Thyroid hormone associated with Acanthosis Nigricans and fat distribution in obese patients

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Abstract

Background: Obesity is more easier exhibiting subclinical hypothyroidism (SH) and acanthosis nigricans (AN). We aimed to elucidate the thyroid hormone levels in obese patients and its association with fat distribution and AN.

Methods: In this cross-sectional study, 202 obese men and 239 obese women were enrolled. Anthropometric measurements, glucose-lipid metabolism, thyroid hormone levels and fat distribution were measured. SH were defined by thyroid stimulating hormone (TSH) less than 2.5 mU/L.

Results: 1) The prevalence of AN was significantly higher in obese group with SH than without SH (47.3% vs. 36.9%, P=0.035). Number of obese women with SH were larger than men (38.1% vs. 28.2%, P=0.029). Obese women have higher TSH levels, lower free triiodothyronine (FT3) and free thyroxin (FT4) than obese men (all P<0.01). Body mass index (BMI), waist/hip ratio (WHR), glycosylated hemoglobin (HGB), homeostasis model of assessment for insulin resistance index (HOMA-IR) were significantly lower in obese women than men (all P <0.05). 2) In all obesity, FT3 was significantly positively associated with height, weight, NC, WC, WHR, SBP, DBP, FINS, UA and negatively with HDL-C (all P <0.05). FT4 was significantly positively associated with height, weight, BMI, NC, WC, SBP, DBP, UA, HGB and FBG (all P <0.05). TSH was negatively with FBG and HGB (all P <0.05). 3) FT3 was positively with Peripheral fatmass, total leanmass and negatively with Total Fat% and Trunk/peripheral fatmass (P=0.025;P=0.029;P<0.001;P=0.034), FT4 was also positively with total leanmass and negatively with Total Fat%(P=0.008; P=0.017), and TSH was positively with Total Fat%(P=0.032).

Conclusion: AN is more likely to happen in the obesity with SH. Obese women have higher probability of SH than men. Relatively slightly insufficient of thyroid function with higher TSH may be protective factor in obese women with better metabolism. Thyroid hormone may beneficial to improving fat distribution and building lean mass in the obesity.

Introduction

With dramatically changing of lifestyle and harmful environment, the prevalence of obesity is increasing that affects many organs and presents many complications. The obese patients are at risk for insulin resistance, hyperinsulinemia, thyroid disorders and metabolic syndrome (Mets). Thyroid disorders especially subclinical hypothyroidism (SH) is common in the obesity. Overt hypothyroidism is held responsible for obesity. However, its association with SH is controversial. Higher thyrotropin(TSH) may be the primary event that alter energy expenditure, resulting in increased body mass index(BMI) and weight[1]. Increasing THS also may be secondary to obesity. The probable mechanism is that the compensatory increased TSH overcome decreased tissue responsiveness to circulating thyroid hormones[2].

The obese patients who have the same BMI may manifest different pattern of fat distribution. Susceptibility to metabolic disorder in relation to obesity is largely dependent on the fat distribution. Obesity can be classified to central(android) and peripheral(gynoid) subtype according to fat distribution[3, 4]. Central obesity has higher risk of having diabetes, MetS and cardiovascular diseases. Thyroid hormones appear to be closely associated with fat distribution.

Acanthosis nigricans (AN) mainly refers to skin of the neck, armpit, elbow, axillary, and inguinal folds color were deepened, rough, thick and has a velvet like texture changes. The pathological features for the skin are papillary tumor and excessive keratinization. Acanthosis nigricans includes benign, obesity related, symptoms, malignant, drug secondary and mixed, etc. The incidence of obesity related AN is increasing year by year. The pathogenesis of AN has not been fully elucidated. Insulin resistance is associated with the appearance of AN[5]. Insulin plays a role in growth by combining insulin-like growth factor 1 receptor (IGF-1Rs) when hyperinsulinemia, tthen stimulus cutin cells and fibroblasts proliferation formation, leading to AN occurrence[6]. Its relationship with thyroid hormone has not been explored.

The causes underlying the alteration in thyroid functions and its association with metabolism in obesity are not fully elucidated. The goal of this study was to find thyroid disorders in obesity and its relationship with AN and fat distribution.

