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ORIGINAL ARTICLE

Retrospective Study

Correlation between diabetic peripheral neuropathy and thyroid hormone sensitivity in elderly patients with type 2 diabetes mellitus

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Abstract

BACKGROUND

Diabetic peripheral neuropathy (DPN) is a common complication of type 2 diabetes mellitus (T2DM), significantly affecting patients' quality of life and imposing a substantial economic burden. Recent studies have highlighted the role of thyroid hormones in diabetes complications, particularly in elderly patients with T2DM. However, the relationship between thyroid hormone sensitivity and DPN remains unclear.

AIM

To investigate the correlation between thyroid hormone sensitivity and DPN in elderly patients with T2DM.

METHODS

In a cohort of 256 elderly patients with T2DM, propensity score matching was used to balance age, sex, and diabetes duration. Clinical data were collected to calculate thyroid hormone sensitivity and analyze its correlation with DPN. A random forest model was used to evaluate the diagnostic value of free triiodothyronine/free thyroxine (FT_3/FT_4) for DPN.

RESULTS

Patients with DPN had a lower FT_3/FT_4 ratio [(0.302 ± 0.053) *vs* (0.316 ± 0.049), P = 0.040]. Quartile stratification showed decreasing DPN prevalence with higher FT_3/FT_4 ratios. Spearman's correlation analysis showed that a lower FT_3/FT_4 ratio was associated with higher glycated hemoglobin, fasting blood glucose, reduced nerve conduction velocity, and electrical skin conductance. Logistic regression indicated a positive relationship between the median FT_3/FT_4 ratio and bilateral

foot electrochemical skin conductance [odds ratio (OR): 1.019; 95%CI: 1.005-1.034; P = 0.007] and sural nerve sensory amplitude (OR: 1.310; 95%CI: 1.008-1.703; P = 0.043). Receiver operating characteristic analysis using a random forest model showed that incorporating FT_3/FT_4 improved predictive performance for DPN, with an area under the curve of 0.74, sensitivity of 0.79, specificity of 0.64, and accuracy of 0.77.

CONCLUSION

In elderly patients with T2DM with euthyroidism, a lower FT_3/FT_4 ratio is correlated with increased DPN incidence, affecting both large and small nerve fibers. FT_3/FT_4 is an effective predictor of DPN.

Key Words: Diabetic peripheral neuropathy; Thyroid hormone sensitivity; Type 2 diabetes mellitus; Elderly; Free triiodothyronine/free thyroxine ratio

Core Tip: In this study, we explore the relationship between thyroid hormone sensitivity and diabetic peripheral neuropathy (DPN) in elderly patients with type 2 diabetes mellitus (T2DM). Our findings indicate that a lower free triiodothyronine/free thyroxine (FT_3/FT_4) ratio is significantly associated with increased DPN incidence, affecting both large and small nerve fibers. The FT_3/FT_4 ratio serves as an effective predictor for DPN, enhancing diagnostic accuracy. These results highlight the importance of assessing thyroid hormone sensitivity in managing and predicting DPN in elderly patients with T2DM, offering new insights into the pathophysiological mechanisms underlying this complication.

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INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a prevalent complication of type 2 diabetes mellitus (T2DM), affecting approximately 50% of patients with diabetes[1]. DPN is characterized by pain and sensory impairment in the limbs and can lead to falls, ulcers, and fractures. In severe cases, it may necessitate amputation, thereby significantly diminishing patients' quality of life and imposing a notable economic burden[1-3].

Thyroid hormones play a crucial role in regulating metabolism, energy balance, and the development and function of the nervous system[4]. Recent studies have gradually uncovered the relationship between thyroid dysfunction and insulin resistance, while chronic complications of diabetes, specifically, thyroid dysfunction has been implicated in the development of DPN[5,6]. Research has found that the prevalence of clinical and subclinical hypothyroidism (SCH) among patients with DPN is 17.7%, with 52.8% of patients with SCH exhibiting severe DPN, significantly higher than the 28.3% observed in the control group. This suggests an independent association between SCH and the severity of DPN[6]. Other studies have found that low triiodothyronine (T_3) syndrome is associated with a higher risk and severity of DPN in patients with T2DM[7]. Elderly individuals are at high risk for thyroid diseases, with studies reporting that 23.79% of elderly patients with T2DM have thyroid dysfunction[8]. Some studies indicate that age influences the upper limit of thyroid-stimulating hormone (TSH) levels[9,10], suggesting that adult diagnostic and treatment protocols for thyroid diseases may not be appropriate for elderly patients. This highlights the need to explore other indicators to better understand the association between thyroid function and DPN in elderly patients with T2DM.

Recent studies suggest that thyroid hormone sensitivity is a more profound indicator of thyroid function status and is associated with T2DM, obesity, metabolic syndrome, and nonalcoholic fatty liver disease[11,12]. Despite this, there remains a lack of clarity regarding how thyroid hormone sensitivity impacts the progression of DPN in elderly patients with T2DM. Therefore, in this study, we aimed to explore the relationship between DPN and thyroid hormone sensitivity in elderly patients with T2DM and euthyroidism.

MATERIALS AND METHODS

Patients

This was a cross-sectional study that included patients who were electively hospitalized for routine diabetes management in the Endocrinology Department of Beijing Hospital from January 2020 to March 2023.

The inclusion criteria were as follows: (1) Age ≥ 65 years; (2) Diagnosis of T2DM, with diagnostic criteria referring to the 2023 guidelines of the American Diabetes Association, which include typical symptoms of diabetes plus either random

blood glucose levels, 2-hour glucose levels during an oral glucose tolerance test, FBG ≥ 7.0 mmol/L, or glycated hemoglobin ≥ 48 mmol/L (6.5%)[13]; and (3) Normal thyroid function.

The exclusion criteria included the following: (1) History of thyroid disease, thyroid surgery, or long-term medication for thyroid disease; (2) Other types of diabetes, including type 1 diabetes mellitus, gestational diabetes, specific types of diabetes, low T_3 syndrome, or acute complications of diabetes; (3) Severe liver dysfunction (aspartate aminotransferase or alanine aminotransferase > 2.5 times the upper limit of normal), severe renal dysfunction (estimated glomerular filtration rate < 30 mL/minute/1.73 m^2), or malignant tumors; (4) History of pituitary disease; and (5) Non-diabetic causes of peripheral neuropathy.

