Relationship between thyroid hormones and metabolic syndrome in a normal thyroid function population in Western China: a cross-sectional study based on both epidemiological and genetic analysis

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To the Editor: Metabolic syndrome (MetS) is defined as a set of metabolic disorders including abdominal obesity, hyperglycemia, hypertension, and dyslipidemia.[1] As thyroid hormones are essential for cellular energy homeostasis and regulation, the levels of serum thyroid hormones are considered to be associated with various metabolic parameters. Over the past decade, the association between thyroid hormones and MetS has been extensively studied in euthyroid subjects, leading to inconsistent results. Some studies suggested that a high level of thyrotropin (TSH) contributed to the increased incidence of MetS or unfavorable metabolic parameters, whereas other studies found no such correlation. Moreover, some researches have shown that free thyroxin (FT4) levels were inversely proportional to various unfavorable metabolic parameters or MetS, while other studies suggested that FT4 levels have no such association or even a positive association with some unfavorable metabolic components after adjustment. These conflicting results may result from different designs, settings, race, exclusion criteria, adjustments, statistical analyses, and definitions of MetS and population iodine intake. Based on these, our study aimed to evaluate the association and causal relationship between thyroid hormones and MetS in people with normal thyroid function through standard epidemiological and Mendelian randomization analysis.

This cross-sectional survey was conducted in Shaanxi Province, as a basic component of the China National Diabetes and Metabolic disorders Study (CNDMDS),[2,3] from June 2007 to May 2008. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and National Research Committee. The study was approved by Xijing Hospital Ethical Committee (No. 07020470055). The approval of the Institutional Review Board covered every participant in the study. A total of 394 individuals were excluded for: (1) thyroid dysfunction; (2) ≤20 years of age; (3) diagnosed as diabetes and took medication meanwhile; (4) had a missing value for waist circumference (WC), blood pressure, the level of fasting blood glucose and serum-free triiodothyronine (FT3), FT4, TSH, triglyceride, or high-density lipoprotein cholesterol (HDL-C). Finally, 2903 individuals (1190 men) with normal thyroid function and complete data were incorporated into the final cohort.

A standardized questionnaire was used to collect data on the demographic characteristics, lifestyle risk factors, personal medical history, and family history of diseases. Data included cigarette smoking, alcohol drinking, body weight and height, the body mass index (BMI), WC, hip circumference, the waist/hip ratio, blood pressure, body fat rate and fasting glucose, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), the area under curve (AUC) of glucose (AUCglu), as well as AUC of insulin (AUCins) were also collected. The serum TSH, FT4, and FT3 levels were measured using electrochemiluminescence immunoassays. Genomic DNA was extracted from the whole blood of participants by phenol–chloroform extraction. The single-nucleotide polymorphisms (SNPs) associated with TSH including *NR3C2* (rs10032216), *PDE10A* (rs753760), *CAPZB* (rs10799824), and *PDE8B* (rs2046045), and with FT3/FT4 including *DIO1* (rs2235544) were performed by Sequenom MassARRAY RS1000 (Sequenom, Inc., San Diego, CA, USA).

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Parametric continuous variables were compared by using unpaired Student's *t* test and the Chi-squared test was adopted to assess the differences in categorical variables between groups. Univariate combined with multivariate linear regression was used to evaluate the linear correlation between thyroid hormones and metabolic parameters, where $P < 0.05$ was considered as a linear correlation between the specific thyroid hormones and metabolic parameters. Multivariate logistic regression analysis was used to identify SNPs independently associated with MetS, where independent SNPs ($P < 0.05$) were then integrated into univariate linear regression to screen those ones independently associated with thyroid hormones (FT3, FT4, FT3/FT4, and TSH), where significant level for independent SNPs was $P < 5 \times 10^{-8}$. Next, the Mendelian randomization analysis was conducted based on the coefficients of the first two steps by using the "Mendelian Randomization" package of R (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria) and inverse variance-weighted method, and $P < 0.05$ was considered that causal relationship has existed between exposure (thyroid hormones) and outcome (MetS).

