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Study on the correlation between oxidized low- density lipoprotein and oxidized high-density lipoprotein with type 2 diabetes complicated by pulmonary tuberculosis

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Abstract

Objectives This study aims to investigate the correlations between oxidized lipoproteins, specifically oxidized low-density lipoprotein (oxLDL) and oxidized high-density lipoprotein (oxHDL), and the comorbidities of T2DM and PTB (T2DM + PTB).

Methods This prospective study included 360 cases from May 2022 to May 2023. The cohort consisted of 60 cases of pure hyperlipidemia, 100 cases of PTB, 100 cases of T2DM, and 100 cases of T2DM + PTB. Each of the PTB, T2DM, and T2DM + PTB groups was further subdivided into a normal lipid subgroup (40 cases) and a hyperlipidemia subgroup (60 cases). Additionally, 40 healthy individuals served as a control group. The age range of participants spanned from 40.8 ± 7.36 to 56.34 ± 11.52 years. Venous blood samples were collected from each group to measure levels of HbA1c, insulin (INS), fasting serum glucose (FSG), total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C, apolipoprotein A-I(ApoA I), apolipoprotein B(Apo B), oxidized low-density lipoprotein (oxLDL), and oxidized high-density lipoprotein (oxHDL). Multivariate logistic regression analysis assessed the association of oxLDL and oxHDL levels with PTB.

Results The levels of oxLDL and oxHDL in the pure hyperlipidemia group, PTB hyperlipidemia subgroup,T2DM hyperlipidemia subgroup, and T2DM + PTB hyperlipidemia subgroup were significantly elevated compared to those in the control group. Correlation analysis demonstrated a positive correlation between TG and LDL-C with oxLDL in the T2DM hyperlipidemia subgroup and the T2DM + PTB hyperlipidemia subgroup. TC and LDL-C were also positively correlated with oxLDL in the PTB hyperlipidemia subgroup. All hyperlipidemia groups exhibited a positive correlation between TG and oxHDL. Multivariate logistic regression analysis showed that oxLDL ≥2362U/L~<4724 U/L (more than 2 times higher than the control group) and oxHDL ≥ 26 μg/L (more than 4 times higher than the control group) were relative risk factors for PTB.

Conclusion Significantly elevated oxLDL and oxHDL levels may be risk factors for PTB and may influence the comorbidity of T2DM and PTB. Further evaluation of pathological levels with oxLDL levels exceeding twice the control group and oxHDL levels exceeding four times the control group is recommended.

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Keywords Type 2 diabetes mellitus, Pulmonary tuberculosis, Oxidized low-density lipoprotein, Oxidized high-density lipoprotein, Blood lipid

Background

Diabetes is a significant risk factor for tuberculosis, promoting metabolic disorders and immune dysfunction. This condition predisposes patients to becoming carriers of latent tuberculosis infection (LTBI), subsequently increasing the likelihood of LTBI progressing to active tuberculosis (ATB). This risk escalates with age [1, 2]. Given that type 2 diabetes mellitus (T2DM) is the predominant form of diabetes among middle-aged and elderly individuals in China, and the incidence of T2DM is on the rise, the confluence of T2DM and tuberculosis is likely to present a considerable health challenge in this region [3, 4]. Currently, tuberculosis mainly presents as pulmonary tuberculosis (PTB), yet the potential pathogenic mechanisms linking T2DM and PTB remain elusive [1–4].

Previous studies [5, 6] indicate that chronic inflammation from PTB prompts significant macrophage accumulation, while T2DM-associated dyslipidemia encourages macrophage foam cell formation, interfering with immune regulation and suggesting an interaction between these conditions. Concurrently, foam cell formation, a hallmark of atherosclerosis, could link T2DM, atherosclerosis, and tuberculosis. Extensive research [5–7] reveals that chronic inflammation in the host provokes a strong oxidative stress response, accompanied by elevated lipid levels leading to various oxidized lipoproteins, such as oxidized low-density lipoprotein (oxLDL) and oxidized high-density lipoprotein (oxHDL). These oxidized lipoproteins can transform macrophages into foam cells, pivotal in both atherosclerosis and tuberculous granuloma formation [7]. However, the interactions between lipid factors in T2DM, atherosclerosis, and tuberculosis remain elusive [3–6]. Thus, this study will examine hyperlipidemia (termed"pure hyperlipidemia"for classification simplicity) as one observational case group, and PTB, T2DM, and T2DM plus PTB comorbidity (termed T2DM + PTB) as the other three case groups to preliminarily investigate the relationships between oxLDL and oxHDL levels across these disease states.

Method

Subjects

From May 2022 to May 2023, we prospectively collected 360 cases at the Chronic Disease Prevention and Control Center in Shenzhen, China (The supplementary registration date for the prospective non-randomized controlled trial.: April 7th, 2025, registration number:MR- 44–25–028332; this trial has been approved by the Ethics Committee of the Shenzhen Chronic Disease Prevention Center), including 60 cases in the pure hyperlipidemia group, 100 cases in the PTB group, 100 cases in the T2DM group, and 100 cases in the T2DM + PTB group, among which the PTB group, T2DM group, and T2DM + PTB group were further divided into a normal lipid subgroup (40 cases) and a hyperlipidemia subgroup (60 cases). Forty healthy individuals were included as the control group. The age range of participants was 40.8 ± 7.36 to 56.34 ± 11.52 years.