Materials And Methods

Subjects

In this cross-sectional study, we included obese patients coming to clinic of Shanghai Tenth People's Hospital who was diagnosed as obesity. Obesity is defined by using BMI over 28 kg/m^2 that fit for Chinese population. BMI was obtained by dividing the weight by the square of the height. Inclusion criteria: 1)BMI ≥ 28 kg/m^2. 2)Patients aged from 18 ~ 60 years old. Exclusion Criteria: 1) patients who had known history of hypothyroidism or hyperthyroidism. 2) patients who had serve hepatic, renal or cardiac dysfunction. 3) those using any medication that affect thyroid hormone levels within 6 months of the enrolment to the study. All the subjects were informed the purpose and they all signed an informed consent. This study was approved by ethical committee of Shanghai Tenth People's Hospital.

Anthropometric Assessment

The anthropometric data including height, weight, neck circumference (NC), waist circumference (WC), hip circumference (HC), and blood pressure were measured for all subjects. Height and weight were measured in these patients with light clothes and without wearing shoes. BMI was calculated as follows: BMI = weight / (height × height). NC refers to the Adam's apple (LAR) node neck girth level. Waist circumference was measured at the smallest horizontal circumference between the ribs and iliac crest at the end of normal expiration. HC was measured the maximum hip circumference at the end of expiration. Waist circumference and hip circumference ratio (WHR) was calculated as HC divided by WC. Blood pressure was measured by mercury sphygmomanometer after the patients resting for 5 min in quite environment in sitting position. Systolic and diastolic BP were measured twice with a 5-min interval and the average of them was recorded.

Lab Data

Venous blood samples of the subjects after 12 hours overnight fasting was collected to test metabolic parameters including thyroid hormone and biochemical profile. Lipid parameters included total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL) and low-density lipoprotein-cholesterol (LDL). Fasting plasma glucose and fasting insulin were measured. Homeostasis model of assessment for insulin resistance index(HOMA-IR) index was calculated to evaluate insulin resistance level using the following formula: HOMA-IR = fasting insulin(uU/L)×fasting glucose□mmol/l□/22.5[7]. Glycosylated hemoglobin (HGB) that represent the mean blood glucose level was also measured. Uric acid□UA□was also tested in all subjects. Thyroid hormone including free triiodothyronine (FT3), free thyroxin (FT4), triiodothyronine (TT3), thyroxin (TT4) and thyroid-stimulating hormone (TSH).

Fat Distribution Measurement

Fat content and its distribution was measured using dual energy X-ray absorptiometry(DEXA)(Hologic QDR4500, USA) with high accuracy and good reproducibility [8]. The patient was in the supine position when they underwent DEXA measurement. We selected the resulted data including total fat%, upper limbs fat mass, lower limbs fat mass, head fat mass,total fat mass□total lean mass, trunk fat mass, trunk fat% and estimated visceral adipose tissue mass. We calculated the peripheral fat mass by add upper limbs fat mass to lower limbs fat mass. Trunk/peripheral fat mass was calculated as peripheral fat mass divided by trunk fat mass.

Definition Of HOMA-IR, SH And Acanthosis Nigricans

HOMA-IR over than 3.2 was considered as insulin resistance. SH levels greater than 2.5 IU/L with normal FT3 and FT4 were defined as subclinical hypothyroidism in this study. The diagnosis of acanthosis nigricans(AN)mainly clinically presentation[9].