To ensure that the peripheral neuropathy observed in this study was specifically attributed to diabetes, we applied strict exclusion criteria, ruling out patients with conditions such as cervical or lumbar spine disease, vitamin B_{12} deficiency, alcohol abuse, or other neurological disorders. Participants were classified into two groups based on the presence of DPN: Those with DPN (n = 161) and those without DPN (NDPN group) (n = 95). The enrollment flowchart is presented in Figure 1. This study received approval from the Research Committee of Beijing Hospital (2024BJYYEC-KY094-01) and was conducted following the principles of the Declaration of Helsinki.

Sample size calculation

The sample size for this study was calculated using G*Power software in the study design phase, and the calculation method was reviewed for ethical approval. We estimated the required sample size based on an assumed effect size (correlation coefficient, r = 0.3), a significance level (α = 0.05), and a statistical power of 80% (1 - β = 0.80). The sample size was calculated using a two-tailed test with the point biserial correlation model, suitable for analyzing a dichotomous and continuous variable. This indicated a need for at least 82 participants per group, with a balanced allocation of DPN and NDPN groups (1:1), totaling 164 participants. The actual sample size was larger, further increasing the study's statistical power and reliability.

Data collection and laboratory measurements

For all participants, we recorded the general demographic and clinical information, including age (years), sex, duration of diabetes (years), height (m), and weight (kg), and calculated the body mass index (BMI) using the formula: BMI (kg/m^2) = weight (kg)/[height $(m)^2$]. We also documented each participant's history of hypertension, smoking, and alcohol use. Biochemical parameters, including total cholesterol, triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), albumin, uric acid, and fasting blood glucose (FBG), were quantitatively assessed using the HITACHI LABOSPECT 008AS automated electrochemiluminescence immunoassay platform. Thyroid function was evaluated by analyzing TSH, free T_3 (FT_3), and free thyroxine (FT_4) levels using the Siemens ADVIA Centaur automated immunoassay system. In addition, glycated hemoglobin (HbA1c) levels were measured using the Premier Hb9210 High-Performance Liquid Chromatography system. The reference ranges for FT_3, FT_4, and TSH were established as 2.3-4.2 pg/mL, 0.89-1.76 ng/dL, and 0.35-5.5 mIU/mL, respectively.

Calculation of thyroid hormone sensitivity indices

The thyroid hormone sensitivity indices were differentiated into central and peripheral categories. Central thyroid hormone sensitivity was assessed using indices such as the TSH Index (TSHI), Thyroid Hormone Resistance Index (TT4RI), and Thyroid Feedback Quantile Index (TFQI). TFQI was calculated using the formula: TFQI = cdfFT_4 (1 - cdfTSH), where cdfFT4 and cdfTSH represent the cumulative distribution functions of FT4 and TSH, respectively, within the study population. These CDF values help assess the relative position of FT4 and TSH levels among the participants. The TFQI values ranged from -1 to 1. Negative TFQI values signified increased pituitary sensitivity to thyroid hormones, indicating a more responsive central sensitivity, whereas positive values denoted reduced sensitivity[11]. Higher TSHI and TT4RI indicated diminished central thyroid hormone sensitivity. The formulas for these indices were as follows: TSHI = Ln [TSH (mlU/L)] + 0.1345 × FT_4 (pmol/L)[14], and TT4RI = FT_4 (pmol/L) × TSH (mIU/L)[11]. For peripheral thyroid hormone sensitivity, the ratio of FT_3 to FT_4 served as the primary indicator, with an elevated FT_3/FT_4 ratio suggesting enhanced peripheral activity. This assessment was based on the premise that FT_3, which is the active form of thyroid hormones, plays a crucial role in peripheral thyroid activity[15,16].

Diagnosis of DPN

A comprehensive five-part screening was conducted to detect DPN. This included evaluation of ankle reflexes, vibration perception testing with a 128 Hz tuning fork, pressure perception testing with a 10 g monofilament, pinprick pain perception testing, and temperature sensitivity testing. Additionally, any experiences of pain symptoms and sensory abnormalities were thoroughly investigated. DPN was defined based on positive findings in two or more of the sensory symptoms, signs, or reflex abnormalities, along with changes in ankle reflexes consistent with distal symmetric polyneuropathy and nerve conduction abnormalities involving two or more nerves, including the median, peroneal, and sural nerves, thus confirming DPN[17]. DPN was treated as a binary outcome, with patients classified into DPN and NDPN groups based on the diagnostic criteria.

Nerve conduction studies

Electrochemical skin conductance (ESC) was measured on both hands and feet, and the nerve fiber conduction velocity, latency, and amplitude were assessed using electromyography. The results were determined by trained professionals to ensure consistency and reliability.

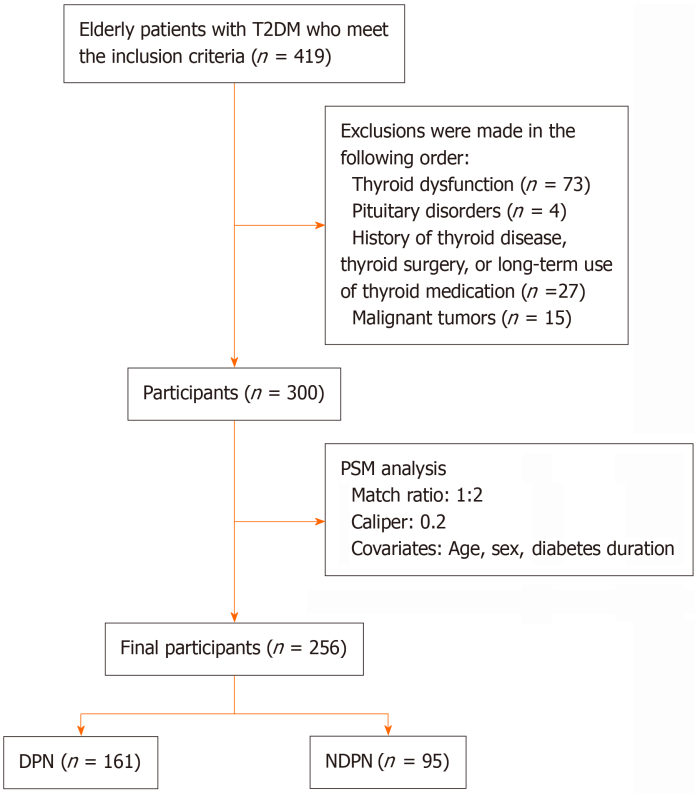

Figure 1 Flow diagram showing the selection of the study population. DPN: Diabetic peripheral neuropathy; NDPN: Non diabetic peripheral neuropathy; PSM: Propensity score matching; T2DM: Type 2 diabetes mellitus.

