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Combined obesity- and lipid-related indices are associated with hypogonadism in Chinese male patients with type 2 diabetes: a cross-sectional study

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Background: There is insufficient attention to hypogonadism in Chinese males with type 2 diabetes mellitus (T2DM). We evaluated the relationship between Combined obesity- and lipid-related indices [Visceral Adiposity Index (VAI), Chinese Visceral Adiposity Index (CVAI), Triglyceride Glucose Index (TyG) and Lipid Accumulation Product (LAP)] with total testosterone (TT) and analyzed the predictive capability of the respective cut-off values.

Methods: We recruited 958 hospitalized male patients with T2DM at the Affiliated Hospital of Qingdao University, collected baseline data and four calculated indices, and obtained their dominance ratio (OR) and corresponding 95% confidence intervals (CI) with TT by multivariate logistic regression. Receiver operating characteristic (ROC) curves were then used to determine cutoff values in predicting hypogonadism (TT< 12 nmol/L), and we also analyzed the combinations between the different indices.

Results: VAI, CVAI, TyG, and LAP all have satisfactory predictive capabilities. The test capability (sensitivity and specificity) of all four indices was better or not worse than that of body mass index (BMI), homeostasis model assessment of insulin resistance (HOMA-IR) and waist circumference (WC). All four indices were effective predictors of hypogonadism at their respective cutoff values (VAI ≥ 2.284, CVAI ≥ 145.779, TyG ≥ 4.308, and LAP ≥ 59.850). Of these, LAP had the largest area under the curve (AUC, AUC = 0.852, Std. Error = 0.014, 95% CI = 0.818-0.873). However, the predictive capability of the combined indices was not significantly improved over the individual indices.

Conclusions: VAI, CVAI, TyG, and LAP are sensitive indices for predicting hypogonadism in Chinese male patients with T2DM. Considering the need for concise and accurate indices in clinical practice, we suggest LAP as a commonly used index.

KEYWORDS

hypogonadism, type 2 diabetes mellitus, visceral adiposity index, Chinese visceral adiposity index, triglyceride glucose index, lipid accumulation product

1 Introduction

Human reproductive function is strictly regulated by the metabolic state. Currently, the prevalence of obesity and diabetes is increasing worldwide (1, 2), and patients are not only at increased risk for cardiovascular events (3–5), but also for complications of the reproductive system. Studies have found that the incidence of reproductive complications in males with obesity and/or type 2 diabetes mellitus (T2DM) can range from 30% to 40%, with patients presenting with hypogonadotropic hypogonadism (6, 7). In contrast, hypogonadism is relatively rare in patients with type 1 diabetes mellitus (T1DM), suggesting that insulin resistance may play an important role (8–10). These patients present with reduced serum total testosterone (TT, recommendations from multiple societies are TT< 12 nmol/L) and clinical symptoms (10, 11), including weakness, decreased libido, erectile and ejaculatory dysfunction, etc. (12, 13). The symptoms have a negative impact on the patient's work, life, and relationships. Meanwhile McPherson et al. found by studying male mice treated with a high-fat diet that the effects of the abnormal metabolic state on the reproductive system carried over even to their offspring raised on a normal diet (14).

There are several difficulties in the current management of male with T2DM in combination with hypogonadism. For one, the receiving physician tends to focus on renal, neurologic, and retinal complications, and rarely discusses reproductive health and refining tests for TT and other sex hormone levels (15). Secondly, in addition to TT deficiency, clinical symptoms may overlap with other complications of diabetes such as weakness, decreased libido, etc. which may be associated with poor glycemic control, vasculopathy (16), and autonomic neuropathy (17, 18). Third, the causes of hypogonadism are complex and, in clinical practice, often require the exclusion of other diseases. Obesity or diabetes results in secondary hypogonadism. It needs to be differentiated from other secondary causes (e.g., traumatic brain injury, tumors of the hypothalamus or pituitary gland, inflammatory and infectious diseases, etc.), and more importantly, primary conditions need to be excluded (e.g., congenital disorders or traumatic injuries of the testes, medications such as ketoconazole and glucocorticoid, and alcohol abuse) (19). Fourth, the appropriateness of long-term testosterone therapy for males with T2DM in the presence of hypogonadism is unclear, and the available studies have mixed results that have been summarized in review articles (20). There are also significant side effects of testosterone therapy (21, 22), which makes early detection of hypogonadism very important.