Statistical analysis

All data were presented as mean ± standard deviation(SD) and analyzed using SPSS 17.0 software. All count data were expressed as the number of columns (n). Non-normally distributed data were logarithmically transformed before any analysis. Quantitative data were compared using Student's t-test. The correlation between TSH and other parameters were assessed using Pearson's correlation test. A P value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 989 obese patients were selected in the clinic of Department of Endocrinology and metabolism. 442 patients including 202 males and 239 females met the inclusion criterion and disagreed with the exclusion criteria were included as showed in Fig. 1. Among 442 obese patients, 148(33.4%) had SH. The prevalence of SH between females and males had a significant difference (38.1% Vs. 28.2%, P = 0.029) as presented Fig. 2. Additionally, the prevalence of AN were significantly higher in obese group with SH than without SH (47.3% vs. 36.9%, P = 0.035) as presented in Fig. 3. Obese women have lower FT3 and FT4 than obese men (4.87 ± 0.65 pmol/l vs. 5.30 ± 0.69 pmol/l and 15.12 ± 2.59 pmol/l vs. 16.19 ± 2.50 pmol/l, all P < 0.01) as presented in Fig. 4. Obese women have higher TSH levels than men (2.32 ± 1.06 vs. 2.03 ± 0.96, P < 0.01) as showed in Fig. 5. The TT3 and TT4 between genders have no significant difference. Additionally, the height, weight, BMI, NC, WC, HC, WHR, systolic blood pressure (SBP), diastolic blood pressure (DBP), UA, HGB and HOMA-IR were significantly higher in males than females as presented in Table 1 (all P < 0.05). HDL was significantly higher in females than males(P < 0.05). As seen in Table 1, there was no difference between the age, DBP, TCH, TG and LDL of genders (all P > 0.05).

Table 1

Summary of baseline parameters by genders

	Male(n = 202)	Female(n = 239)
Age, years old	31.06 ± 8.6	32.54 ± 10.38
Weight, kg	110.57 ± 15.49**	89.73 ± 13.38
BMI, kg/m^2	35.40 ± 4.20**	33.67 ± 4.16
NC, cm	44.14 ± 3.05**	38.65 ± 3.17
WC, cm	114.79 ± 10.58**	104.59 ± 11.22
HC, cm	115.70 ± 10.10**	112.38 ± 9.24
WHR	0.99 ± 0.06**	0.93 ± 0.06
Fat%	32.29 ± 3.08**	38.51 ± 3.06
SBP, mmHg	137.85 ± 17.42**	130.90 ± 17.53
DBP, mmHg	88.48 ± 11.98	87.16 ± 11.28
TCH, mmol/l	4.92 ± 0.97	4.96 ± 1.36
TG, mmol/l	2.04 ± 1.22*	1.93 ± 1.56
HDL, mg/l	1.01 ± 0.17**	1.13 ± 0.27
LDL, mg/l	3.12 ± 0.82	3.11 ± 0.87
UA, umol/l	455.04 ± 103.46**	371.15 ± 87.18
FBG, mmol/l	5.91 ± 2.02	5.62 ± 1.49
FINS, mmol/l	28.71 ± 22.28	26.05 ± 21.32
HGB, %	6.51 ± 1.60**	5.87 ± 1.05
HOMA-IR	7.87 ± 7.83*	6.55 ± 5.65

BMI: body mass index; NC: neck circumference; WC: waist circumference; HC: hip circumference; WHR: waist to hip ratio; SBP: systolic pressure; DBP: diastolic pressure; TCH: total cholesterol; TG: triglyceride; HDL: high density lipoprotein; LDL: low density lipoprotein; UA: uric acid; FBG: fasting blood glucose; FINS: fasting insulin. *P < 0.05; **P < 0.001.

Correlation Between Thyroid Hormone And Metabolic Parameters

As showed in Table 2, FT3 was significantly positively associated with height, weight, NC, WC, WHR, SBP, DBP, FINS, UA and negatively with HDL-C in all obesity. FT3 was also significantly positively related to height, WHR, SBP, TCH and negatively with HGB in males. FT4 was significantly positively associated with height, weight, BMI, NC, WC, SBP, DBP, UA, HGB and FBG in all obesity. FT4 was negatively with NC and HC in males. FT4 was also positively associated with weight, BMI, NC, WC, HC, DBP, UA, FBG and HOMA-IR in females. TSH was negatively with age FBG and HGB in all obesity. It was also positively with age, FBG and negatively with UA in females.