Statistical analysis

Data processing and analysis were conducted using SPSS version 23 (IBM SPSS, Chicago, IL, United States) and Python 3.11. Propensity score matching (PSM) analysis was conducted to adjust for imbalances in age, sex, and duration of diabetes. Matching was performed at a 1:2 ratio with a caliper width of 0.2[18,19]. The Kolmogorov-Smirnov test was first applied to assess the normality of the data. For data following a normal distribution, the metric was presented as the mean ± SD and compared between groups using the independent samples *t*-test; data not following a normal distribution are represented by the median (P25-P75) and were compared using the non-parametric Mann-Whitney *U* test. Categorical data are expressed as percentages (%) and were analyzed using the χ^2 test. Missing values in the data were imputed using regression estimation. Spearman's correlation analysis was used to assess the relationship between thyroid hormone sensitivity nerve conduction indices, and skin conductance levels. Furthermore, logistic regression models were applied to explore the associations between FT_3/FT_4 ratio stratification nerve conduction indices and skin conductance levels. A two-sided P value < 0.05 was considered statistically significant. Finally, the random forest model was applied to plot the receiver operating characteristic (ROC) curve to evaluate the effectiveness of FT_3/FT_4 in predicting DPN.

RESULTS

Comparison of general characteristics and biochemical indices of the study participants

Following the inclusion and exclusion criteria and after PSM, 161 patients with DPN (DPN group) and 95 patients without DPN (NDPN group) were enrolled in the study. Compared to the NDPN group, the DPN group had a lower FT_3/FT_4 ratio [(0.302 ± 0.053) *vs* (0.316 ± 0.049), P = 0.040], and lower HDL-C levels [1.03 (0.92-1.21) *vs* 1.19 (1.01-1.36), P = 0.001]. A comparison of baseline data between the two groups is presented in Table 1.

Correlation between FT_3/FT_4 stratification and DPN

The study population was divided into four groups based on the quartiles of the FT_3/FT_4 ratio (Supplementary Figure 1). The proportion of DPN in each group was compared. Results showed that as the FT_3/FT_4 ratio increased, the proportion of DPN decreased, with the percentages of DPN in the four groups being 70.8%, 65.6%, 58.5%, and 56.5%, respectively (P = 0.021). There was a significant difference in the proportion of DPN across the FT_3/FT_4 ratio quartiles, suggesting a potential correlation between the two.

Correlation between thyroid hormone sensitivity and metabolic indicators

Further analysis explored the relationship between thyroid hormone sensitivity indicators and metabolic markers

Table 1 Comparison of the general characteristics and biochemical indices between the two groups, *n* (%)

Variables	DPN (*n* = 161)	NDPN (*n* = 95)	*P* value
Age (year)[1]	67.0 (63.0-70.0)	66.0 (63.0-70.0)	0.976
Sex (female)	77 (47.8)	56 (58.9)	0.112
Duration of diabetes (years)[2]	15.46 ± 8.23	15.70 ± 7.79	0.820
BMI (kg/m^2)[1]	24.97 (23.2-27.62)	24.40 (22.50-26.04)	0.137
FT_3 (pg/mL)[2]	2.97 ± 0.31	3.03 ± 0.34	0.118
FT_4 (ng/dL)[1]	1.16 (1.07-1.32)	1.12 (1.05-1.28)	0.158
TSH (IU/mL)[1]	1.81 (1.21-2.67)	1.84 (1.40-2.78)	0.646
TT4RI[1]	27.61 (18.57-38.48)	27.73 (20.74-39.06)	0.869
TSHI[2]	2.64 ± 0.57	2.62 ± 0.61	0.755
FT_3/FT_4[2]	0.302 ± 0.053	0.316 ± 0.049	0.040
TFQI[1]	-0.10 (-0.32-0.14)	-0.16 (-0.31-0.06)	0.287
ALB (g/L)[1]	40.00 (38.00-42.00)	40.0 (38.00-42.00)	0.186
UA (umol/L)[1]	346.00 (291.00-400.00)	327.00 (263.00-388.00)	0.276
FBG (mol/L)[1]	7.40 (5.90-9.50)	6.95 (5.90-8.70)	0.185
TC (mmol/L)[1]	4.10 (3.33-5.00)	4.25 (3.42-4.98)	0.404
TG (mmol/L)[1]	1.35 (0.98-1.93)	1.25 (0.88-1.66)	0.198
LDL-C (mmol/L)[1]	2.27 (1.73-3.08)	2.39 (1.69-3.07)	0.691
HDL-C (mmol/L)[1]	1.03 (0.92-1.21)	1.19 (1.01-1.36)	0.001
HbA1c (%)[1]/(mmol/mol)	8.60 (7.50-10.20)/70 (58-88)	8.60 (7.00-9.60)/70 (53-81)	0.073
Hypertension	118 (73.2)	59 (62.1)	0.083
Smoking	66 (40.9)	29 (30.5)	0.123
Drinking	56 (34.1)	27 (28.4)	0.417

[1]The Kruskal-Wallis test was used to analyze non-normally distributed data.
[2]The independent samples *t*-test was used to compare data that conformed to a normal distribution.
Values are expressed as the median (P25-P75), mean ± SD, or numbers and percentages. The χ^2 test was used to compare sex, hypertension, current smoking, and alcohol intake. BMI: Body mass index; DPN: Diabetic peripheral neuropathy; FT_3: Free triiodothyronine; FT_4: Free thyroxine; FT_3/FT_4: Free triiodothyronine/free thyroxine ratio; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; NDPN: Non-diabetic peripheral neuropathy; TC: Total cholesterol; TG: Triglycerides; TSH: Thyroid-stimulating hormone; TSHI: Thyroid-stimulating hormone index; TT4RI: Thyroxine resistance index; TFQI: Thyroid feedback quantile index; UA: Uric acid.