Taken together, we hope to identify clinical and or biochemical indices that can be routinely used by physicians to predict hypogonadism and to be able to recommend timely andrological evaluations. There is currently 1 trial conducted in Italy that discussed the relationship between Visceral Adiposity Index (VAI) (23), Triglyceride Glucose Index (TyG) (24), and Lipid Accumulation Product (LAP) (25), three common obesity- and lipid-related indices and TT levels in males with T2DM, and found that all three indices were negatively correlated with TT levels, and corresponding cut-off values were given (26). However, considering the significant differences in adipose tissue distribution between Caucasians and Asians (27), we therefore introduced Chinese visceral adiposity index (CVAI) (27, 28), a metric used to assess visceral adiposity dysfunction in Chinese that has been shown to be associated with obesity and multiple complications of diabetes (29–31), in the assessment of gonadal dysfunction. Similarly, we also analyzed the other three indices. To our knowledge, no studies have evaluated these four indices in Chinese males with T2DM.

To fill this gap, we clarified the strength of association of the four obesity- and lipid-related indices mentioned above in predicting hypogonadism in Chinese people, and gave their predictive cut-off values in identifying hypogonadism and analyzed the diagnostic capability of the indices when they were combined.

2 Materials and methods

2.1 Participants and methods

We set up a database at the Affiliated Hospital of Qingdao University, from which we retrieved data on 958 male patients with T2DM who had complete sex hormone and lipid data and met the American Diabetes Association (ADA) 2023 criteria. The following were exclusion criteria:(a) Being younger than 18 or older than 70 years of age, (b) having acute complications of T2DM (e.g., diabetic ketoacidosis, hyperglycemic hyperosmolar state, etc.) or severe chronic complications of T2DM (e.g., diabetic nephropathy requiring dialysis, diabetic retinopathy with blindness or severe visual impairment, etc.), (c) malignant tumors and hematologic disorders, including after radiation or chemotherapy or surgery (d) concomitant failure of any other organ (e) infectious states or suffering from autoimmune disorders (f) hormone therapy or medications interfering with testosterone levels for any reason, and (g) any known organic hypogonadal condition (e.g., testicular inflammation, post-testicular trauma, testicular torsion, Klinefelter syndrome, Kallmann syndrome, etc.) or previous history of infertility. We demonstrated the patient inclusion process through a flowchart (Figure 1).

Baseline data for all subjects included age, height, weight, blood pressure, waist circumference (WC), hip circumference, duration of diabetes, as well as complication status and medication use. Body mass index (BMI) is calculated by dividing weight (kg) by the square of height (m). The circumference of the midpoint line between the lowest point of the rib cage and the upper edge of the iliac crest, measured at the end of exhalation before inhalation, defined as WC (32). And we collected blood samples from patients who had fasted for more than 8 hours to test the following items: fasting blood glucose, fasting insulin, fasting C-peptide (taking into account the use of exogenous insulin in some patients), triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), follicle-stimulating hormone (FSH), luteinizing hormone (LH), TT, estradiol (E2), creatinine, etc. We also calculated the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) to assess insulin resistance in patients, calculated as the product of fasting plasma insulin (mU/

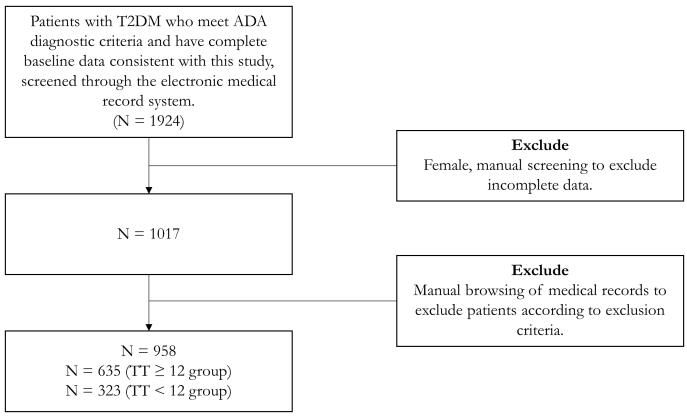

FIGURE 1
Flowchart of patient inclusion process. TT, total testosterone; T2DM, type 2 diabetes mellitus; ADA, American Diabetes Association.

L) times fasting blood glucose (mmol/L) divided by 22.5 (33, 34). To reduce the variability of the TT assay, all tests were performed in the Central Laboratory of the Affiliated Hospital of Qingdao University (electrochemiluminescence immunoassay).

The study complied with the ethical standards of the Declaration of Helsinki (2013) and was approved by the Ethics Committee of the Affiliated Hospital of Medical College Qingdao University (QYFY WZLL 28100). All enrolled participants signed the informed consent form.

