2	24.5±3.2	24.3±3.3	23.9±3.5	<0.01
Thyroid function				
FT4, ng/dL	1.11±0.08	1.28±0.04	1.47±0.09	<0.01
TSH, μIU/mL	2.38±1.10	2.19±1.04	2.15±1.05	<0.01
Thyroid peroxidase antibody, IU/mL	15.8±70.1	13.1±42.6	11.7±41.5	0.29
Prediabetes				
FPG, mg/dL	96.7±9.7	95.2±9.3	93.6±9.4	<0.01
IFG	285 (35.6)	231 (28.9)	199 (24.9)	<0.01
HbA1c, %	5.61±0.35	5.56±0.33	5.45±0.34	<0.01
High risk HbA1c concentration	361 (45.1)	300 (37.5)	202 (25.3)	<0.01
Prediabetes	479 (59.9)	399 (49.9)	312 (39.1)	<0.01
Metabolic syndrome				
Waist circumference, cm	85.2±8.9	84.4±9.1	83.2±9.4	<0.01
Systolic BP, mm Hg	120.9±15.0	117.9±13.2	117.0±13.3	<0.01
Diastolic BP, mm Hg	79.1±10.2	77.8±9.7	77.4±10.1	<0.01
HDL-C, mg/dL	47.2±11.4	48.4±10.7	49.4±11.1	<0.01
Triglycerides, mg/dL	181.6±161.4	152.0±114.4	137.3±102.7	<0.01
Metabolic syndrome	230 (28.8)	190 (23.8)	127 (15.9)	<0.01
Biochemistry				
Blood urea nitrogen, mg/dL	14.9±4.2	14.4±3.7	14.3±3.7	<0.01
Creatinine, mg/dL	0.95±0.22	0.96±0.12	0.97±0.13	<0.01
Urine iodine creatinine ratio	5.42±13.56	3.96±9.31	3.81±19.15	0.05
Past history				
Past history of HTN	133 (17.3)	91 (11.7)	65 (8.4)	<0.01
Past history of hyperlipidemia	77 (10.0)	64 (8.2)	30 (3.9)	<0.01
Familial history				
Familial history of diabetes	152 (19.0)	158 (19.8)	134 (16.8)	0.29
Familial history of thyroid disease	26 (3.3)	38 (4.8)	36 (4.5)	0.27
Social history				
Heavy alcoholics	156 (20.3)	168 (21.6)	164 (21.3)	0.79
Smoking history (never/ex-/current)	177/292/301	195/248/335	225/217/328	0.52

Values are presented as mean±standard deviation or number (%). All P values were obtained by using analysis of variance and chi-square test.
BMI, body mass index; FT4, free thyroxine; TSH, thyrotropin; FPG, fasting plasma glucose; IFG, impaired fasting glucose; HbA1c, glycosylated hemoglobin; BP, blood pressure; HDL-C, high density lipoprotein cholesterol; HTN, hypertension.

Fasting glucose and HbA1c concentrations and the prevalence of prediabetes in the FT4 tertiles

Table 2 shows the levels of FPG and HbA1c and the prevalence of prediabetes in each FT4 tertiles after adjusting for multiple confounding factors (age, BMI, blood urea nitrogen, creatinine, I/Cr ratio, past history of HTN or hyperlipidemia, family history of diabetes or thyroid disease, heavy alcohol consumption, smoking history, and markers of metabolic syndrome [WC, systolic and diastolic BP, HDL-C, and TG]). We also observed similar results in euthyroid female (Supplementary Ta-

Table 2. FPG and HbA1c levels and the prevalence of prediabetes in euthyroid male in different free thyroixine tertiles

Variable	T1	T2	T3	*P* for trend
All subjects				
FPG, mg/dL	95.23±0.32	95.22±0.31	94.75±0.32	0.49
IFG	1.08 (0.83–1.39)	1.02 (0.79–1.32)	Ref	0.57
HbA1c, %	5.55±0.01[a]	5.55±0.01[a]	5.51±0.01	<0.01
High risk HbA1c	1.54 (1.21–1.95)[a]	1.40 (1.10–1.77)[a]	Ref	<0.01
Prediabetes	1.43 (1.13–1.81)[a]	1.19 (0.95–1.50)	Ref	<0.01
Age <50 yr				
FPG, mg/dL	93.84±0.38	92.78±0.37	92.84±0.38	0.09
IFG	1.23 (0.87–1.74)	0.89 (0.62–1.27)	Ref	0.20
HbA1c, %	5.49±0.01[a]	5.47±0.01[a]	5.42±0.01	<0.01
High risk HbA1c	1.91 (1.38–2.65)[a]	1.67 (1.20–2.33)[a]	Ref	<0.01
Prediabetes	1.61 (1.19–2.16)[a]	1.19 (0.88–1.60)	Ref	<0.01
Age ≥50 yr				
FPG, mg/dL	97.70±0.55	99.00±0.54	98.45±0.55	0.24
IFG	0.80 (0.55–1.15)	1.20 (0.83–1.73)	Ref	0.23
HbA1c, %	5.65±0.02	5.70±0.021	5.67±0.02	0.22
High risk HbA1c	0.91 (0.64–1.29)	1.15 (0.81–1.63)	Ref	0.60
Prediabetes	0.93 (0.64–1.35)	1.19 (0.81–1.74)	Ref	0.71