Table 2

Correlation between thyroid hormone and metabolic parameters

Index	FT3			FT4			TSH		
	total	male	female	total	male	female	total	male	female
age	-0.148(0.002)	NS	NS	NS	NS	NS	-0.137(0.004)	NS	-0.164(0.011)
Height	0.311(< 0.001)	0.184(0.010)	NS	0.211(< 0.001)	NS	NS	NS	NS	NS
Weight	0.202(< 0.001)	NS	NS	0.184(< 0.001)	NS	0.220(0.001)	NS	NS	NS
BMI	NS	NS	NS	0.099(0.043)	NS	0.212(0.001)	NS	NS	NS
NC	0.213(< 0.001)	NS	NS	0.158(0.002)	-0.186(0.013)	0.198(0.004)	NS	NS	NS
WC	0.145(0.002)	NS	NS	0.131(0.009)	NS	0.150(0.027)	NS	NS	NS
HC	NS	NS	NS	NS	-0.160(0.032)	0.225(0.001)	NS	NS	NS
WHR	0.183(< 0.001)	0.154(0.040)	NS	NS	NS	NS	NS	NS	NS
SBP	0.163(0.002)	0.193(0.012)	NS	0.177(0.001)	NS	NS	NS	NS	NS
DBP	0.113(0.034)	NS	NS	0.174(0.001)	NS	0.200(0.007)	NS	NS	NS
TCH	NS	0.164(0.028)	NS	NS	NS	NS	NS	NS	NS
TG	NS	NS	NS	NS	NS	NS	NS	NS	NS
HDL	NS	NS	NS	NS	NS	NS	NS	NS	NS
LDL	NS	NS	NS	NS	NS	NS	NS	NS	NS
UA	0.116(0.030)	NS	NS	0.123(0.021)	NS	0.195(0.009)	NS	NS	0.170(0.020)
FBG	NS	NS	NS	0.146(0.003)	NS	0.156(0.022)	-0.118(0.016)	NS	-0.157(0.019)
FINS	0.127(0.012)	NS	NS	NS	NS	NS	NS	NS	NS
HGB	NS	-0.302(0.011)	NS	0.203(0.012)	NS	NS	-0.222(0.005)	NS	NS
HOMA-IR	NS	NS	NS	NS	NS	0.155(0.029)	NS	NS	NS

FT3: free triiodothyronine; FT4: free thyroxin; TSH: Thyroid Stimulating Hormone; BMI: body mass index; NC: neck circumference; WC: waist circumference; HC: hip circumference; WHR: waist to hip ratio; SBP: systolic pressure; DBP: diastolic pressure; TCH: total cholesterol; TG: triglyceride; HDL: high density lipoprotein; LDL: low density lipoprotein; UA: uric acid; FBG: fasting blood glucose; FINS: fasting insulin; NS: No significant.

Association Of Fat Distribution With TSH

As showed in Table 3, in obesity, FT3 was positively with Peripheral fatmass, total leanmass and negatively with Total Fat% and Trunk/peripheral fatmass (r = 0.242,P = 0.025; r = 0.252,P = 0.029; r=-0.204,P < 0.001; r=-0.232,P = 0.034), FT4 was also positively with total leanmass and negatively with Total Fat%(r = 0.302,P = 0.008; r=-0.122,P = 0.017), and TSH was positively with Total Fat%(r = 0.107,P = 0.032). In females, FT3 was also positively associated with Peripheral fat mass and negatively Trunk/peripheral fatmass (r = 0.327, P = 0.016; r=-0.336, P = 0.014).

Table 3
Correlation between thyroid hormone and fat distribution

Index	FT3			FT4			TSH		
	total	male	female	total	male	female	total	male	female
Trunkfatmass	NS	NS	NS	NS	NS	NS	NS	NS	NS
Peripheral fatmass	0.242(0.025)	NS	0.327(0.016)	NS	NS	NS	NS	NS	NS
Trunk/peripheral fatmass	-0.232(0.034)	NS	-0.336(0.014)	NS	NS	NS	NS	NS	NS
Trunk fat%	NS	NS	NS	NS	NS	NS	NS	NS	NS
Head fatmass	NS	NS	NS	NS	NS	NS	NS	NS	NS
Total fatmass	NS	NS	NS	NS	NS	NS	NS	NS	NS
Total leanmss	0.252(0.029)	NS	NS	0.302(0.008)	NS	NS	NS	NS	NS
Total Fat%	-0.204(< 0.001)	NS	NS	-0.122(0.017)	NS	NS	0.107(0.032)	NS	NS
FT3: free triiodothyronine; FT4: free thyroxin; TSH: Thyroid Stimulating Hormone; NS: No significant.									