Criteria for inclusion criteria

Diagnosis of pure hyperlipidemia [8]: A diagnosis of hyperlipidemia is confirmed when total cholesterol (TC) ≥ 5.2 mmol/L, or triglycerides (TG) ≥ 1.7 mmol/L, or low-density lipoprotein cholesterol (LDL-C) ≥ 3.4 mmol/L. The diagnostic criteria for type 2 diabetes mellitus (T2DM) are based on T2DM diagnostic standards [9]: T2DM is diagnosed when the patient exhibits typical diabetes symptoms such as polyuria, polydipsia, and polyphagia, and fasting blood glucose (FSG) ≥ 7.0 mmol/L, or random blood glucose ≥ 11.1 mmol/L, or oral glucose tolerance test 2-h blood glucose ≥ 11.1 mmol/L, or glycated hemoglobin (HbA1c) ≥ 6.5%. The diagnosis of pulmonary tuberculosis (PTB) primarily relies on microbiological examinations (including bacteriological and molecular biology tests), combined with epidemiological history, clinical presentations, and chest imaging, to make a comprehensive assessment with microbiological results serving as confirmation [10]. The diagnosis of T2DM + PTB requires meeting the diagnostic criteria for both T2DM and PTB. All included cases must undergo body mass index (BMI) testing (normal = 18.5 ~ 23.9 kg/m^2, overweight = 24.0 ~ 27.9 kg/m^2, obesity ≥ 28.0 kg/m^2), and inquire about the duration of the disease, relevant medication history, and complications. Exclusion criteria: ①Extrapulmonary tuberculosis. ②Pregnant women. ③Patients with malignant tumors. ④Patients with autoimmune-related diseases and malignant hematologic diseases. ⑤Use of immunosuppressive drugs or immunodeficiency in the past six months. ⑥Patients with negative sputum culture. ⑦Identification of non-tuberculous mycobacteria. ⑧History of type 1 diabetes.

The laboratory indices of the study

Sample collection for the control group, pure hyperlipidemia group, PTB group, T2DM group, and T2DM + PTB group was completed within 24 h of outpatient visits. Fasting venous blood was drawn in the morning, and anticoagulated whole blood was retained for HbA1c analysis; serum was collected for FSG, TC, TG, HDL-C, LDL-C, apolipoprotein A-I (ApoA I), apolipoprotein B (Apo B), and insulin (INS) analysis. The Mindray H50 automatic glycosylated hemoglobin analyzer was used to determine the percentage content of HbA1c in anticoagulated whole blood; the New Industry MAGLUMI2000 fully automated chemiluminescent immunoassay analyzer employed the sandwich immunoassay method to measure fasting INS and calculate the insulin resistance index (HOMA-IR); the Beckman Coulter AU5800 fully automated biochemical analyzer was used to analyze fasting blood biochemical indicators: the hexokinase method for FSG, enzyme colorimetry for TC, TG, HDL-C, LDL-C, and immunoturbidimetry for ApoA I and Apo B levels, with all necessary reagents and calibration standards being compatible. During sample testing, all detection systems were ensured to operate smoothly without faults, and the quality control for the tested items was in a controlled state.

Detection of oxHDL and oxLDL

The determination of oxHDL was performed using the ELISA sandwich enzyme-linked immunosorbent assay, and the determination of oxLDL was done using the ELISA competitive inhibition enzyme-linked immunosorbent assay. For specific procedures, please refer to the instruction manuals of the human oxHDL ELISA kit (catalog number: MBS7606426) and the oxLDL ELISA kit (catalog number: 705063) produced by MyBiosource in San Diego, California, USA. The absorbance was read at a center wavelength of 450 nm using the Thermo microplate reader analysis system and was corrected at a calibration wavelength of 570 nm. The concentrations of oxLDL (U/L) and oxHDL (μg/L) were calculated accordingly.

Statistical analysis

Descriptive statistics for all variables are presented as $X \pm S$. Data analysis was conducted using SPSS 23.0 and SAS 9.4, while GraphPad Prism 9.0 and Origin Pro 2023 were utilized for graph creation. For normally distributed continuous data, ANOVA was used to compare multiple groups; for non-normally distributed data, the Kruskal–Wallis H test was employed. The Pearson correlation coefficient was used to analyze correlations in normally distributed data, whereas the Spearman correlation coefficient was applied to non-normally distributed data. For continuous data represented as percentages, group comparisons were performed using the chi-square test ($n > 5$) or Fisher's exact test ($n \leq 5$). Multivariate logistic regression analysis, accounting for potential confounding factors such as age, gender, history of lipid-lowering treatment, and BMI, was used to evaluate the association between oxLDL and oxHDL levels and the incidence of PTB. The relative risk of predictors was expressed as RR values with 95% confidence intervals (CI). A P-value < 0.05 was considered statistically significant.