Values are presented as mean±standard error (analyzed by analysis of covariance) or odds ratio (95% confidence interval) (analyzed by multivariable logistic regression). The model was adjusted for age, body mass index, blood urea nitrogen, creatinine, urine iodine: creatinine ratio, past history of hypertension or hyperlipidemia, family history of diabetes or thyroid disease, heavy alcohol consumption, smoking history, and markers of the metabolic syndrome (waist circumference, systolic and diastolic blood pressure, high density lipoprotein cholesterol, and triglycerides). FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; IFG, impaired fasting glucose.
[a]$P<0.01$.

ble 2). After adjustment for confounding factors, the association of FPG with and the prevalence of IFG in the FT4 tertile disappeared (FPG, $P=0.489$ in T3 vs. T1; IFG, odds ratio [OR] in tertile 1=1.075; 95% confidence interval [CI], 0.831 to 1.389). However, HbA1c concentration and the prevalence of high risk HbA1c remained significantly higher in tertile 1 than in tertile 3 (HbA1c, $P<0.01$ in T3 vs. T1; high risk HbA1c, OR in tertile 1=1.535; 95% CI, 1.207 to 1.954). The OR for prediabetes was also significantly associated with FT4 tertile (OR in tertile 1=1.426; 95% CI, 1.126 to 1.806). In addition, levels of FT4 were continuously associated with the prevalence of prediabetes (Supplementary Table 3). Since age is strong contributing factor in the development of prediabetes, we further performed subgroup analysis after dividing at age 50. The association between FT4 and the prevalence of prediabetes was more prominent in the younger subjects. By contrast, there was no association of FT4 with FPG, HbA1c, and the prevalence of prediabetes in older subjects.

DISCUSSION

Studies of the relationship between type 2 diabetes mellitus and thyroid disorders have generated conflicting results [13,14]. Recently, several studies suggested that both hyperthyroidism and hypothyroidism increase the risk of diabetes [15,16]. However, in the euthyroid state, it has not been clearly determined whether low or high levels of thyroid hormone increase the risk of diabetes. A recent study showed that low-normal thyroid function increases the risk of a prediabetic patient developing diabetes [17]. Given that several studies have shown a relationship between low-normal thyroid function and metabolic syndrome, it may be that low-normal thyroid function increases insulin resistance and represents a potential risk factor for diabetes. In the present study, we found that low-normal FT4 was associated with high-risk HbA1c concentrations and prediabetes after adjusting for markers of the metabolic syndrome. These results suggest that low FT4 levels, even

in the euthyroid state, have adverse effects on carbohydrate metabolism, independent of the metabolic syndrome. However, in this study, FPG was not associated with low-normal FT4. Because thyroid hormone influences various organs, including pancreatic islets, muscle, and adipose tissue, we cannot explain this apparent discrepancy in the relationships of low-normal FT4 with HbA1c and FPG. In subgroup analysis, the associations of FT4 with HbA1c and the prevalence of prediabetes were observed only in young subjects. The reference value of normal thyroid function may differ between old subjects and young subjects due to the relationship between age and thyroid hormone level [18]. The present study had some limitations. First, it was a cross-sectional study, and therefore we are unable to conclude that there is a causal relationship between low-normal thyroid function and the risk of prediabetes. Second, because some variables, including fasting insulin levels, were not measured in the KNHANES, we could not evaluate the relationships between levels of FT4 and insulin resistance. Third, although we observed that low FT4 levels in euthyroid female were associated with prediabetes, we could not analyze the relationship between low FT4 and prediabetes in both male and female because of the disproportion in the sex ratio in the tertiles and other hormonal variables such as menopause.

In summary, this study shows that relatively low FT4 levels in euthyroid male are significantly associated with high HbA1c and high-risk HbA1c concentrations. However, FPG and IFG were not associated with serum FT4 in euthyroid male. These results suggest that low FT4 is a potential risk factor for prediabetes even in euthyroid subjects.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2018.0222.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: S.W.K., J.H.J., J.S.M., E.J.J., M.K.K.
Acquisition, analysis, or interpretation of data: S.W.K.
Drafting the work or revising: I.K.L., J.B.S.
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Supplementary Table 1. Baseline clinical characteristics of the study participants