Demographic and metabolic indexes showed a significant difference between genders. Compared with male subjects, body fat percentage, heart rate, the level of TSH, and HDL-C were significantly higher, while other indicators were all lower in female subjects [Supplementary Table 1, http://links.lww.com/CM9/A702]. Serum FT3, FT4, and log-TSH levels were negatively correlated with HDL-C levels ($P < 0.005$) after adjustment for age, sex, smoking, and alcohol history, FT3 and FT4 were positively correlated with BMI, WC, systolic blood pressure (SBP), and various blood glucose-related indexes, while TSH was negatively correlated with blood glucose-related indexes ($P < 0.05$). However, the FT3/FT4 ratio was negatively correlated with most of the metabolic parameters ($P < 0.05$) [Supplementary Table 2, http://links.lww.com/CM9/A702]. The incidence of MetS was positively correlated with the level of FT3 and TSH, while negatively correlated with that of FT3/FT4 [Supplementary Figure 1, http://links.lww.com/CM9/A595]. Moreover, rs10799824 G-G, rs10799824 G-A, rs2235544 C-C, and rs2235544 C-A were independently related to MetS ($P < 0.05$), and among them, rs2235544 C-C was the only one independently related to thyroid hormones (FT3/FT4) ($P = 2.38 \times 10^{-8}$) [Figure 1, Supplementary Table 3, http://links.lww.com/CM9/A702]. Then, the regression coefficients of rs2235544 C-C and MetS and rs2235544 C-C and FT3/FT4 were included in one-stage Mendelian randomization, and results of the inverse variance-weighted method suggested that a causal relationship has existed between FT3/FT4 and MetS ($P = 0.015$). The relationship between rs2235544 polymorphism of *DIO1* gene and the risk of thyroid hormone levels, HOMA-IR, and MetS were shown in Supplementary Table 4, http://links.lww.com/CM9/A702. The FT4 level of C/A and A/A genotypes was higher than that of the C/C genotype ($P = 0.001$), and the FT3/FT4 ratio was lower than that of the C/C genotype ($P < 0.0001$). In addition, C/A or A/A genotype subjects had higher MetS prevalence compared with subjects with C/C genotype ($P = 0.005$). For the three models analyzing the relationship between SNP and MetS risk, in the co-dominant model, genotype "C/A" and "A/A" increased MetS risk by 1.46 times and 1.40 times, respectively. In the dominant model, genotype "C/A-A/A" increased MetS risk by 1.44 times. These results suggest that rs2235544 C-C is positively correlated with FT3/FT4, but negatively correlated with MetS, which indirectly proves that FT3/FT4 is negatively correlated with MetS.

Regarding the *DIO1* gene, the SNPs in the human *DIO1* gene will affect the serum T3:T4 ratio. The SNP-rs2235544 located in intron 3 of the human *DIO1* gene