Results

Basic information

The duration of the disease in the T2DM group and the T2DM + PTB group was relatively long (1 to 8 years), primarily using metformin for blood glucose control. A small number of individuals in the pure hyperlipidemia group and the T2DM group received lipid-lowering treatments such as statins or niacin (about 18% and 11% of subjects, respectively), while about 5% of subjects in other groups received lipid-lowering medication. Individuals with a history of tuberculosis received standardized anti-tuberculosis chemotherapy, with an average adherence rate exceeding 95%. The specific characteristics of age, gender, BMI, and laboratory parameters for each group are detailed in Table 1. The specific observations mainly described the signs of lipid abnormalities, including: the BMI in the T2DM hyperlipidemia subgroup was the highest, followed by the pure hyperlipidemia group, both significantly higher than the control group, PTB group, and T2DM + PTB group (both $P^1 < 0.01$). The levels of INS, FSG, TC, and TG in the four hyperlipidemia groups were higher than those in the control group (both $P^{2,3} < 0.05$). The TC, LDL-C, and TG in the pure hyperlipidemia group were the highest (both $P^{4,5,6} < 0.01$). The levels of ApoA I and Apo B in the T2DM hyperlipidemia subgroup were significantly higher than those in the pure hyperlipidemia group and PTB hyperlipidemia subgroup (both $P^7 < 0.05$). The levels of oxLDL in the pure hyperlipidemia group, T2DM hyperlipidemia subgroup, and T2DM + PTB hyperlipidemia subgroup were more than doubled compared to the control group, while the oxLDL levels in the PTB hyperlipidemia subgroup were significantly higher than those in the control group ($P^8 < 0.05$). The oxLDL levels in the T2DM hyperlipidemia subgroup were not only significantly higher than those in the PTB hyperlipidemia subgroup but also significantly higher than those in the T2DM normal lipid subgroup, and the oxLDL levels in the T2DM group and T2DM + PTB group in the normal lipid subgroup were significantly higher than those in the control group. The levels of oxHDL in the T2DM hyperlipidemia subgroup

Table 1 Basic information of enrolled individual

Parameters	Control	Pure HLP	PTB		T2DM		T2DM + PTB		Statistical value	*P* value
			HLP (-)	HLP (+)	HLP (-)	HLP (+)	HLP (-)	HLP (+)		
No. of cases	40	60	40	60	40	60	40	60		
Age, years (X ± S)	40.8 ± 7.36	44.8 ± 8.51	46.1 ± 8.93	49.3 ± 10.72	54.59 ± 10.78	56.34 ± 11.52	52.89 ± 10.68	55.69 ± 9.78	F = 16.04	< 0.01
Sex									χ2 = 23.492	< 0.01
Men [n (%)]	28 (46.6)	36 (60)	30 (75)	45 (75)	27 (67.5)	48 (80)	34 (85)	39 (65)		
Women [n (%)]	32 (53.3)	24 (40)	10 (25)	15 (25)	13 (32.5)	12 (20)	6 (15)	21 (35)		
BMI (Kg/m2)	21.41 ± 1.47	27.48 ± 2.21	20.98 ± 1.57	24.37 ± 2.37	22.57 ± 2.05	29.67 ± 2.48 [1]	23.75 ± 1.35	26.3 ± 3.28	H = 257.61	< 0.01
Insulin (μIU/mL)	9.43 ± 2.23 [2]	11.48 ± 4.42	9.23 ± 2.2	10.05 ± 3.28	12.94 ± 6.38	14.43 ± 10.54 [3]	10.71 ± 3.93	12.63 ± 5.81[3]	H = 35.36	< 0.01
HOMA-IR	2.02 ± 0.46	2.68 ± 1.08	2.13 ± 0.5	2.5 ± 0.85	4.51 ± 2.67	5.86 ± 4.4	3.96 ± 2.06	5.11 ± 2.69[7]	H = 186.19	< 0.01
HbA_1c (%)	5.25 ± 0.29	4.9 ± 0.55	5.32 ± 0.38	5.36 ± 0.41	7.38 ± 1.47	7.6 ± 1.79[3]	7.92 ± 2.91	8.23 ± 3.58[3]	H = 261.75	< 0.01
FSG (mmol/L)	4.88 ± 0.53 [2]	5.29 ± 0.33	5.21 ± 0.46	5.59 ± 0.46	7.81 ± 1.81	9.27 ± 3.39 [3]	8.41 ± 2.78	9.36 ± 3.3 [3]	H = 264.27	< 0.01
TC (mmol/L)	4.69 ± 0.62 [2]	6.44 ± 0.75 [4]	4.61 ± 0.69	5.97 ± 1.17	4.53 ± 0.66	6.21 ± 1.53	4.33 ± 0.75	5.69 ± 1.48	H = 159.68	< 0.01
LDL-C (mmol/L)	2.99 ± 0.37	4.55 ± 0.53 [5]	3.09 ± 0.5	3.97 ± 0.93	3.08 ± 0.46	3.98 ± 1.03	2.91 ± 0.62	3.73 ± 1.12	F = 28.49	< 0.01
TG (mmol/L)	1.14 ± 0.42[2]	3.56 ± 2.29 [6]	1.13 ± 0.31	2.12 ± 1.03	1.21 ± 0.32	2.99 ± 2.32	1.15 ± 0.29	2.34 ± 1.5	H = 191.32	< 0.01
HDL-C (mmol/L)	1.43 ± 0.27	1.48 ± 0.27	1.42 ± 0.31	1.5 ± 0.33	1.34 ± 0.26	1.42 ± 0.4	1.34 ± 0.36	1.35 ± 0.39	F = 1.89	> 0.05
ApoA I (g/L)	1.49 ± 0.28	2.46 ± 0.24	1.49 ± 0.24	1.72 ± 0.38	1.76 ± 0.43	4.0 ± 1.06 [7]	1.55 ± 0.24	2.05 ± 0.38	H = 141.83	< 0.01
Apo B (g/L)	0.79 ± 0.18	0.86 ± 0.31	0.78 ± 0.13	0.9 ± 0.24	1.02 ± 0.18	1.2 ± 0.61 [7]	0.92 ± 0.16	0.94 ± 0.22	H = 105.54	< 0.01
oxLDL(U/L)	1180.95 ± 237.6 [8]	2465.45 ± 894.67	1632.3 ± 484.25	1987.25 ± 450.13	2086.6 ± 552,85	2932.43 ± 1216.45	1992.93 ± 386.47	2458.5 ± 1262.06	H = 143.13	< 0.01
oxHDL (μg/L)	6.42 ± 3.22	14.88 ± 4.26	11.03 ± 3.87	14.48 ± 6.54	19.54 ± 6.52	28.47 ± 19.56	16.42 ± 6.24	23.48 ± 19.13 [9]	H = 147.32	< 0.01