2.2 Indices evaluation

The four indices involved in this study can be calculated from WC (cm), TG (mmol/L), LDL-C (mmol/L), HDL-C (mmol/L), and fasting blood glucose. Below we give the formulas for VAI, CVAI, LAP and TyG (23–25, 27). Where the calculation of VAI, CVAI and LAP varies for males and females, here we give only the male (Equations 1–4).

$$VAI = \frac{WC}{39.68+1.88\times BMI} \times \frac{TG}{1.03} \times \frac{1.31}{HDL-C} \quad (1)$$

$$CVAI = -267.93 + 0.68 \times age + 0.03 \times BMI + 4.00 \times WC + 22.00 \times \log_{10} TG - 16.32 \times (HDL - C) \quad (2)$$

$$LAP = (WC - 65) \times TG \quad (3)$$

$$TyG = \ln \frac{TG\ (mg/dl) \times glucose(mg/dl)}{2} \quad (4)$$

2.3 Statistical analysis

We used SPSS software v.24.0 (SPSS IBM Corporation, Armonk, NY, USA) for statistical analysis. Quantitative variables are expressed as mean ± standard deviation or median and quartiles depending on whether they conform to a normal distribution (by the Kolmogorov-Smirnov test), and all values of qualitative variables are expressed as percentages, and comparisons between groups were made using the t-test or nonparametric Mann-Whitney U test for the quantitative variables and Fisher's exact test or χ 2 test for the qualitative variables. Factors associated with hypogonadism were estimated using multivariate logistic regression. Considering that the indices may correlate with each other strongly, we performed calculations and presented a bivariate correlation matrix (Supplementary Material Table 1), and we also evaluated the covariance, giving the respective variance inflation factor (VIF) and tolerance (criteria: VIF > 10 or tolerance of approximately 0.1, Supplementary Material Table 2). Selected variables were not collinear. We plotted the ROC (Receiver operating characteristic) curves of the four indices to evaluate the sensitivity, specificity, and optimal cut-off values of different indices in prediction, and we also analyzed the combinations between the different indices. All statistical analyses were bilateral and P< 0.05 was considered statistically significant.

3 Results

3.1 Comparison of baseline characteristics between the two groups

Table 1 (general characteristics of the two groups) and Table 2 (test results and indices between the two groups) show the baseline characteristics of the participants grouped according to the TT level in a total of 958 patients, 33.72% of whom had a TT level below the hypogonadism threshold of 12 nmol/L.

Age, duration of diabetes, height, systolic blood pressure, diastolic blood pressure, smoking and alcohol consumption, comorbidities (retinopathy and nephropathy), and insulin, α-glucosidase inhibitor, and statin medications were similar between the two groups in Table 1 (P > 0.050). However, weight, BMI, WC, and hip circumference were significantly different (P< 0.001), and the median of all four measures was greater in the TT< 12 nmol/L group than in the TT normal group.

As shown in Table 2, patients with TT< 12 nmol/L had similar levels of fasting glucose levels, LDL-C, TC, creatinine, and eGFR as

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TABLE 1 General characteristics of the two groups (nmol/l).

	TT ≥ 12	TT< 12	P Value
N (%)	635 (66.28%)	323 (33.72%)	
Age (year)	61.00 (54.00, 68.00)	60.00 (51.00, 69.00)	0.315
Duration of diabetes (year)	10.00 (5.00, 16.00)	10.00 (4.00, 16.00)	0.179
Height (cm)	172.00 (170.00, 176.00)	173.00 (170.00, 176.00)	0.431
Weight (kg)	75.00 (68.00, 82.00)	81.00 (73.00, 90.00)	P< 0.001
BMI (kg/m^2)	25.10 (23.39, 27.31)	27.18 (24.93, 29.69)	P< 0.001
WC (cm)	95.00 (88.00, 101.00)	100.00 (93.00, 108.00)	P< 0.001
Hip circumference (cm)	100.00 (95.00, 104.00)	102.00 (97.00, 108.00)	P< 0.001
SBP (mmHg)	139.00 (127.00, 151.00)	140.00 (127.00, 153.00)	0.257
DBP (mmHg)	80.00 (72.00, 88.00)	80.00 (73.00, 89.00)	0.502
Tobacco intake (%)	337 (53.41)	164 (50.93)	0.469
Alcohol intake (%)	329 (52.31)	157 (48.91)	0.322
Retinopathy (%)	223 (35.12)	107 (33.13)	0.540
Nephropathy (%)	169 (26.61)	93 (28.79)	0.475
Insulin (%)	426 (67.09)	199 (61.61)	0.092
Metformin (%)	442 (69.61)	265 (82.04)	P< 0.001
α-glucosidase inhibitor (%)	428 (67.40)	220 (68.11)	0.824
DPP-4i (%)	378 (59.53)	161 (49.85)	0.004
GLP-1RA (%)	31 (4.88)	48 (14.86)	P< 0.001
Statin (%)	483 (76.06)	252 (78.02)	0.498
Fibrates (%)	15 (2.36)	22 (6.81)	0.001

TT, total testosterone; BMI, Body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; DPP4i, Dipeptidyl peptidase 4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonist.