(Supplementary Figure 2). The findings revealed a negative correlation between the FT_3/FT_4 ratio and both HbA1c (%) (r = -0.1944, P = 0.003) and FBG levels (r = -0.197, P = 0.002).

Correlation analysis between FT_3/FT_4 levels and neuro conductivity and skin conductance indicators

A correlation analysis was conducted between FT_3/FT_4 levels and neuro conductivity and skin conductance indicators (Table 2). The results indicated that FT_3/FT_4 levels were positively correlated with motor velocity in the median nerve (r = 0.156, P = 0.013), as well as with ESC in both feet (r = 0.177, P = 0.005) and hands (r = 0.154, P = 0.015).

Correlation between FT_3/FT_4 stratification and neuro conductivity and skin conductance indicators

Participants were categorized into two groups based on the median FT_3/FT_4 ratio. Binary logistic regression analysis was used to compare the correlation between these groups and neuroconductivity and skin conductance indicators. Model 1 adjusted for variables that showed statistical differences in the correlation analysis: Median nerve motor velocity, ESC in both feet, and ESC in both hands. Model 2 was adjusted for median nerve motor latency, median nerve motor amplitude, median nerve motor velocity, peroneal nerve motor latency, peroneal nerve motor amplitude, peroneal nerve motor velocity, median nerve sensory amplitude, peroneal nerve sensory latency, peroneal nerve sensory amplitude, peroneal nerve sensory velocity, ESC in both feet and ESC in both hands. The results are presented in Table 3, indicating that an increase in the FT_3/FT_4 ratio was associated with an increase in ESC in both feet [odds ratio (OR): = 1.019; 95%CI: 1.005-1.034; P = 0.043].

Table 2 Correlation analysis between free triiodothyronine/free thyroxine levels and neuro conductivity and skin conductance indicators

	r	*P* value
Median nerve motor latency (millisecond)	-0.093	0.139
Median nerve motor amplitude (mV)	0.076	0.226
Median nerve motor velocity (m/second)	0.156	0.013
Common peroneal nerve motor latency (millisecond)	0.012	0.848
Common peroneal nerve motor amplitude (mV)	-0.027	0.670
Common peroneal nerve motor velocity (m/second)	0.027	0.667
Median nerve sensory latency (millisecond)	-0.103	0.101
Median nerve sensory amplitude (mV)	0.107	0.089
Median nerve sensory velocity (m/second)	0.098	0.117
Common peroneal nerve sensory latency (millisecond)	-0.028	0.662
Common peroneal nerve sensory amplitude (mV)	0.076	0.225
Common peroneal nerve sensory velocity (m/second)	0.040	0.526
F-min (millisecond)	-0.084	0.186
M-latency (millisecond)	-0.088	0.161
Two-legged ESC (microsecond)	0.177	0.005
Two-handed ESC (microsecond)	0.154	0.015

F-min: Minimum latency of the F-wave; M-latency: Median nerve motor evoked potential latency; ESC: Electrochemical skin conductance.

Table 3 Association between free triiodothyronine/free thyroxine stratification and neuro conductivity, skin conductance indicators

		Odds ratio	95%CI	*P* value
Model 1	Two-legged ESC (microsecond)	1.017	1.004-1.031	0.013
Model 2	Two-legged ESC (microsecond)	1.019	1.005-1.034	0.007
	Common peroneal nerve sensory amplitude (mV)	1.310	1.008-1.703	0.043

ESC: Electrochemical skin conductance.

Evaluation of the predictive value of FT_3/FT_4 for DPN using ROC curve analysis

To evaluate the predictive value of FT_3/FT_4 for DPN, a random forest model was employed to generate ROC curves (Figure 2). Initially, a model was constructed using known risk factors for DPN[20] (including age, sex, duration of diabetes, hypertension, smoking, LDL-C, TG, HbA1c, FBG, and BMI) to generate the original ROC curve (labeled as "original"). Subsequently, FT_3/FT_4 was added as an additional feature, and a new ROC curve was generated (labeled as "FT_3/FT_4"). In the original model without FT_3/FT_4, the accuracy was 0.73, the area under the curve (AUC) was 0.68, the sensitivity was 0.53, and the specificity was 0.86. After including FT_3/FT_4, the model's accuracy increased to 0.77, the AUC improved to 0.74, the sensitivity rose to 0.79, and the specificity decreased to 0.64. The AUC serves as a comprehensive evaluation index of sensitivity and specificity. The inclusion of FT_3/FT_4 resulted in the highest AUC and accuracy, indicating that FT_3/FT_4 is a valuable biomarker in assisting in the diagnosis of DPN and enhancing the performance of the diagnostic model.

DISCUSSION

In this study, we thoroughly investigated the correlation between DPN and thyroid hormone sensitivity among elderly patients with T2DM who had normal thyroid function. By employing PSM to adjust for age, sex, and duration of diabetes, it was discovered that in elderly patients with T2DM, a decrease in the FT_3/FT_4 ratio, indicative of reduced peripheral sensitivity to thyroid hormones, significantly increased the incidence of DPN. The FT_3/FT_4 ratio was positively correlated with the motor velocity of the median nerve, ESC in both hands, and ESC in both feet. FT_3/FT_4 is an effective