Values are n (%) or mean ± SD

Pure HLP: pure hyperlipidemia group; HLP (-): Normal blood lipid group; HLP (+): Dyslipidemia subgroup

1: Comparison within the BMI group, $P < 0.01$; 2,3: Comparison within Insulin, FBG, TC, TG, HbA1c, and FSG groups, $P < 0.05$;.4,5,6: Comparison within TC, LDL, and TG, $P < 0.05$; 7, Comparison within ApoA I, and Apo B groups, $P < 0.05$;. 8:Comparison within the oxLDL group, $P < 0.01$. 9:Comparison within the oxHDL group, $P < 0.01$

and T2DM + PTB hyperlipidemia subgroup were more than quadrupled compared to the control group, while the oxHDL levels in the pure hyperlipidemia group, PTB hyperlipidemia subgroup, T2DM normal lipid subgroup, and T2DM + PTB normal lipid subgroup were more than doubled compared to the control group, with the T2DM hyperlipidemia subgroup significantly higher than the pure hyperlipidemia group and PTB groups (all $P^{9} < 0.05$).

Comparison of oxLDL/LDL-C, oxLDL/HDL-C, oxHDL/HDL-C, and oxHDL/LDL-C between different groups

Figure 1A shows that oxLDL/LDL is highest in the T2DM hyperlipidemia subgroup, significantly higher than in the simple hyperlipidemia group and PTB group (both H = 92.403; both $P^{a1} < 0.05$), followed by the T2DM + PTB group, which is significantly higher than the PTB hyperlipidemia subgroup (both H = 81.636; both $P^{b1} < 0.05$), but the T2DM + PTB hyperlipidemia subgroup does not show a statistically significant difference from the simple hyperlipidemia group (H = 52.367, P > 0.05). Similarly, oxLDL/HDL is also highest in the T2DM hyperlipidemia subgroup, significantly higher than in the PTB group (both H = 129.425, both $P^{a2} < 0.01$), and the T2DM + PTB group and the simple hyperlipidemia group are significantly higher than in the PTB normolipidemia subgroup (both H = 101.029, both $P^{b2} < 0.01$). All case groups have ratios higher than the control group (both $P^{c1,c2} < 0.01$).

Figure 1B shows that the ratios of oxHDL/HDL-C and oxHDL/LDL-C in the PTB hyperlipidemia subgroup, T2DM hyperlipidemia subgroup, and T2DM + PTB hyperlipidemia subgroup were significantly higher than those in the control group (both H = 170.828; both $P_{a3,a4} < 0.05$)), with the T2DM hyperlipidemia subgroup having the highest ratio, followed by the T2DM + PTB hyperlipidemia subgroup, both of which were significantly higher than the PTB hyperlipidemia subgroup, with statistically significant differences (both H = 90.717; both $P^{b3,\ b4} < 0.05$), and the T2DM hyperlipidemia subgroup was significantly higher than the simple hyperlipidemia group, with statistically significant differences (both H = 103.804; both $P^{c3,\ c4} < 0.05$). In addition, the ratios of oxHDL/HDL-C and oxHDL/LDL-C in the T2DM normolipidemia subgroup, T2DM + PTB normolipidemia subgroup, and PTB normolipidemia subgroup were all significantly higher than those in the control group (both H = 165.246; both $P^{d3,\ d4} < 0.05$).

Correlation analysis

The relevant analysis of this study focuses on the relationships between two groups of variables (the first group: oxLDL; the second group: oxHDL) and the laboratory parameters of four groups of hyperlipidemia patients. In