Discussion

Obesity accompanied by excess body fat accumulation has an adverse effect on health. It is an important determinant of type 2 diabetes mellitus, hypertension, metabolic syndrome and cardiovascular disease risk. Obesity and SH are two common clinical manifestation that may interact with each other. Hypothyroidism even if SH has been verified closely associated with a higher BMI and prevalence of obesity[10].This article suggested a meaningful association between metabolic parameters and thyroid function in obese patients. Additionally, as we known, the fat distribution is more meaningful than total fat content in evaluating metabolic disorder. The goal of this study was also to the assess the association of thyroid hormone levels with AN and fat distribution.

The previous study has shown that TSH levels are slightly increased in obesity and are associated with BMI[1]. The underlying mechanism are not fully known. A defense mechanism may exist in obesity to counteract the fat accumulation by increasing thyroid function to increase energy expenditure[11]. Another probable mechanism it the increased leptin in obesity irritate the transcription of pro-thyrotropin-releasing hormone (TRH) in central and consequently that of TSH[2]. The prevalence of SH is 33.4% in obesity and it is significantly higher in females in this study. Also, the obese women have lower FT3, FT4 and higher TSH levels than obese men. However, the causality of obesity and increasing TSH is also controversial and need further study.

Thyroid hormone take part in regulating basal metabolism, thermogenesis and also play an important role in glucose-lipid metabolism[12]. Previous study has shown that FT3/FT4 ratio negatively associated with HDL-C and positively with TG in euthyroid adolescents[13]. In this study, we found that FT3 was significantly negatively with HDL-C in all obesity. FT3 was also significantly positively with TCH in obese men.

About glucose metabolism, TSH is positively correlated with 2 h-glucose and HOMA-IR in youth with euthyroid [13]. FT3/FT4 ratio was positively with fasting and 2 h-glucose, fasting insulin and HOMA-IR[13]. Serum TSH was positively associated with HOMA-IR in obese Brazilian adolescents [14]. However, in this study, we found that FT3 was significantly positively associated with FINS in all obesity. It was also significantly negatively with HGB in males. FT4 was significantly positively associated with HGB and FBG in all obesity. FT4 was also positively associated with FBG and HOMA-IR in females. TSH was negatively with FBG and HGB in all obesity. It was also positively with FBG in females. We infer the results may stem from that the thyroid insufficiency in obesity lead to low metabolism rate. Therefore, the obesity with adequate thyroid have better glucose metabolism. However, the correlation between thyroid hormone and glucose need further investigated in obesity. The increased TSH in obesity may be a protective function in obesity in Chinese. Additionally, inflammatory cytokines may inhibit sodium/iodide symporter mRNA expression and iodide uptake activity. In this study, TSH was positively with UA in obese women in this study.

Obesity related metabolic disease is largely dependent on the fat distribution [15]. Obesity with central type are more at risk of developing metabolic disorder and cardiovascular disease[16, 17]. Fat deposition was associated with increased TSH in obesity[18]. Also the change in FT3/FT4 may be results from the fat distribution[19]. In this study, FT3 was positively with peripheral fatmass and negatively with trunk/peripheral fatmass and total fat% in all obesity. It also associated positively with peripheral fat mass and negatively trunk/peripheral fat mass in females. FT4 was also negatively associated with Total Fat% and TSH was positively with Total Fat% in all obesity. The relatively adequate thyroid function in obesity may be helpful in improving total fat context and fat distribution. Decreased lean mass increased the risk of developing metabolic disorder and cardiovascular disease [20]. In this study, FT3 and FT4 was also positively with total lean mass in all obesity.

The obesity related skin manifestations include soft fibromas, xerosis, striae, skin infections, AN and so on[21]. Obesity is a risk factor for developing AN and AN is a cutaneous marker of hyperinsulinemia in the obesity. AN is significantly associated with type 2 diabetes and obesity [22]. The risk of developing cardiovascular disease is increased in obesity with AN [23]. In this study, we found that the increased TSH obese group has higher prevalence of AN than the obesity without increased TSH. The underlying mechanism needs further investigated.