TABLE 2 Test results and indices between the two groups (nmol/l).

	TT ≥ 12	TT< 12	P Value
Glucose (mmol/L)	6.64 (5.27, 8.51)	6.88 (5.34, 8.51)	0.826
C-peptide (ng/mL)	1.71 (1.10, 2.54)	2.29 (1.59, 3.01)	P< 0.001
Insulin (pmol/L)	6.16 (3.66, 10.36)	9.06 (5.49, 14.09)	P< 0.001
HbA1c (%)	8.05 (6.90, 9.57)	8.40 (7.20, 9.50)	0.302
HOMA-IR	0.31 (0.17, 0.56)	0.43 (0.23, 0.82)	P< 0.001
LDL-C (mmol/L)	2.55 (1.93, 3.11)	2.49 (1.87, 3.17)	0.451
HDL-C (mmol/L)	1.21 (1.06, 1.44)	1.09 (0.91, 1.27)	P< 0.001
TG (mmol/L)	1.21 (0.87, 1.86)	3.75 (1.99, 5.02)	P< 0.001
TC (mmol/L)	4.33 (3.51, 5.11)	4.20 (3.45, 5.14)	0.467
ALT (U/L)	17.00 (13.00, 25.00)	21.00 (15.00, 31.00)	P< 0.001
AST (U/L)	17.00 (14.00, 20.00)	18.00 (15.00, 24.00)	P< 0.001
mAlb (mg/L)	8.12 (4.82, 31.73)	10.90 (5.59, 34.55)	0.049
Creatinine (μmol/L)	61.00 (53.00, 71.00)	59.00 (52.00, 70.00)	0.128
eGFR (mL/min/1.73 m^2)	115.85 (97.84, 136.69)	120.89 (99.78, 142.76)	0.110
LH (mIU/mL)	7.85 (5.90, 10.31)	7.29 (5.19, 10.35)	0.044
FSH (mIU/mL)	9.60 (6.84, 13.21)	8.92 (6.20, 14.39)	0.266
TT (nmol/l)	16.26 (14.09, 19.64)	9.25 (7.81, 10.63)	P< 0.001
E2 (pmol/L)	106.80 (83.03, 137.60)	83.29 (60.28, 109.00)	P< 0.001
LAP	35.64 (22.31, 56.99)	113.40 (73.80, 189.00)	P< 0.001
VAI	1.36 (0.87, 2.28)	4.29 (2.53, 7.09)	P< 0.001
CVAI	115.47 ± 44.37	140.29 ± 46.36	P< 0.001
TyG	4.12 (3.93, 4.34)	4.55 (4.29, 4.75)	P< 0.001

TT, total testosterone; LAP, Lipid Accumulation Product; VAI, Visceral Adiposity Index; CVAI, Chinese visceral adiposity index; TyG, Triglyceride Glucose Index; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; TG, triglycerides; TC, total cholesterol; ALT, Alanine Aminotransferase; AST, Alanine Aminotransferase; mAlb, microscale albuminuria; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TT, testosterone; E2, estradiol.

those with TT ≥ 12 nmol/L (P > 0.050), but they had higher levels of fasting insulin, C-peptide, TG, HOMA-IR, and lower HDL-C (P< 0.001). Regarding the hypothalamic-pituitary–testicular axis, patients with TT< 12 nmol/L had lower LH but similar levels of FSH. Primarily, for the indices we want to discuss (VAI, CVAI, LAP and TyG), the levels of all four were higher in the TT< 12 nmol/L group than in the TT ≥ 12 nmol/L group (P< 0.001).

3.2 Logistic regression for VAI, CVAI, LAP and TyG

We performed multivariate analysis by logistic regression, after we adjusted for fasting insulin, C-peptide, TG, HDL-C, fibrates, and statins, as well as other confounders that may affect TT levels, these four indices remained predictors of a low TT (Table 3).

TABLE 3 Adjusted parameters of logistic regression for VAI, CVAI, LAP and TyG.

Indices	β Value	SE	Wald	P Value	OR	95% CI
BMI	0.092	0.041	4.978	0.026	1.097	1.011 - 1.189
WC	0.016	0.028	0.313	0.036	1.018	1.003 - 1.040
HOMA-IR	0.181	0.084	4.599	0.032	1.198	1.016 – 1.413
LAP	0.010	0.004	5.706	0.017	1.010	1.002 - 1.019
VAI	0.155	0.089	3.025	0.032	1.167	1.008 - 1.389
CVAI	0.007	0.005	1.413	0.035	1.009	1.002 - 1.017
TyG	0.937	0.461	4.135	0.042	2.551	1.034 - 6.292

BMI, Body mass index; WC, waist circumference; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; LAP, Lipid Accumulation Product; VAI, Visceral Adiposity Index; CVAI, Chinese visceral adiposity index; TyG, Triglyceride Glucose Index.