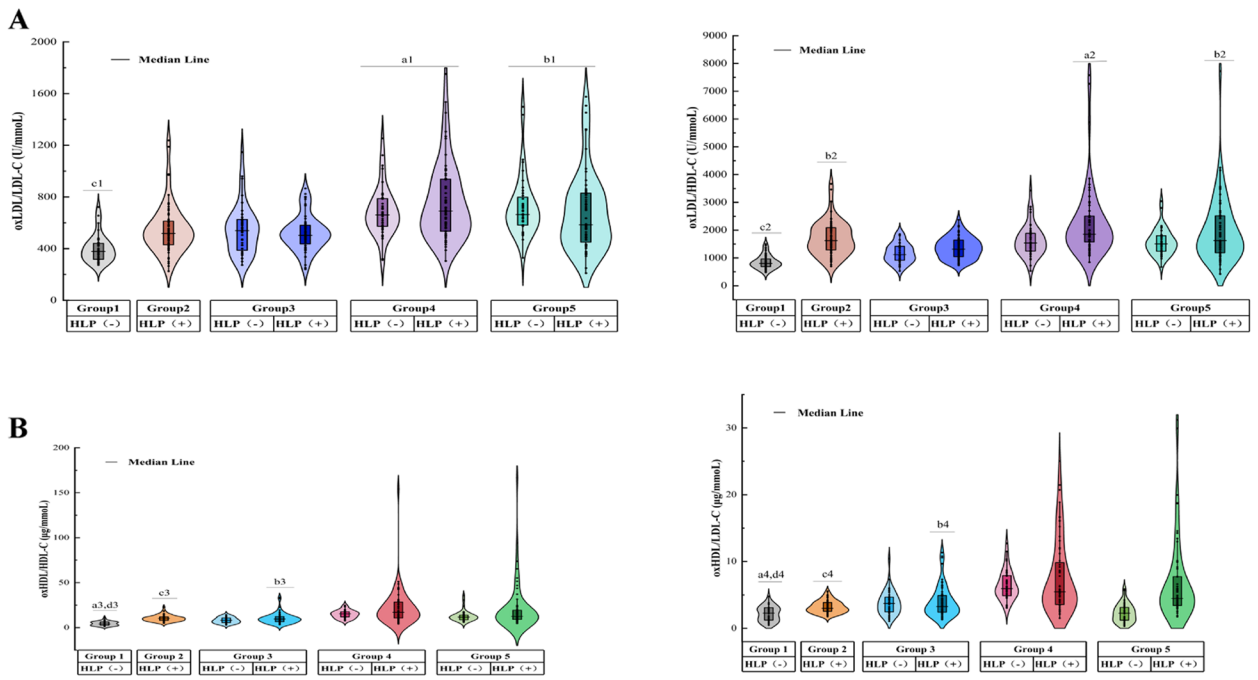

Fig. 1 Comparison of oxLDL/LDL, oxLDL/HDL、oxHDL/HDL, and oxHDL/LDL in the groups **A** Comparison of oxLDL/LDL and oxLDL/HDL in each group; **B** Comparison of oxHDL/HDL and oxHDL/LDL in each group; Group 1: control group; Group 2: pure hyperlipidemia group; Group 3: PTB group; Group 4: T2DM group; Group 5: T2DM + PTB group; HLP (-): Normal lipid subgroup; HLP (+): Hyperlipidaemia subgroup

the pure hyperlipidemia group, significant positive correlations were found between TG, ApoB and the first group oxLDL (both $r = 0.594$; $P < 0.01$), In the PTB hyperlipidemia subgroup, CHOL and LDL were positively correlated with oxLDL (both $r = 0.441$; both $P < 0.05$), whereas TG was positively correlated with oxHDL ($r = 0.318$; $P < 0.05$). In the T2DM hyperlipidemia subgroup, TG and LDL were positively correlated with oxLDL (both $r = 0.384$; both $P < 0.01$), and TG was also positively correlated with oxHDL ($r = 0.339$; both $P < 0.01$). The T2DM + PTB hyperlipidemia subgroup showed positive correlations between HbA1c, FSG, TG, LDL and the oxLDL (both $r = 0.287$; both $P < 0.05$), while TG exhibited a strong positive correlation with the oxHDL ($r = 0.736$; $P < 0.01$). Correlation curve analysis showed a there was a moderate positive correlation between oxLDL and oxHDL in the T2DM hyperlipidema subgroup (r=298 0.369; $P < 0.01$). See Figs. 2 and 3 for details.

Multivariable logistic regression analysis

The oxLDL levels of the included cases were all lower than 5741 U/L, and the cases with elevated levels ≥2362 U/L ~ < 5741 U/L accounted for about 36%, mainly at levels more than 2 times higher than those in the control group; the oxHDL levels of the included cases were all lower than 52 μg/L, and the cases with elevated levels ≥13 μg/L ~ < 52 μg/L accounted for about 71%, mainly at levels more than 4 times higher than those in the control group. According to this, we divided the levels of oxLDL and oxHDL into ≥2362 U/L ~ < 4724 U/L and ≥4724 U/L for oxLDL and ≥13 μg/L ~ < 26 μg/L and ≥26 μg/L for oxHDL. Multivariate logistic regression analysis was performed to observe the effect of oxLDL and oxHDL on PTB prevalence(T2DM as reference), and two batches of confounding factors were added for correction analysis; the first batch includes TG and LDL (which are positively correlated with elevated oxHDL and oxLDL in the PTB group, respectively), and the second batch includes age, gender, lipid-lowering medications, and BMI. The results showed that oxLDL and oxHDL were relative risk factors for PTB before and after adjusting for the first batch of confounders. However, after adjusting for the second batch of confounders, only oxHDL remained a relative risk factor for PTB. OxLDL levels in the range of ≥2362 U/L ~ <4724 U/L (more than 2 times higher than the control group) and oxHDL levels of ≥26 μg/L (more than 4 times higher than the control group) were relative risk factors for PTB before and after adjusting for both the first and second batches of confounders. See Table 2 for details.