Conclusion

Our study results suggest that relatively insufficient of thyroid function was more serious in obese women than obese men even if the BMI was lower in obese women. AN is more likely to occur in obese patients with thyroid relative insufficiency. Thyroid hormone may beneficial to improving fat distribution and building lean mass in the obesity.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

SQ designed the study. XCW performed the experiment and drafted the manuscript. YC and BWM participated in the data collection and statistical analysis. CJS and PY assisted the manuscript revision and took part in language editing. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets during and/or analysed during the current study are available

from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was approved by the ethics committee of Shanghai Tenth People's Hospital.

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Endnotes

Not applicable.

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Figures

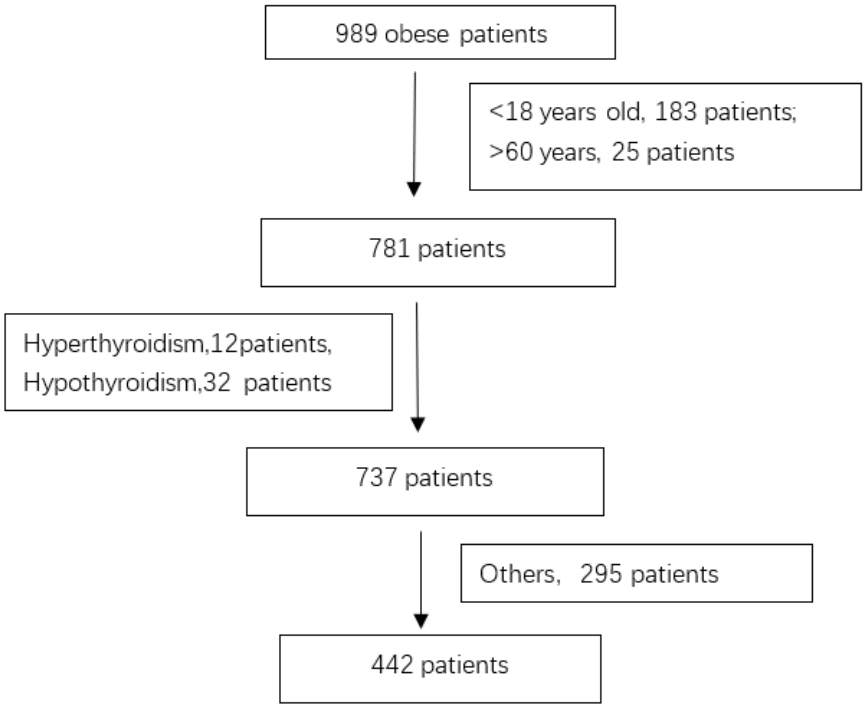
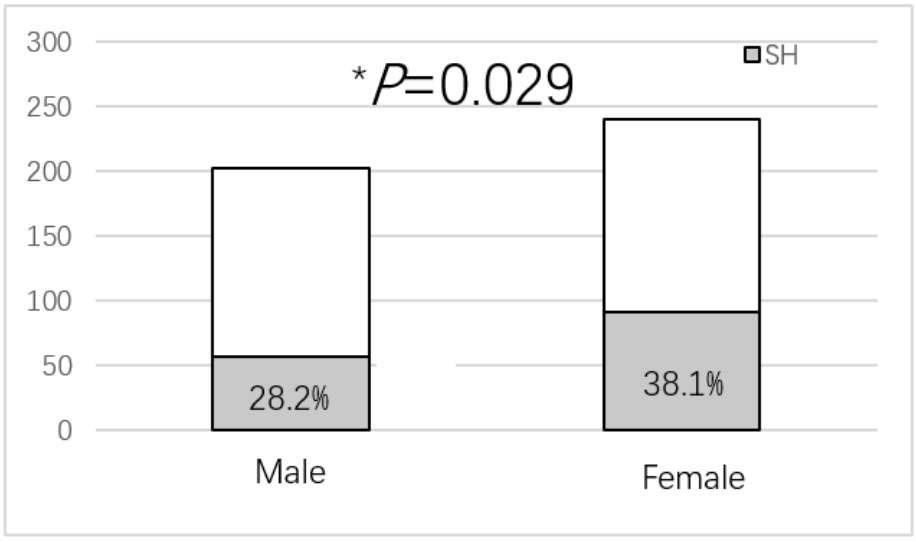