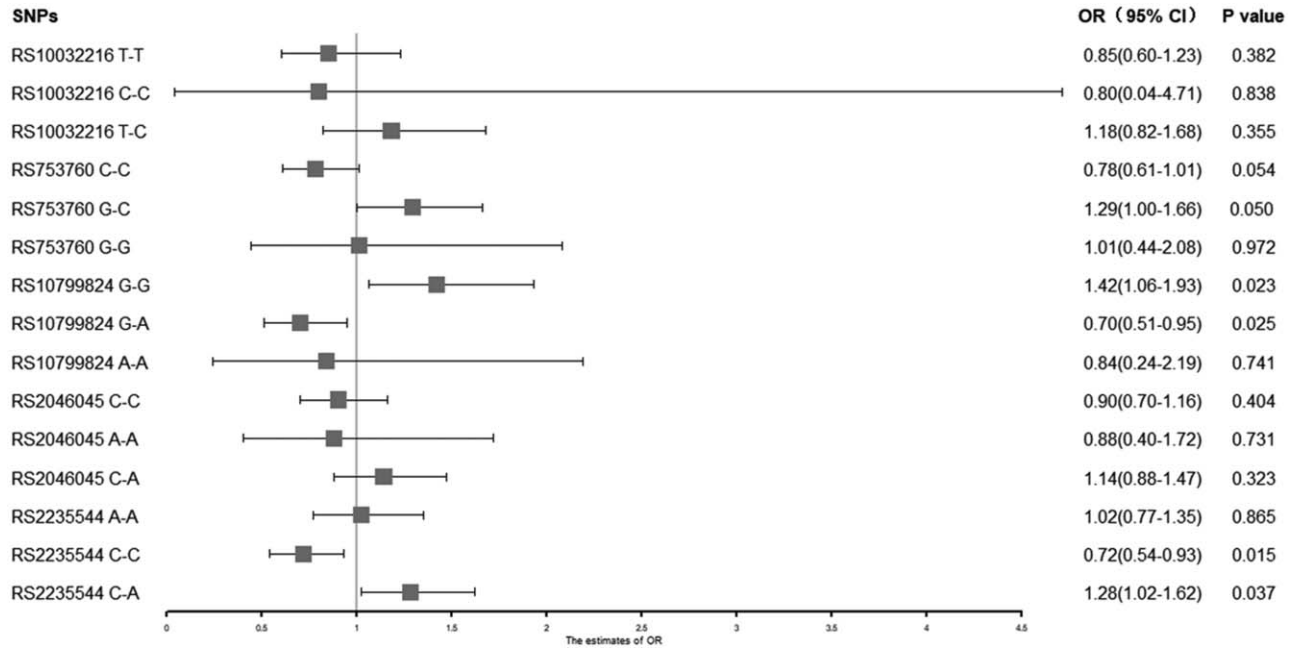

Figure 1: rs10799824 G-G, rs10799824 G-A, rs2235544 C-C, and rs2235544 C-A were independently related to MetS ($P < 0.05$). MetS: Metabolic syndrome.

is one of the important genetic determinants of *DIO1* activity. This polymorphism is associated with the circulating FT3/FT4 ratio in both patients with thyroid hormone replacement and large healthy populations.[4] Based on the previous studies, the minor allele "A" was associated with a decreased FT3/FT4 ratio and increased FT4 levels. In our study, allele "C" of rs2235544 in the *DIO1* gene was significantly positively correlated with FT3/FT4, while negatively correlated with MetS. Through co-dominant model and dominant model analysis, allele "A" of rs2235544 in *DIO1* gene increased MetS risk and FT4 level and decreased FT3/FT4 ratio. These two conclusions indirectly support the negative correlation between MetS risk and the FT3/FT4 ratio, which is also consistent with the results of previous studies. And we know that changes at the genetic level are inborn and that the exposure factor they determine to disease is unaffected by acquired confounders. And Mendelian randomization test was conducted on the correlation between allele "C" of rs2235544 and FT3/FT4 and MetS, and the results supported the causal association that allele "C" of rs2235544 affected MetS through FT3/FT4. Therefore, according to the results of this part of the gene association study, we are more inclined to think that the decreased FT3/FT4 ratio is the cause of MetS increased risk rather than the result.

The highlight of this study was that the MetS risk was negatively associated with the FT3/FT4 ratio in the euthyroid Chinese population. These results were not consistent with those reported by some other studies,[5] which might be because of the differences in results of the associations between FT4 level and metabolic parameters. As for FT4 and metabolic parameters, we are consistent with several Korean studies, so we believe that the study population with different genetic factors may influence the relationship between thyroid hormone levels and MetS components. And we also used genetic association analysis to confirm the nature of the association between FT3/FT4 ratio and MetS. Taken together, this suggests that the balance of FT3 and FT4 may be more important than has been previously recognized.

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Conflicts of interest

None.

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