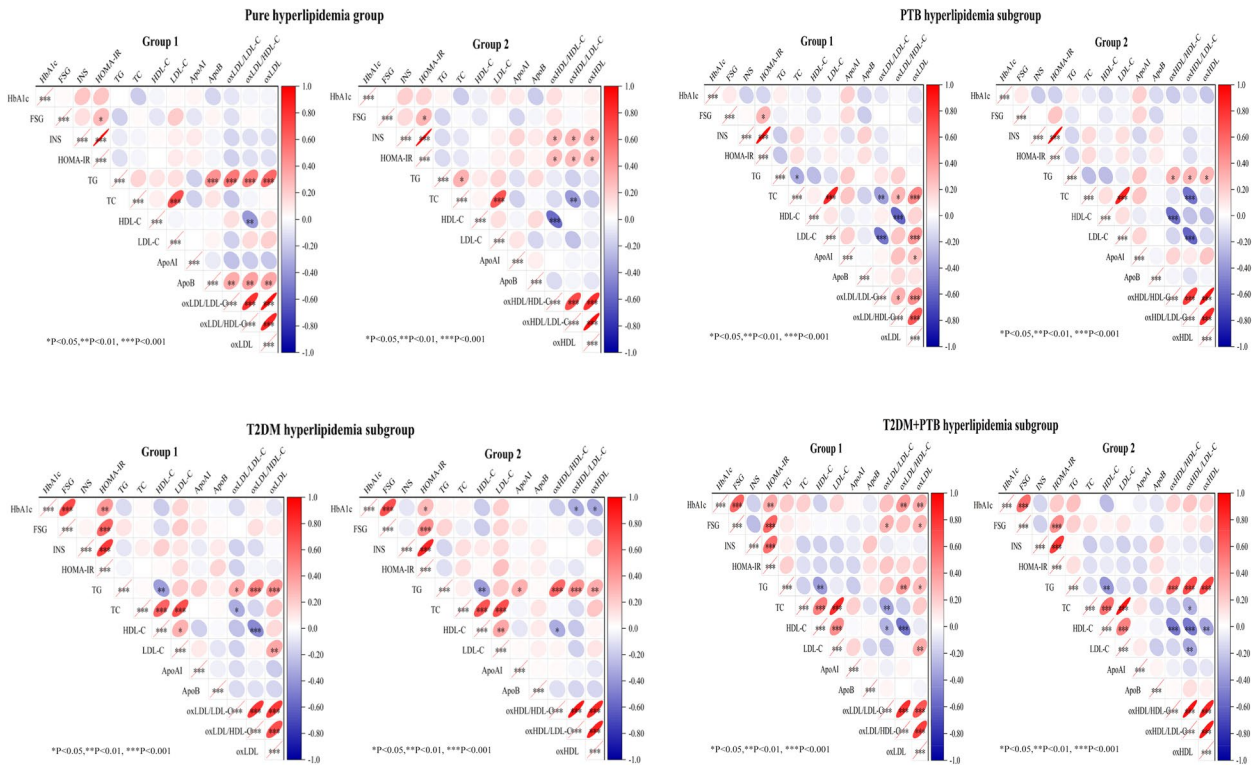

Fig. 2 Correlation heatmap analysis of four experimental groups Group 1: Correlation analysis of oxLDL, oxLDL/LDL, and oxLDL/HDL with 10 suspected variables, respectively. Group 2: Correlation analysis of oxHDL, oxHDL/HDL, and oxHDL/LDL with 10 suspected variables, respectively

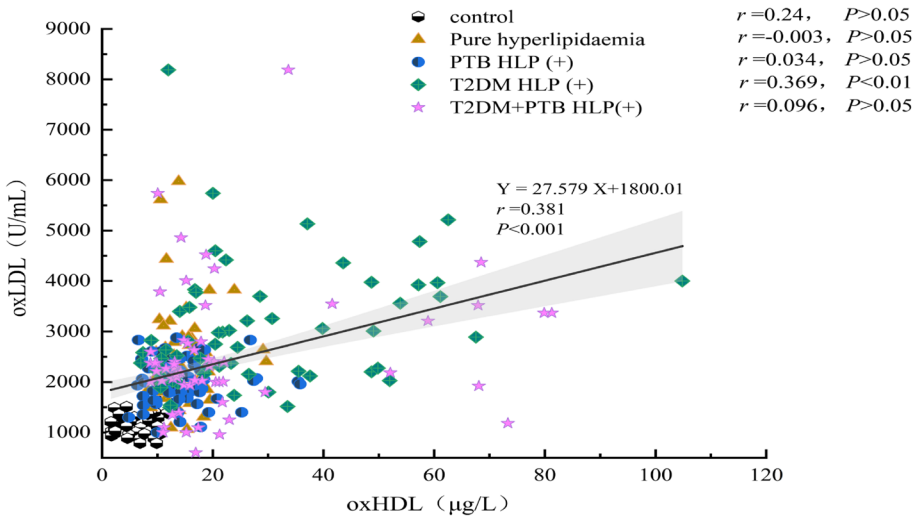

Fig. 3 Correlation curve analysis of oxLDL with oxHDL in five experimental groups

Table 2 Multivariate logistic regression analysis of oxLDL(U/L) and oxHDL(μg/L) levels and their graded categories in PTB