Figure 1

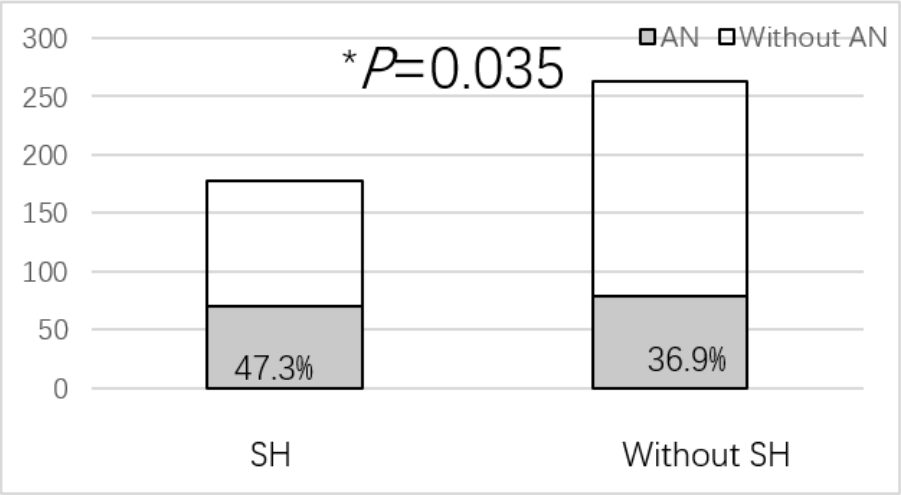
The flow of inclusion and exclusion of subjects



SH: Subclinical hypothyroidism; *P<0.05.

Figure 2

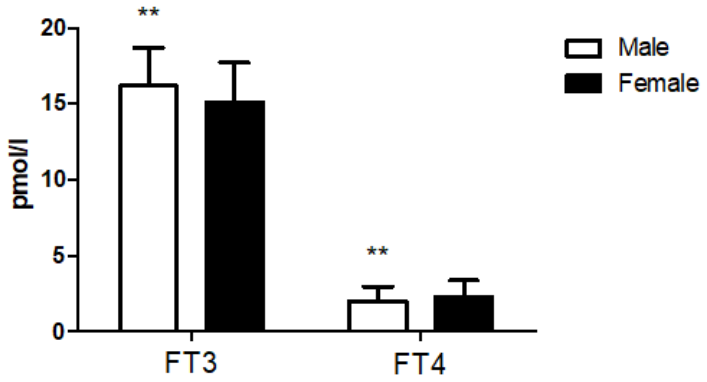
The prevalence of SH in males and females with obesity



SH: Subclinical hypothyroidism; AN: Acanthosis Nigricans; *P<0.05.

Figure 3

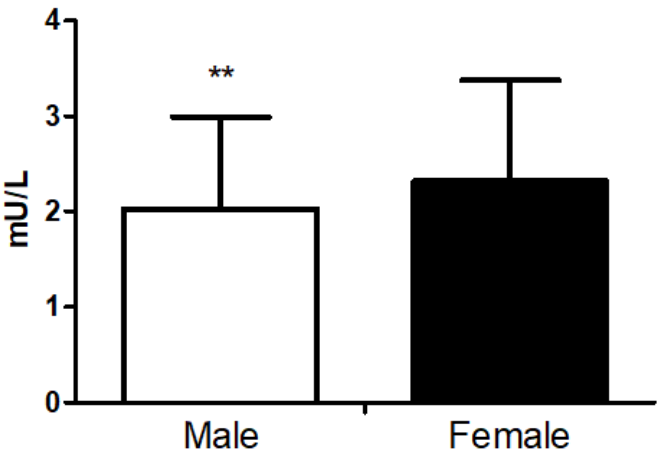
The prevalence of AN in obesity with SH and without SH



FT3: free triiodothyronine; FT4: free thyroxin; **P<0.001.

Figure 4

Thyroid hormone between genders in the obesity



TSH: Thyroid Stimulating Hormone; **P<0.001.

Figure 5

TSH between genders in the obesity