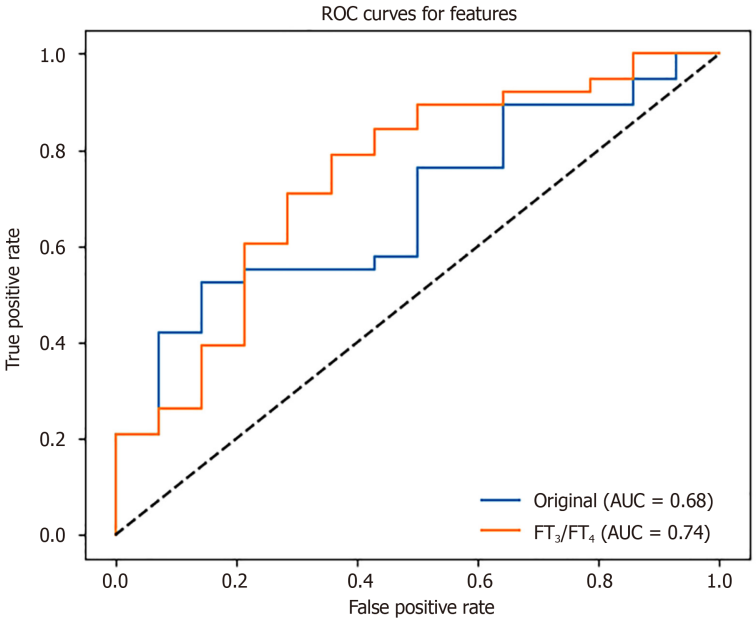

Figure 2 Receiver operating characteristic curve of free triiodothyronine/free thyroxine for predicting diabetic peripheral neuropathy. The receiver operating characteristic (ROC) curve plotted based on the random forest model evaluates the value of free triiodothyronine/free thyroxine (FT_3/FT_4) in predicting DPN. First, we used age, sex, duration of diabetes, hypertension, smoking, low-density lipoprotein cholesterol, triglycerides, hormglycated, fasting blood glucose, and body mass index to construct the model and generate the ROC curve (labeled as "original"). Then, we included FT_3/FT_4 as an additional feature in the model and generated a new ROC curve (labeled as "FT_3/FT_4"). ROC: Receiver operating characteristic; AUC: Area under the curve; FT_3/FT_4: Free triiodothyronine/free thyroxine ratio.

predictor of DPN. Additionally, the FT_3/FT_4 ratio was found to negatively correlate with glycemic metabolic indicators. Importantly, as shown in Table 1, the duration of diabetes was well-balanced between the DPN and NDPN groups (P = 0.820), indicating that diabetes duration did not act as a confounding factor in our analysis.

The relationship between thyroid dysfunction and DPN is a topic worth exploring. A study by Zhao *et al*[5], which included 605 patients with T2DM, found that TSH was an independent risk factor for DPN (OR = 1.365, P < 0.01). More recently, a study involving 580 patients with T2DM explored whether thyroid function indicators affect DPN in patients with T2DM with normal thyroid function. They discovered that FT_4 levels were inversely related to the prevalence of DPN in patients with normal thyroid function. Specifically, when FT_4 levels were below 18.3 pmol/L, the incidence of DPN significantly increased, whereas no significant correlation was observed between TSH, FT_3, thyroxine (T_4), and T_3 levels and DPN[21]. However, another study reached different conclusions, suggesting that FT_4 levels were positively correlated with the prevalence of DPN, whereas FT_3 levels were inversely related[22]. These findings indicate that using TSH or thyroid hormones alone is insufficient to explain the complex relationship between thyroid hormones and DPN. Therefore, we explored the correlation between thyroid hormone sensitivity, a more in-depth indicator of thyroid function status, and DPN. Our study found that thyroid hormone sensitivity was related to the occurrence of DPN in elderly patients with T2DM and normal thyroid function, suggesting that thyroid hormones plays a role not only in the regulation of systemic metabolism but may also directly or indirectly affect the health of the nervous system.

To ensure that the peripheral neuropathy observed in this study was primarily due to diabetes and not age-related factors, we applied strict inclusion and exclusion criteria. We excluded patients with non-diabetic causes of neuropathy, such as spine disease, vitamin B_{12} deficiency, or alcohol abuse. All patients had confirmed DPN based on clinical symptoms and nerve conduction studies. Additionally, we used PSM to adjust for age, and as shown in Table 1, there was no significant age difference between the DPN and NDPN groups (P = 0.976). These steps ensured that the observed associations between thyroid hormone sensitivity and neuropathy were specific to diabetes.

The underlying mechanisms linked to FT_3 with DPN remain unclear. Degeneration of peripheral vascular endothelial cells is considered one of the characteristic changes in DPN[23,24], in which the associated reduction in nitric oxide (NO) due to endothelial dysfunction plays a key role[25]. Studies have shown that T_3 mediates NO production in endothelial cells, reducing DPN by protecting the microvascular endothelium[26]. Furthermore, the production of 3,5-diiodothyronine through the deiodination pathway of T_3 may help to reverse the progression of DPN by regulating the expression of Sirtuin 1 protein[27]. The study by Bessede *et al*[28] demonstrated that T_3 can promote the regeneration of the cavernous nerve and sciatic nerve, further supporting the role of T_3 in nerve regeneration and repair. These findings are consistent with the negative correlation between FT_3 levels, abnormalities in nerve conduction, and the risk of DPN. Specifically, T_3 has been shown to have a direct or indirect impact on vascular endothelial function, assisting in the improvement of endothelial function by relaxing vascular smooth muscles. Meanwhile, low levels of FT_3 may promote the development of DPN by affecting endothelial function[29]. Further research indicates that T_3 can reduce the activity of phosphatidylinositol 3-kinase and increase the expression of transforming growth factor-β1[30], potentially accelerating the progression of DPN[31]. This suggests a close correlation between FT_3 levels and the development of DPN.

The conversion of FT_4 into the more active FT_3 exerts potent biological effects on target organs and tissues, primarily catalyzed by type II deiodinase (DIO2), and the FT_3/FT_4 ratio reflects the activity of DIO2[22]. Activation of DIO2 can reduce oxidative stress and diminish inflammatory responses. However, in patients with T2DM, reduced activity of DIO2 leads to decreased production of FT_3, increased oxidative stress, and inflammation, which in turn promotes the development of DPN[32]. Bapputty *et al*[33] found that DIO2 expression was significantly reduced in the retinas of diabetic mice, and a high-glucose environment further impaired DIO2 activity, suggesting that downregulation of DIO2 may play a role in diabetes-related complications. Although direct evidence linking DIO2 to DPN is lacking, it is plausible that reduced DIO2 activity may also contribute to the progression of DPN. The relationship between thyroid hormone levels and the occurrence of DPN is complex. For the early diagnosis and prevention of DPN, it is recommended that patients with normal thyroid function and diabetes undergo regular screening and thyroid hormone testing.