Characteristic	Euglycemic (n=1,209)	Prediabetes (n=1,190)	P value
Age, yr	38.2±14.0	48.2±13.5	<0.01
BMI, kg/m^2	23.6±3.2	24.9±3.4	<0.01
Prediabetes			
FPG, mg/dL	89.6±5.8	100.8±9.3	<0.01
HbA1c, %	5.32±0.23	5.76±0.30	<0.01
Thyroid function			
FT4, ng/dL	1.31±0.16	1.26±0.16	<0.01
TSH, μIU/mL	2.23±1.07	2.25±1.07	0.58
Thyroid peroxidase antibody, IU/mL	10.3±26.4	16.8±70.4	<0.01
Metabolic syndrome			
Waist circumference, cm	82.2±8.7	86.3±9.1	<0.01
Systolic BP, mm Hg	116.0±12.4	121.2±14.9	<0.01
Diastolic BP, mm Hg	76.6±9.6	79.6±10.2	<0.01
HDL-C, mg/dL	49.3±10.9	47.4±11.2	<0.01
Triglycerides, mg/dL	141.8±120.4	172.4±137.4	<0.01
Metabolic syndrome	77 (9.1)	280 (36.1)	<0.01
Biochemistry			
Blood urea nitrogen, mg/dL	14.1±3.8	14.9±3.9	<0.01
Creatinine, mg/dL	0.96±0.19	0.96±0.13	0.62
Urine iodine: creatinine ratio	4.28±16.86	4.51±11.81	0.70
Past history			
Past history of HTN	62 (7.7)	136 (17.4)	<0.01
Past history of hyperlipidemia	36 (4.5)	71 (10.3)	<0.01
Family history			
Family history of diabetes	124 (16.4)	162 (20.7)	<0.01
Family history of thyroid disease	30 (4.4)	32 (4.0)	0.59
Social history			
Heavy alcohol consumers	149 (18.8)	171 (23.3)	0.10
Smoking history (never/ex-/current)	238/235/307	164/274/322	<0.01

Values are presented as mean±standard deviation or number (%). All P values were obtained using analysis of variance or the chi-square test.
BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; FT4, free thyroxine; TSH, thyrotropin; BP, blood pressure; HDL-C, high density lipoprotein cholesterol; HTN, hypertension.

Supplementary Table 2. FPG and HbA1c levels and the prevalence of prediabetes in euthyroid female in different free thyroixine tertiles

Female	T1 (n=790)	T2 (n=789)	T3 (n=789)	P for trend
FPG, mg/dL				
Unadjusted model	92.85±0.33[a]	91.99±0.31	91.24±0.30	<0.01
Adjusted model	92.28±0.30	91.95±0.30	92.13±0.31	0.74
IFG				
Unadjusted model	1.58 (1.21–2.06)[a]	1.36 (1.03–1.78)[b]	Ref	<0.01
Adjusted model	1.16 (0.85–1.58)	1.10 (0.81–1.51)	Ref	0.33
HbA1c, %				
Unadjusted model	5.56±0.01[a]	5.50±0.01[a]	5.44±0.01	<0.01
Adjusted model	5.55±0.01[a]	5.50±0.01	5.49±0.01	<0.01
High risk HbA1c				
Unadjusted model	1.95 (1.56–2.42)[a]	1.36 (1.07–1.68)[b]	Ref	<0.01
Adjusted model	1.40 (1.08–1.82)[b]	0.96 (0.73–1.26)	Ref	0.01
Prediabetes				
Unadjusted model	1.83 (1.49–2.25)[a]	1.39 (1.12–1.71)[a]	Ref	<0.01
Adjusted model	1.29 (1.00–1.69)[b]	1.00 (0.78–1.30)	Ref	0.04

Values are presented as mean±standard error (analyzed by analysis of covariance) or odds ratio (95% confidence interval) (analyzed by multivariable logistic regression). The model was adjusted for age, body mass index, blood urea nitrogen, creatinine, urine iodine: creatinine ratio, past history of hypertension or hyperlipidemia, family history of diabetes or thyroid disease, heavy alcohol consumption, smoking history, markers of the metabolic syndrome (waist circumference, systolic and diastolic blood pressure, high density lipoprotein cholesterol, and triglycerides), and menopause status.

FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; IFG, impaired fasting glucose.

[a]P<0.01, [b]P<0.05.

Supplementary Table 3. The association of FPG and HbA1c levels with free thyroxine levels in euthyroid subjects

Variable	Unadjusted model	*P* value	Adjusted model	*P* value
FPG	–0.146	<0.01	–0.028	0.21
IFG	0.25 (0.15–0.44)	<0.01	0.90 (0.47–1.73)	0.75
HbA1c	–0.192	<0.01	–0.057	0.01
High risk HbA1c	0.10 (0.06–0.18)	<0.01	0.40 (0.22–0.75)	<0.01
Prediabetes	0.11 (0.07–0.18)	<0.01	0.45 (0.25–0.83)	0.01

Values are presented as β standardized regression coefficient (analyzed by multivariable regression analysis) or odds ratio (95% confidence interval) (analyzed by multivariable logistic regression). The model was adjusted for age, body mass index, blood urea nitrogen, creatinine, urine iodine: creatinine ratio, past history of hypertension or hyperlipidemia, family history of diabetes or thyroid disease, heavy alcohol consumption, smoking history, and markers of the metabolic syndrome (waist circumference, systolic and diastolic blood pressure, high density lipoprotein cholesterol, and triglycerides).
FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; IFG, impaired fasting glucose.