3.3 ROC curves and parameters for VAI, CVAI, LAP and TyG

Table 4 demonstrates the parameters of the ROC curves for VAI, CVAI, LAP and TyG, all four of which were statistically significant (p<0.001), with LAP having the largest area under the curve (AUC, AUC = 0.852, Std. Error = 0.014, 95% CI = 0.818 - 0.873, and optimal cutoff value = 59.850), followed by VAI (AUC = 0.846, Std. Error = 0.014, 95% CI = 0.818 - 0.873, and optimal cutoff value = 2.284), TyG (AUC = 0.786, Std. Error = 0.016, 95% CI = 0.754 - 0.818, and optimal cutoff value = 4.308) and CVAI (AUC = 0.655, Std. Error = 0.021, 95% CI = 0.615 - 0.696, and optimal cutoff value = 145.779), all of which had test efficacies that were either better or not worse than those of WC (AUC = 0.643, Std. Error = 0.020, 95% CI = 0.604 - 0.683, and optimal cutoff value = 96.000), HOMA-IR(AUC = 0.603, Std. Error = 0.020, 95% CI =0.564 - 0.641, and optimal cutoff value = 0.370) or BMI (AUC = 0.669, Std. Error = 0.019, 95% CI =0.632 - 0.706, and optimal cutoff value = 26.704).

In addition, we tried the combination between different indices and the results of the combinations of 2 indices are shown in Table 5, but the predictive capability of the combined indices was not significantly improved (no significant change in AUC or sensitivity, Table 5). Among them, the combination of VAI and LAP had the highest AUC (AUC = 0.857, Std. Error = 0.014, 95% CI = 0.830 - 0.884) but no increase in sensitivity. We show the results for a combination of 3 indices and a combination of 4 indices at the same time in Supplementary Table 3. The ROC curves for BMI, WC, and HOMA-IR are shown in Figure 2 for reference. The ROC curves for the four individual indices are displayed in Figure 3, and the ROC curves for the combination of 2 indices are plotted in Figure 4.

4 Discussion

This is the first study to investigate the relationship between obesity- and lipid-related indices (VAI, CVAI, LAP and TyG) and hypogonadism in males with T2DM in Chinese population. A total of 958 male patients with T2DM were included in our study, of which 323 patients with hypogonadism, a proportion of 33.72%, was similar to the proportion in previous studies (6, 7). By analyzing

TABLE 4 Parameters of the ROC curves for VAI, CVAI, LAP and TyG.

Indices	AUC	SE	95% CI	P Value	Optimal cutoffs	J-Youden	Sensitivity (%)	Specificity (%)	(+) Likeli-hood ratio	(–) Likeli-hood ratio
BMI	0.669	0.019	0.632 - 0.706	< 0.001	26.704	0.278	57.59	70.24	1.93	0.60
WC	0.643	0.020	0.604 - 0.683	< 0.001	96.000	0.209	61.87	59.12	1.51	0.64
HOMA-IR	0.063	0.0198	0.564 - 0.641	< 0.001	0.370	0.194	60.13	59.28	1.48	0.67
LAP	0.852	0.014	0.825 - 0.880	< 0.001	59.850	0.619	85.24	76.66	3.65	0.19
VAI	0.846	0.014	0.818 - 0.873	< 0.001	2.284	0.558	80.74	75.05	3.24	0.26
CVAI	0.655	0.021	0.615 - 0.696	< 0.001	145.779	0.273	49.26	78.02	2.24	0.65
TyG	0.786	0.016	0.754 - 0.818	< 0.001	4.308	0.472	74.60	72.56	2.72	0.35

BMI, Body mass index; WC, waist circumference; LAP, Lipid Accumulation Product; VAI, Visceral Adiposity Index; CVAI, Chinese visceral adiposity index; TyG, Triglyceride Glucose Index.

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TABLE 5 Parameters of the ROC curves for combinations of 2 indices.

Combination	AUC	SE	95% CI	P Value	J-Youden	Sensitivity (%)	Specificity (%)	(+) Likelihood ratio	(–) Likelihood ratio
VAI and CVAI	0.842	0.015	0.813 - 0.870	< 0.001	0.571	79.55	77.50	3.54	0.26
VAI and LAP	0.857	0.014	0.830 - 0.884	< 0.001	0.605	79.26	81.19	4.21	0.26
VAI and TyG	0.835	0.015	0.806 - 0.865	< 0.001	0.563	83.52	72.81	3.07	0.23
CVAI and LAP	0.85	0.014	0.822 - 0.878	< 0.001	0.609	84.81	76.04	3.54	0.20
CVAI and TyG	0.801	0.017	0.769 - 0.834	< 0.001	0.508	75.66	75.14	3.04	0.32
LAP and TyG	0.845	0.015	0.816 - 0.874	< 0.001	0.603	80.22	80.07	4.03	0.25

BMI, Body mass index; WC, waist circumference; LAP, Lipid Accumulation Product; VAI, Visceral Adiposity Index; CVAI, Chinese visceral adiposity index; TyG, Triglyceride Glucose Index.

this population, we found that all four indices were predictors of low TT and gave the corresponding ORs. At the same time, we made ROC curves for these four indices, confirming that they can be a more effective and reliable predictor of hypogonadism, and giving cut-off values.