In the assessment of thyroid function, FT_3 and FT_4 are crucial indicators representing the levels of active and stored thyroid hormones in the body, respectively. The FT_3/FT_4 ratio is used to assess the efficiency of conversion from T_4 to T_3, indirectly reflecting peripheral sensitivity to thyroid hormones. T_3 is one of the most important stimulatory factors in peripheral nerve regeneration. Research has shown that local application of T_3 significantly increases the number of regenerating axons and myelination following the transection of the sciatic nerve in rats[34]. Furthermore, local and single administration of T_3 within biodegradable nerve conduits can notably improve the regeneration of severed peripheral nerves and accelerate functional recovery[35]. However, there remains a lack of research exploring the correlation between thyroid hormone sensitivity and the function of large and small nerve fibers. This study pioneers the proposition that a decrease in peripheral sensitivity to thyroid hormones may simultaneously impair both large and small nerve fibers. Given the absence of a unified standard for assessing peripheral sensitivity to thyroid hormones, further validation of this conclusion requires multicenter studies with large sample sizes.

Using a random forest model to plot the ROC curve, we found that the FT_3/FT_4 ratio is a powerful indicator in predicting DPN. The random forest model, as a machine learning method capable of handling complex data relationships, combined with the ROC curve, provides a reliable means of evaluating diagnostic performance. In this study, the inclusion of the FT_3/FT_4 ratio led to an increase in the model's AUC value and classification accuracy, indicating a strong correlation between FT_3/FT_4 and the risk assessment of DPN. This finding may be related to the critical role of thyroid hormones in maintaining nerve health. In clinical practice, prioritizing sensitivity in DPN screening is crucial for early detection and timely intervention. Although the specificity decreased slightly, this trade-off is acceptable to minimize missed diagnoses, which can lead to severe complications.

This study also discovered a correlation between thyroid hormone sensitivity and glycemic metabolism, with the FT_3/FT_4 ratio found to be negatively associated with HbA1c and FBG levels. A decrease in peripheral sensitivity to thyroid hormones coincided with higher blood glucose levels. Poor long-term glycemic control is a risk factor for DPN[36]. Numerous studies have indicated that thyroid hormones play a significant role in glucose metabolism, with no shortage of research on the impact of thyroid hormone levels on glycemic metabolism. Elevated levels of FT_3 are associated with improved insulin resistance, decreased gluconeogenesis, and reduced hyperglucagonemia[37]. Gu *et al*[38] found that low levels of free thyroid hormones within the normal range are significantly associated with high blood glucose levels and severe insulin resistance. Falkowski *et al*[39] conducted a study on patients with type 1 diabetes mellitus and normal thyroid function and reported that lower levels of FT_3 were linked to a higher rate of neurovascular complications and poorer diabetes metabolic control. These findings suggest that thyroid hormone sensitivity indirectly promotes the occurrence of DPN by affecting glycemic metabolism.

This study has several limitations. First, as an observational study, it could not establish causality. Second, the methods for assessing thyroid hormone sensitivity were not standardized, and criteria may vary across studies. Third, the small sample size limited the robustness of our conclusions, and larger studies are needed. Additionally, restricting the study to patients aged 65 and older may limit generalizability to younger populations. Furthermore, the sensitivity and specificity of neuroconductivity and skin conductance indicators may have affected the diagnostic accuracy, potentially leading to underdiagnosis or overdiagnosis of DPN. Lastly, we did not analyze the effects of medications that could influence thyroid function or DPN, which future studies should consider to strengthen the findings.

CONCLUSION

In summary, among elderly patients with T2DM and normal thyroid function, a decrease in peripheral thyroid hormone sensitivity was associated with an increased incidence of DPN. FT_3/FT_4 is an effective predictor of DPN. In addition, a decrease in peripheral thyroid hormone sensitivity may affect both large and small nerve fiber pathology. This discovery provides new insights into the complex pathophysiological mechanisms underlying DPN.

FOOTNOTES

Author contributions: Pan Q, Guo LX and Fei SJ conceptualized and designed the research; Fei SJ, Luo JY and Wang WH screened patients and acquired clinical data; Fei SJ, Luo JY and Wang WH performed Data analysis; Fei SJ wrote the paper; All authors have reviewed and approved the final version of the manuscript for publication. Pan Q and Guo LX have both played essential and indispensable roles in the research design, data interpretation, and manuscript preparation as co-corresponding authors. Pan Q applied for and secured the funding for this research project. Pan Q conceptualized, designed, and supervised the entire project, conducted a literature review, and drafted the initial manuscript with a focus on the relationship between thyroid hormone sensitivity and diabetic

peripheral neuropathy. Guo LX was instrumental in data re-analysis and interpretation, figure plotting, comprehensive literature review, and the preparation and submission of the current manuscript version, which focuses on FT_3/FT_4 as a potential predictor of peripheral neuropathy in elderly patients with type 2 diabetes. The collaboration between Pan Q and Guo LX is crucial for the publication of this manuscript.

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REFERENCES

1 **Wang W**, Ji Q, Ran X, Li C, Kuang H, Yu X, Fang H, Yang J, Liu J, Xue Y, Feng B, Lei M, Zhu D. Prevalence and risk factors of diabetic peripheral neuropathy: A population-based cross-sectional study in China. *Diabetes Metab Res Rev* 2023; **39**: e3702 [PMID: 37490047 DOI: 10.1002/dmrr.3702]

2 **Pop-Busui R**, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care* 2017; **40**: 136-154 [PMID: 27999003 DOI: 10.2337/dc16-2042]

3 **Pop-Busui R**, Ang L, Boulton AJM, Feldman EL, Marcus RL, Mizokami-Stout K, Singleton JR, Ziegler D. Diagnosis and Treatment of Painful Diabetic Peripheral Neuropathy. Arlington (VA): American Diabetes Association, 2022 [PMID: 35544662 DOI: 10.2337/db2022-01]

4 **Yen PM**. Physiological and molecular basis of thyroid hormone action. *Physiol Rev* 2001; **81**: 1097-1142 [PMID: 11427693 DOI: 10.1152/physrev.2001.81.3.1097]

5 **Zhao W**, Zeng H, Zhang X, Liu F, Pan J, Zhao J, Zhao J, Li L, Bao Y, Liu F, Jia W. A high thyroid stimulating hormone level is associated with diabetic peripheral neuropathy in type 2 diabetes patients. *Diabetes Res Clin Pract* 2016; **115**: 122-129 [PMID: 26822260 DOI: 10.1016/j.diabres.2016.01.018]