Indicator	N	Before adjusting for confounding factors			Adjusting the first bach for confounding factors			Adjusting the second bach for confounding factors		
		RR	95%*CI*	*P*	RR	95%*CI*	*P*	RR	95%*CI*	*P*
oxLDL	100	0.305	0.162 ~ 0.577	< 0.01	0.448	0.263 ~ 0.762	0.003	0.589	0.348 ~ 0.999	0.050
≥ 2362 ~ < 4724	18	0.371	0.186 ~ 0.739	0.005	0.291	0.149 ~ 0.570	< 0.01	0.387	0.193 ~ 0.775	0.007
≥ 4724	5	1.066	0.271 ~ 4.178	0.927	0.534	0.142 ~ 2.006	0.353	0.802	0.215 ~ 2.982	0.742
oxHDL	100	0.191	0.112 ~ 0.325	< 0.01	0.213	0.127 ~ 0.357	< 0.01	0.23	0.136 ~ 0.389	< 0.01
≥ 13 ~ < 26	42	0.259	0.128 ~ 0.521	< 0.01	0.252	0.125 ~ 0.505	< 0.01	0.248	0.118 ~ 0.519	< 0.01
≥ 26	7	0.079	0.028 ~ 0.220	< 0.01	0.069	0.024 ~ 0.200	< 0.01	0.078	0.027 ~ 0.223	< 0.01

Discuss

Lipid abnormalities caused by hyperlipidemia can be classified into primary and secondary types. Primary lipid abnormalities are less common, while secondary lipid abnormalities are mainly seen in systemic diseases such as diabetes and hypertension [11]. Hyperglycemia and lipid abnormalities in chronic diabetes (commonly seen in T2DM) promote the production of oxygen free radicals and oxidative stress, leading to high levels of oxLDL, usually accompanied by increased oxHDL. This may affect the lipid metabolism of lung macrophages infected with MTB, making lung tissue more susceptible to MTB invasion [11–14]. Analyzing the correlation between oxLDL and oxHDL with the comorbidity of T2DM and PTB may provide insights for further exploration of biological factors assessing disease progression in such conditions.

First, we categorized the PTB group, T2DM group, and T2DM + PTB group into hyperlipidemia subgroups and normal lipid subgroups based on the BMI, FSG, blood lipids, and HOMA-IR of the case group. This stratification aims to compare and observe the effects of dyslipidemia on oxLDL and oxHDL levels under uniform disease conditions. Preliminary research indicate that the T2DM hyperlipidemia subgroup is the oldest and has the highest BMI, exhibiting converging characteristics of glucose and lipid metabolism with the T2DM + PTB hyperlipidemia subgroup.The T2DM + PTB cases demonstrate distinct metabolic traits in glucose, lipids, and proteins compared to T2DM patients, with the primary difference centered on protein metabolism [5]. However, the limitations of the research indicators focusing only on glucose and lipids may lead to inconsistent results. A more comprehensive understanding of the metabolic characteristics of T2DM + PTB patients requires an expansion of research indicators.

The elevated glycol-oxidative environment in T2DM patients, when coupled with hyperlipidemia, facilitates the production of oxLDL and oxHDL. This reflects the overall oxidative stress intensity in the body [11–14]. Our

results indicated that while the proportion of patients receiving lipid-lowering therapy, such as statins or niacin, was significantly higher in the pure hyperlipidemia group compared to the T2DM group, patients with hyperlipidemia alone still exhibited higher levels of three lipid profiles (TC, TG, and LDL-C) than those in the T2DM hyperlipidemia subgroup. Additionally, oxLDL levels in the T2DM hyperlipidemia subgroup were more than twice those in the control group and significantly higher than those in the pure hyperlipidemia group. This phenomenon was also observed in the T2DM + PTB hyperlipidemia subgroup, suggesting that the oxidative characteristics of lipoproteins and the specific inflammatory features of T2DM and T2DM + PTB may interact [14–19]. Given that the proportion of patients taking lipid-lowering medications in this study was relatively small, further evaluation of the oxidative effects of these drugs on lipoproteins is warranted, ideally by expanding the sample size included in future research. Moreover, oxHDL levels in the T2DM hyperlipidemia subgroup are more than four times greater than those in the control group, including those in the T2DM group with normal blood lipids, where they are more than twice as high as the control group; this pattern recurs in the T2DM + PTB group. In comparison, oxHDL levels in the T2DM + PTB hyperlipidemia subgroup are higher than those in both the pure hyperlipidemia and the PTB hyperlipidemia subgroups, yet lower than those in the T2DM hyperlipidemia subgroup. Existing literature correlates hyperglycemia, dyslipidemia, and tuberculosis with increased oxidative stress and reduced antioxidant capacity [5, 14]. The oxLDL and oxHDL levels in the T2DM + PTB group are lower than those in the T2DM group, potentially due to the metabolic demands in PTB patients, primarily manifested by reduced amino acids, cholesterol, fatty acids, and phospholipid metabolites. When T2DM and PTB coexist, the plasma of T2DM + PTB patients may display distinct metabolic characteristics of both conditions, such as weight loss marked by decreased concentrations of amino acids (histidine, alanine, glutamine), and dyslipidemia evidenced by elevated TG levels. The metabolic characteristics dominated by weight loss in some T2DM + PTB patients may contribute to the observed lower oxLDL and oxHDL levels in T2DM + PTB compared to those in T2DM alone [12].