Reduced TT is relatively rare in patients with type 1 diabetes, unless the patient is comorbidly obese, but are not uncommon in patients with T2DM (6, 7). A bilinear relationship between T2DM and male hypogonadism has been recognized (35), but the exact physiological mechanisms are not clear (20). It has been shown that prolonged hyperglycemia and more severe insulin resistance (both central and peripheral) affect TT synthesis and secretion (8–10), and low levels of TT are thought to exacerbate insulin resistance and even lead to diabetes (36). In our study, we found that hypogonadism was not associated with age (P = 0.315) and duration of diabetes (P = 0.179), similar to some of the previous studies (26, 37), and some of them different (38, 39). From these studies (all considering TT), age seems to be an ambiguous factor,

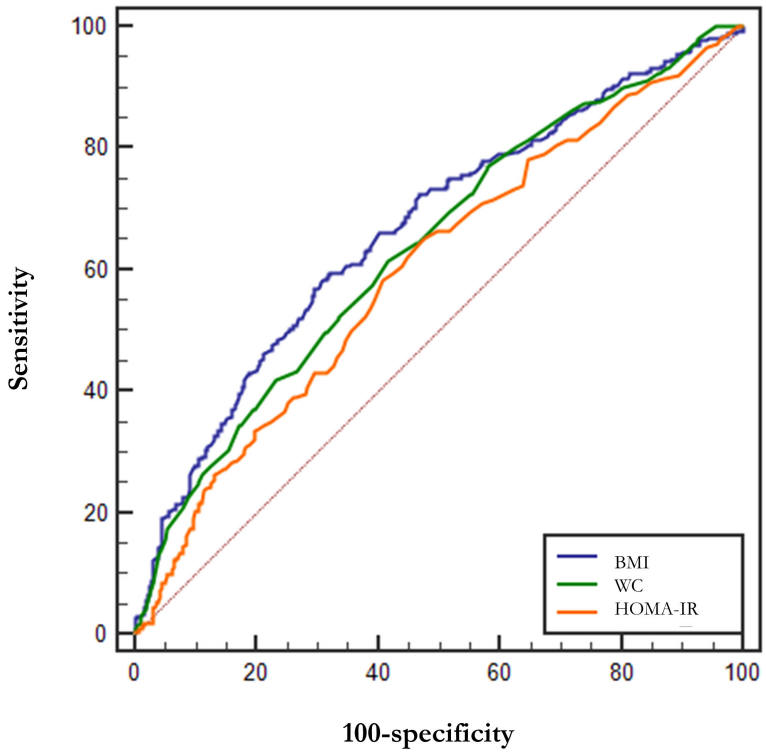

FIGURE 2
ROC curves for BMI, WC, and HOMA-IR. BMI, Body mass index; WC, waist circumference; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance.