6 **Allam MA**, Nassar YA, Shabana HS, Mostafa S, Khalil F, Zidan H, Abo-Ghebsha M, Abdelghaffar A, Essmat A, Elmahdi E. Prevalence and Clinical Significance of Subclinical Hypothyroidism in Diabetic Peripheral Neuropathy. *Int J Gen Med* 2021; **14**: 7755-7761 [PMID: 34785933 DOI: 10.2147/IJGM.S337779]

7 **He W**, Pang C, Chen L, Zeng Y, Gao L, Huang H, Zhang W, Wang X, Deng B. Low T3 syndrome is associated with peripheral neuropathy in patients with type 2 diabetes mellitus. *Muscle Nerve* 2022; **66**: 723-729 [PMID: 36089765 DOI: 10.1002/mus.27719]

8 **Zhu Y**, Xu F, Shen J, Liu Y, Bi C, Liu J, Li Y, Wang X, Gao Z, Liang L, Chen Y, Sun W, Guan Q, Zhang J, Luo Z, Guo L, Cai X, Li L, Xiu L, Yan L, Li C, Shi X, Zhu M, Kuang J, Li G, Ji L. Prevalence of thyroid dysfunction in older Chinese patients with type 2 diabetes-A multicenter cross-sectional observational study across China. *PLoS One* 2019; **14**: e0216151 [PMID: 31048873 DOI: 10.1371/journal.pone.0216151]

9 **Zhai X**, Zhang L, Chen L, Lian X, Liu C, Shi B, Shi L, Tong N, Wang S, Weng J, Zhao J, Teng X, Yu X, Lai Y, Wang W, Li C, Mao J, Li Y, Fan C, Li L, Shan Z, Teng W. An Age-Specific Serum Thyrotropin Reference Range for the Diagnosis of Thyroid Diseases in Older Adults: A Cross-Sectional Survey in China. *Thyroid* 2018; **28**: 1571-1579 [PMID: 30351201 DOI: 10.1089/thy.2017.0715]

10 **Liu YS**, Shan ZY; Endocrine Metabolic Diseases Group of the Chinese Geriatrics Society, Thyroid Group of the Chinese Society of Endocrinology, Chinese Medical Association. [Expert consensus on diagnosis and treatment for elderly with thyroid diseases in China (2021)]. *Zhonghua Laonian Yixue Zazhi* 2021; **40**: 399-418 [DOI: 10.3760/cma.j.issn.0254-9026.2021.05.001]

11 **Laclaustra M**, Moreno-Franco B, Lou-Bonafonte JM, Mateo-Gallego R, Casasnovas JA, Guallar-Castillon P, Cenarro A, Civeira F. Impaired Sensitivity to Thyroid Hormones Is Associated With Diabetes and Metabolic Syndrome. *Diabetes Care* 2019; **42**: 303-310 [PMID: 30552134 DOI: 10.2337/dc18-1410]

12 **Li R**, Zhou L, Chen C, Han X, Gao M, Cheng X, Li J. Sensitivity to thyroid hormones is associated with advanced fibrosis in euthyroid patients with non-alcoholic fatty liver disease: A cross-sectional study. *Dig Liver Dis* 2023; **55**: 254-261 [PMID: 35853822 DOI: 10.1016/j.dld.2022.06.021]

13 **ElSayed NA**, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Hilliard ME, Isaacs D, Johnson EL, Kahan S, Khunti K, Leon J, Lyons SK, Perry ML, Prahalad P, Pratley RE, Seley JJ, Stanton RC, Gabbay RA; American Diabetes Association. Erratum. 2. Classification and diagnosis of diabetes: Standards of Care in Diabetes-2023. Diabetes Care 2023;46(Suppl. 1):S19-S40. *Diabetes Care* 2023;

46: 1106 [PMID: 36724041 DOI: 10.2337/dc23-er05]

14 **Jostel A**, Ryder WD, 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 [PMID: 19226261 DOI: 10.1111/j.1365-2265.2009.03534.x]

15 **Chen S**, Sun X, Zhou G, Jin J, Li Z. Association between sensitivity to thyroid hormone indices and the risk of osteoarthritis: an NHANES study. *Eur J Med Res* 2022; **27**: 114 [PMID: 35820977 DOI: 10.1186/s40001-022-00749-1]

16 **Nie X**, Ma X, Xu Y, Shen Y, Wang Y, Bao Y. Increased Serum Adipocyte Fatty Acid-Binding Protein Levels Are Associated with Decreased Sensitivity to Thyroid Hormones in the Euthyroid Population. *Thyroid* 2020; **30**: 1718-1723 [PMID: 32394790 DOI: 10.1089/thy.2020.0011]

17 **Pop-Busui R**, Braffett BH, Wessells H, Herman WH, Martin CL, Jacobson AM, Sarma AV. Diabetic Peripheral Neuropathy and Urological Complications in Type 1 Diabetes: Findings From the Epidemiology of Diabetes Interventions and Complications Study. *Diabetes Care* 2022; **45**: 119-126 [PMID: 34728530 DOI: 10.2337/dc21-1276]

18 **Austin PC**. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011; **10**: 150-161 [PMID: 20925139 DOI: 10.1002/pst.433]

19 **Stuart EA**. Matching methods for causal inference: A review and a look forward. *Stat Sci* 2010; **25**: 1-21 [PMID: 20871802 DOI: 10.1214/09-STS313]

20 **ElSayed NA**, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Gibbons CH, Giurini JM, Hilliard ME, Isaacs D, Johnson EL, Kahan S, Khunti K, Leon J, Lyons SK, Perry ML, Prahalad P, Pratley RE, Seley JJ, Stanton RC, Sun JK, Gabbay RA; on behalf of the American Diabetes Association. 12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes-2023. *Diabetes Care* 2023; **46**: S203-S215 [PMID: 36507636 DOI: 10.2337/dc23-S012]

21 **He Q**, Zeng Z, Zhao M, Ruan B, Chen P. Association between thyroid function and diabetes peripheral neuropathy in euthyroid type 2 diabetes mellitus patients. *Sci Rep* 2023; **13**: 13499 [PMID: 37596396 DOI: 10.1038/s41598-023-40752-y]

22 **Lin J**, Xiang X, Qin Y, Gui J, Wan Q. Correlation of thyroid-related hormones with vascular complications in type 2 diabetes patients with euthyroid. *Front Endocrinol (Lausanne)* 2022; **13**: 1037969 [PMID: 36465631 DOI: 10.3389/fendo.2022.1037969]