The research [14–16] suggests that the ratios of oxLDL/LDL-C, oxLDL/HDL-C, oxHDL/HDL-C, and oxHDL/LDL-C can reflect the effects of oxidative stress on LDL-C and HDL-C metabolism, serving as stable metabolic indicators for assessing the risk of diseases related to hyperlipidemia. The study results indicate that differences in oxLDL/LDL-C and oxLDL/HDL-C among the four case groups correspond to variations in oxLDL levels within those groups. However, comparisons of oxHDL/HDL-C and oxHDL/LDL-C among the groups reveal significantly higher oxHDL ratios in the normal lipid subgroup of PTB compared to the control group, although the oxHDL levels do not show statistically significant differences. To objectively assess the oxidative stress risk in plasma metabolic profiles of groups with signs of glucose and lipid metabolism disorders, this study incorporated the ratios of oxHDL/HDL-C and oxHDL/LDL-C as observed variables. It analyzed the correlation of laboratory indicators with oxHDL, oxHDL/HDL-C, and oxHDL/LDL-C, finding that TG in the T2DM hyperlipidemia subgroup and the T2DM + PTB hyperlipidemia subgroup showed a moderate positive correlation with oxLDL/HDL-C, and a positive correlation with oxLDL. Additionally, the TG levels in both groups also exhibited a moderate positive correlation with oxHDL/HDL-C and oxHDL/LDL-C, indicating that elevated TG may be a significant risk factor for hyperlipidemia in T2DM and T2DM + PTB patients, and high TG levels could exacerbate immune dysfunction and cellular damage in individuals with a history of T2DM [14, 17, 18]. The high TG level in the pure hyperlipidemia group were positively correlated with oxLDL/LDL-C and oxLDL/HDL-C, but no significant correlation with oxHDL. We believe that lipid oxidation may be more closely related to DM characteristics other than obesity [18], which is worthy of further study. The oxidative characteristics of lipoproteins may be more closely associated with inflammatory features related to individuals with a history of T2DM, [14–19]. In addition, abnormal lipid levels in the T2DM population demonstrate a moderate linear correlation between oxLDL and oxHDL, suggesting that accumulated lipid oxidation products may facilitate the oxidation of HDL, thus exacerbating oxidative stress [12–18]. The HbA1c levels in the T2DM + PTB hyperlipidemia subgroup were the highest among the four groups, reaching 8.23 ± 3.58%, with a significant positive correlation between oxLDL and HbA1c observed, indicating that elevated blood sugar levels could exacerbate the body's inflammatory response, potentially intensifying oxidative damage. Persistent high blood sugar and inflammation are likely to promote increased levels of oxLDL and oxHDL, significantly impacting the comorbid relationship between T2DM and PTB [18, 19].

This study further assessed the impact of elevated oxLDL and oxHDL levels on the risk of PTB and found that both oxLDL and oxHDL elevation were relative risk factors for PTB before adjusting for confounders. However, after adjusting for confounders such as lipid-lowering medications and BMI, only elevated oxHDL levels remained a relative risk factor for PTB, while elevated oxLDL levels were no longer a relative risk factor. This suggests that lipid-lowering drugs, such as statins

or niacin, may primarily influence LDL oxidation sensitivity [20]. Additionally, we found that 49% of samples in the PTB group had oxHDL levels more than twice that of the control group, while 23% of samples had oxLDL levels more than twice that of the control group. This suggests that HDL's oxidative stress response may be more sensitive than LDL's [13, 15, 18]. Since only 5% of the PTB group had a history of lipid-lowering medication use, the relatively low rate of lipid-lowering treatment may not fully highlight its impact on the higher oxidative ratio of HDL [21]. Notably, oxLDL levels in the range of ≥2362 U/L ~ <4724 U/L (more than twice that of the control group) were relative risk factors for PTB before and after adjusting for both the first and second batches of confounders. We believe this could still be related to the lower rate of lipid-lowering medication use [21]. Similarly, we do not rule out the possibility that LDL and HDL may respond differently to lipid-lowering treatments [20, 21], and the effect of lipid-lowering drugs on oxidative stress in lipoproteins needs to be further evaluated by including more cases with medication histories. Given the cytotoxic effects of oxLDL and oxHDL on monocyte-macrophages, significantly elevated levels of oxLDL and oxHDL and their regulatory mechanisms in the comorbidity of T2DM and PTB require further in-depth investigation.

Therefore, further research is needed to obtain more relevant data and further explore this issue. In summary, significantly elevated levels of oxLDL and oxHDL may be risk factors for PTB and could influence the comorbid relationship between T2DM and PTB. It is recommended that pathological levels of oxLDL greater than twice that of the control group and oxHDL levels more significant than four times that of the control group be further evaluated.

Supplementary Information

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Supplementary Material 1.

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The information above has been confirmed by the authors.

A Clinical Trial Number
202,205,171, this study is classified as a clinical trial.

Authors'contributions
J. G. designed the study, J. G., F. W, and CY. H drafted the manuscript and performed the statistical analysis. Y.F,H.Y and YM. C revised the manuscript. All authors have read and approved the final manuscript.

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Data availability
Data is provided within the supplementary information files, and in the manuscript, it is—We have all the original data for this research, which is genuine and reliable. Still, all the authors agree that it would be inappropriate to share the data temporarily until it is confirmed that the research manuscript has not been officially published. Once it is officially accepted for publication, all research data is shared by the corresponding author, Jing Gui: guij80@163.com. Data is provided within the supplementary information files.

Declarations

Ethics approval and consent to participate
Each participant inT2DM and PTB which was conducted under the Ethics Committee of Shenzhen Chronic Disease Prevention Center before taking part (SZCCC- 2022–010 - 01 -YJ). All participants have given informed consent for this study. The Ethics Committee of Shenzhen Chronic Disease Prevention Center approved this study. In addition, the Declaration of Helsinki was followed during our research. The necessary standards and legislation were followed in the execution of all procedures, including the declarations in.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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