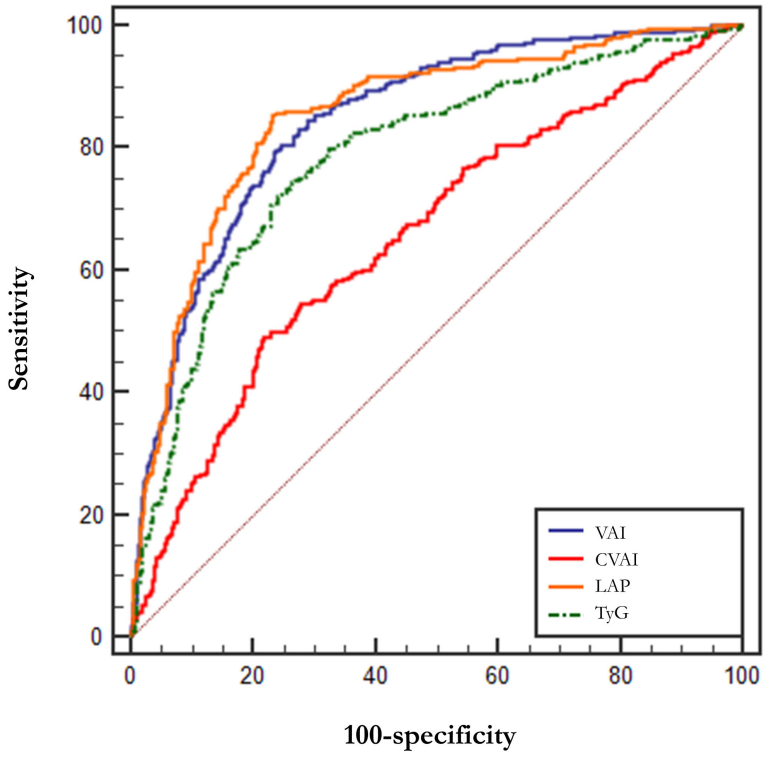

FIGURE 3
ROC curves for VAI, CVAI, LAP and TyG. LAP, Lipid Accumulation Product; VAI, Visceral Adiposity Index; CVAI, Chinese visceral adiposity index; TyG, Triglyceride Glucose Index.

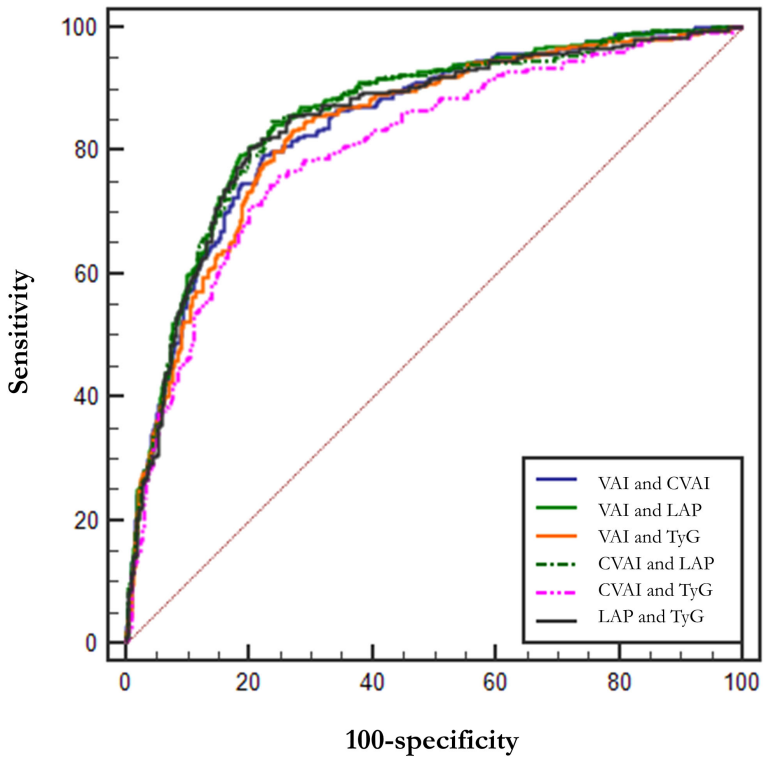

FIGURE 4
ROC curves for combined indices. LAP, Lipid Accumulation Product; VAI, Visceral Adiposity Index; CVAI, Chinese visceral adiposity index; TyG, Triglyceride Glucose Index.

but a cross-sectional study in Europe that included 3200 people found that TT levels appear to remain essentially stable with age until the age of 70, when elevated LH suggests functional testicular failure, while free testosterone declines progressively in the 40s and sex hormone-binding globulin (SHBG) was elevated (19, 40). Therefore, we consider that, firstly, when considering TT, age below 70 years may not be a significant influencing factor. Secondly, free testosterone, although difficult to obtain data, may be a more accurate index of gonadal function. Also to the best of our knowledge, there are no studies that discuss the relationship between age and these four indices.

In addition, we found that these patients had higher insulin and C-peptide levels, which corresponded to the more severe insulin resistance described above, as confirmed by the difference in HOMA-IR between the two groups ($p< 0.001$), suggesting to us that hypogonadism may be more related to diabetes control. In addition, there were differences in weight, WC, hip circumference, and BMI between the two groups (all $P< 0.001$), all of which have been found and repeatedly elucidated in previous studies to be associated with lower TT in males with T2DM (26, 37–39, 41), and there was a significant difference in BMI between the two groups in the present study, which fell in the obese and overweight ranges, respectively, and thus we considered BMI in the subsequent analyses.

Meanwhile, our study found a possible relationship between TT and TG and HDL-C (i.e., TT was positively correlated with HDL-C), which is consistent with many studies (26, 42, 43). This may be one of the reasons why hypogonadism is susceptible to cardiovascular disease complications (44–46), and this risk is certainly more prominent in the group of patients with T2DM. However, basic experiments yielded contradictory results, as Langer et al. found that TT upregulated the expression of scavenger receptor B1 (SR-B1) in HepG2 hepatocytes, leading to a decrease in HDL-C levels, and induced the cholesterol efflux from macrophages and retrograde transport toward the liver, and thus concluded that TT could prevent atherosclerosis (47). Taken together, the potential mechanisms underlying the association between TT and dyslipidemia in males are unclear and contradictory conclusions seem to emerge from clinical and basic studies, so further research is needed to clarify more detailed mechanisms of the relationship under the overall conditions.