23 **Malik RA**, Newrick PG, Sharma AK, Jennings A, Ah-See AK, Mayhew TM, Jakubowski J, Boulton AJ, Ward JD. Microangiopathy in human diabetic neuropathy: relationship between capillary abnormalities and the severity of neuropathy. *Diabetologia* 1989; **32**: 92-102 [PMID: 2721843 DOI: 10.1007/BF00505180]

24 **Giannini C**, Dyck PJ. Ultrastructural morphometric abnormalities of sural nerve endoneurial microvessels in diabetes mellitus. *Ann Neurol* 1994; **36**: 408-415 [PMID: 8080248 DOI: 10.1002/ana.410360312]

25 **Horton WB**, Barrett EJ. Microvascular Dysfunction in Diabetes Mellitus and Cardiometabolic Disease. *Endocr Rev* 2021; **42**: 29-55 [PMID: 33125468 DOI: 10.1210/endrev/bnaa025]

26 **Gaynullina DK**, Schubert R, Tarasova OS. Changes in Endothelial Nitric Oxide Production in Systemic Vessels during Early Ontogenesis-A Key Mechanism for the Perinatal Adaptation of the Circulatory System. *Int J Mol Sci* 2019; **20**: 1421 [PMID: 30901816 DOI: 10.3390/ijms20061421]

27 **Chandrasekaran K**, Salimian M, Konduru SR, Choi J, Kumar P, Long A, Klimova N, Ho CY, Kristian T, Russell JW. Overexpression of Sirtuin 1 protein in neurons prevents and reverses experimental diabetic neuropathy. *Brain* 2019; **142**: 3737-3752 [PMID: 31754701 DOI: 10.1093/brain/awz324]

28 **Bessede T**, Alsaid B, Ferretti L, Pierre M, Bernabé J, Giuliano F, Karam I, Benoît G, Droupy S. Effect of a local delivery of triiodothyronine (T3) within neuroregenerative guide on recovery of erectile function in a rat-model of cavernous nerve injury. *J Sex Med* 2010; **7**: 1798-1806 [PMID: 20214723 DOI: 10.1111/j.1743-6109.2010.01706.x]

29 **Li MF**, Ke JF, Li S, Wang JW, Zhu ZH, Li JB. Serum free triiodothyronine is inversely associated with diabetic peripheral neuropathy but not with carotid atherosclerotic lesions in euthyroid patients with type 2 diabetes. *Diabetol Metab Syndr* 2021; **13**: 142 [PMID: 34863289 DOI: 10.1186/s13098-021-00760-2]

30 **Lin Y**, Sun Z. Thyroid hormone ameliorates diabetic nephropathy in a mouse model of type II diabetes. *J Endocrinol* 2011; **209**: 185-191 [PMID: 21307121 DOI: 10.1530/JOE-10-0340]

31 **Hussain G**, Rizvi SA, Singhal S, Zubair M, Ahmad J. Serum levels of TGF-β1 in patients of diabetic peripheral neuropathy and its correlation with nerve conduction velocity in type 2 diabetes mellitus. *Diabetes Metab Syndr* 2016; **10**: S135-S139 [PMID: 26559756 DOI: 10.1016/j.dsx.2015.10.011]

32 **Sagliocchi S**, Cicatiello AG, Di Cicco E, Ambrosio R, Miro C, Di Girolamo D, Nappi A, Mancino G, De Stefano MA, Luongo C, Raia M, Ogawa-Wong AN, Zavacki AM, Paladino S, Salvatore D, Dentice M. The thyroid hormone activating enzyme, type 2 deiodinase, induces myogenic differentiation by regulating mitochondrial metabolism and reducing oxidative stress. *Redox Biol* 2019; **24**: 101228 [PMID: 31153038 DOI: 10.1016/j.redox.2019.101228]

33 **Bapputty R**, Sapa H, Masaru M, Gubitosi-Klug RA. Diabetes Modulates Iodothyronine Deiodinase 2 Expression in the Mouse Retina: A Role for Thyroid Hormone in the Pathogenesis of Diabetic Retinopathy. *Invest Ophthalmol Vis Sci* 2023; **64**: 3 [PMID: 38038617 DOI: 10.1167/iovs.64.15.3]

34 **Panaite PA**, Barakat-Walter I. Thyroid hormone enhances transected axonal regeneration and muscle reinnervation following rat sciatic nerve injury. *J Neurosci Res* 2010; **88**: 1751-1763 [PMID: 20127814 DOI: 10.1002/jnr.22344]

35 **Barakat-Walter I**, Kraftsik R. Stimulating effect of thyroid hormones in peripheral nerve regeneration: research history and future direction toward clinical therapy. *Neural Regen Res* 2018; **13**: 599-608 [PMID: 29722302 DOI: 10.4103/1673-5374.230274]

36 **Yang CP**, Li CI, Liu CS, Lin WY, Hwang KL, Yang SY, Li TC, Lin CC. Variability of fasting plasma glucose increased risks of diabetic polyneuropathy in T2DM. *Neurology* 2017; **88**: 944-951 [PMID: 28179465 DOI: 10.1212/WNL.0000000000003682]

37 **Biondi B**, Kahaly GJ, Robertson RP. Thyroid Dysfunction and Diabetes Mellitus: Two Closely Associated Disorders. *Endocr Rev* 2019; **40**: 789-824 [PMID: 30649221 DOI: 10.1210/er.2018-00163]

38 **Gu L**, Yang J, Gong Y, Ma Y, Yan S, Huang Y, Wang Y, Peng Y. Lower free thyroid hormone levels are associated with high blood glucose and insulin resistance; these normalize with metabolic improvement of type 2 diabetes. *J Diabetes* 2021; **13**: 318-329 [PMID: 32981234 DOI: 10.1111/1753-0407.13118]

39 **Falkowski B**, Rogowicz-Frontczak A, Grzelka A, Uruska A, Schlaffke J, Araszkiewicz A, Zozulinska-Ziolkiewicz D. Higher free triiodothyronine concentration is associated with lower prevalence of microangiopathic complications and better metabolic control in adult euthyroid people with type 1 diabetes. *Endocrine* 2018; **60**: 458-465 [PMID: 29603069 DOI: 10.1007/s12020-018-1582-8]

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