VAI, CVAI, TyG, and LAP are common obesity- and lipid-related indices that reflect the distribution of fat and indirectly glyco-metabolic (48, 49). Our study also found that these indices are also sensitive predictors of hypogonadism in Chinese males with T2DM. The test capability (sensitivity and specificity) of VAI, LAP and TyG were significantly better than that of WC, HOMA-IR, and BMI, and the test capability of CVAI was not inferior to that of WC, HOMA-IR, and BMI. We also tried combinations between these four indices, but there was no significant improvement in AUC, sensitivity, and specificity. Therefore, we suggest LAP (AUC = 0.852, Std. Error = 0.014, 95% CI = 0.818 - 0.873, and optimal cutoff value = 59.850) as a commonly used index.

The relationship between low TT and obesity- and lipid-related abnormalities is currently unclear, but possible mechanisms are discussed below: First, previous studies suggested that low TT was due to increased aromatase activity in adipose tissue and increased conversion of TT to E2, which inhibits the hypothalamic-pituitary-gonadal (HPG) axis, but several more recent studies have found a positive correlation between TT and E2 (50), and our study also had similar findings ($P< 0.001$). And a partial explanation may be given by the study of Brüning et al. They selectively deleted insulin receptors in mice neurons, leading to hypogonadotropic hypogonadism in addition to metabolic symptoms (9). Moreover, it is known from *in vitro* experiments that insulin promotes the secretion of gonadotropin-releasing hormone (GnRH) from hypothalamic neurons, a physiological effect that is mainly mediated through phosphatidylinositol 3-kinase (PI3K) and the mitogen-activated protein kinases (MAPK) signaling pathways, two classical signaling pathways of insulin (51, 52), which activate the expression of the *c-fos* and *EGR-1* genes, and then the GnRH mRNA levels are elevated (53), and it is clear that the impedance of the signaling in the insulin-resistant state affects the expression of GnRH as well. Thus, when obesity- and lipid-related abnormalities are present, the reduction of TT and E2 suggests the possible presence of insulin resistance in neurons of the HPG axis, whereas the role of aromatase may not be significant. Second, visceral fat is also an active endocrine tissue, increased secretion of adipose-specific cytokines (e.g., leptin, IL-6, and TNF-α) in patients with obesity or abnormal adipose distribution also inhibits gonadotropin secretion, which in turn inhibits HPG axis (54, 55). This explains the lower LH in hypogonadism patients in the present study ($P = 0.044$) and corresponds to previous studies (56). Third, insulin resistance in abnormal fat distribution and T2DM result in a decrease in sex hormone-binding globulin (SHBG) (57), secondary to a decrease in TT.

However, our study also has limitations. First, this was a retrospective study, so we lacked the testicular examination (to assess volumes through Prader's orchidometer), and International Index of erectile function-5 (IIEF-5), International Prostatic Symptoms Score (IPSS) and Aging Male Symptom Score (AMSS) questionnaires, and we also did not measure some important obesity-derived adipokines (e.g., Adiponectin, Leptin, Chemerin, and Nesfatin-1), which some studies suggest are associated with obesity and hypogonadism (58–60), as well as SHBG, which is used to calculate free testosterone, a more accurate reflection of actual testosterone levels. In addition, all of us recruited were hospitalized patients, so there may be some bias, such as higher age being one of them. It is also worth noting that a number of other factors can affect TT, such as statins have been found to reduce TT, particularly atorvastatin, which may be due to the fact that statins affect testicular uptake of cholesterol, the raw material for TT synthesis, and statins may lead to a reduction in SHBG (61). We also look forward to subsequent studies that incorporate relevant indices.

5 Conclusions

VAI, CVAI, TyG, and LAP are sensitive indicators for predicting hypogonadism in Chinese male patients with T2DM, and we give possible cutoff values, where we recommend LAP as a commonly used assessment index, and indices combinations are

often unnecessary because they do not increase predictive capability. We expect to facilitate cooperation between different departments (endocrinologists and andrologists) and to contribute to the early detection and early treatment of patients with reproductive system complications.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Affiliated Hospital of Medical College Qingdao University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YY: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. YYW: Data curation, Formal analysis, Writing – review & editing. LX: Methodology, Project administration, Writing – review & editing. WL: Data curation, Formal analysis, Writing – review & editing. YGW: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1319582/full#supplementary-material

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