Peripheral Neuropathy Is Associated With High Serum Levels of Small Dense Low-density Lipoprotein-cholesterol in Patients With Type 2 Diabetes Mellitus

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Research

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Abstract

Background: A high plasma level of small dense low-density lipoprotein cholesterol (sdLDL-C) is one of the key features of diabetic dyslipidemia. However, the relationship between sdLDL-C and diabetic peripheral neuropathy (DPN) has not been investigated. Therefore, we measured sdLDL-C in patients with type 2 diabetes mellitus (T2DM) $\pm$ DPN, determined the factors affecting sdLDL-C levels, and characterized the relationship between sdLDL-C and DPN in T2DM.

Methods: sdLDL-C was measured in the T2DM patients with (n=702) and without (n=780) DPN and the characteristics of these two groups were compared. Correlation analysis was used to identify factors associated with sdLDL-C levels. Finally, multiple regression analysis was used to further characterize the relationship between sdLDL-C and DPN in patients with T2DM.

Results: The serum sdLDL-C levels were higher in T2DM patients with DPN than in those without. sdLDL-C positively correlated with systolic blood pressure, diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, urinary microalbumin–creatinine ratio, and urinary microalbumin in T2DM patients with DPN ($P=0.017$, $P<0.001$, $P<0.001$, $P<0.001$, $P=0.005$, and $P=0.002$, respectively) and negatively correlated with high-density lipoprotein cholesterol ($P=0.01$). Furthermore, sdLDL-C was independently associated with DPN in patients with T2DM (odds ratio=5.857, 95% confidence interval [CI]: 2.60–13.20, $P<0.001$). Receiver operating characteristic analysis was performed to identify the optimal cut-off value of sdLDL-C for the prediction of DPN, which was found to be 0.985 mmol/L (area under the curve=0.571; 95% CI: 0.541–0.600; sensitivity, 64.8%; specificity, 47.7%, $P<0.001$).

Conclusions: sdLDL-C was increased in T2DM patients with DPN and was found to be an independent predictor of the presence of DPN.

Introduction

Type 2 diabetes mellitus (T2DM) and its complications are a major global health threat. Diabetic peripheral neuropathy (DPN) is a chronic microvascular complication of T2DM, results in decreased sensation, poor mobility, and high risk of foot ulceration and amputation [1–3]. Várkonyi et al [4]. and Sugimoto et al. [5]. showed that chronic hyperglycemia is the most important etiological factor. Although there is strong evidence of the efficacy of intensive glycemic control for the prevention of DPN in T2DM, the results of several studies have suggested that this strategy may not substantially reduce the risk of DPN [6]. Furthermore, there is increasing evidence that factors such as obesity, hyperlipidemia, hypertension, coronary artery disease (CAD), peripheral arterial disease (PAD), and genetic polymorphisms also play roles in the pathogenesis of DPN in patients with T2DM [7, 8]. Therefore, the identification of factors that are associated with DPN is essential to improve understanding of the pathogenesis of the disease and to develop more effective prevention and/or treatment strategies.

The circulating small dense low-density lipoprotein cholesterol (sdLDL-C) level was found to be positively associated with the presence of CAD in the Atherosclerosis Risk in Community studied [9]. Furthermore, a

study performed by Koba et al. indicated that sdLDL-C is more closely associated with the severity of CAD than LDL-C [10]. A high plasma level of sdLDL-C is a key feature of diabetic dyslipidemia [11]. sdLDL-C is also closely associated with diabetic macrovascular complications. However, furthermore, Brownrigg et al.[12]. reported that a previous diagnosis of DPN is associated with a higher risk of a first cardiovascular event. Therefore, there is a relationship between macro- and micro-vascular complications.

Previous studies have demonstrated that the circulating triacylglycerol level correlates with the progression of neuropathy in patients with T2DM. However, the relationship between sdLDL-C and DPN has not been investigated, and whether sdLDL-C plays a role in the development of DPN remains unclear. Therefore, in the present study, we aimed to measure the circulating sdLDL-C levels in T2DM patients with and without DPN, determine which factors affect the sdLDL-C levels, and characterize the relationship between sdLDL-C and DPN in patients with T2DM.

Materials And Methods

Study participants

We analyzed the records of 2,626 T2DM patients who were hospitalized in Shandong Provincial Hospital, Shandong University (Jinan, China) between January 2017 and December 2019. The exclusion criteria were age < 17 or > 75 years; PAD; chronic renal failure; other potential causes of neuropathy such as cervical and lumbar diseases (nerve root compression, spinal stenosis, and cervical and lumbar degenerative diseases); cerebral infarction; Guillain-Barré syndrome; severe arteriovenous vascular disease (venous embolism or lymphangitis), acute or chronic infection or inflammation; hematologic disease; and the use of statins, anti-inflammatory agents, or antibiotics during the preceding 3 months [1]. On this basis, 1,144 patients were excluded, and the study sample comprised 1,482 participants with T2DM, of whom 926 (62.5%) were men and 556 (37.5%) were women.

Diagnosis of diabetic peripheral neuropathy was based on guidelines for the prevention and treatment of type 2 diabetes in China. The diagnostic criteria were (1) a definite history of diabetes; (2) a diagnosis of neuropathy made at the time of or subsequent to the diagnosis of diabetes; (3) the presence of clinical symptoms and signs consistent with DPN; and (4) for patients with clinical symptoms (for example, pain, numbness, or paresthesia), and have any one of the five abnormal results of abnormal ankle reflex, pinprick pain, abnormal vibration perception threshold (VPT), pressure paresthesia, or temperature paresthesia; or for patients without clinical symptoms, abnormality in any two of the five. The participants were allocated to groups according to the presence or absence of DPN (n = 702 and n = 780, respectively).

Measurements

The authors retrieved the data from the hospital records of the participants, and physical examination and blood analyses were performed by clinicians when the patients were admitted to the hospital. Body

mass index (BMI) was calculated as weight (kg)/square of height (m²). Venous blood was collected after an overnight fast and an automatic biochemistry analyzer (Beckman Coulter Analyzer AU58 Series, Brea, CA, USA) was used to measure the plasma total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), sdLDL-C, high-density lipoprotein-cholesterol (HDL-C), fasting plasma glucose (FPG), and uric acid (UA) concentrations. Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography using a hemoglobin A1c analyzer (Tosoh Corporation, Tokyo, Japan). Urinary microalbumin–creatinine ratio(uACR) and urinary microalbumin(uMALB) were measured in spot urine samples using a BIOSTEC BA-400 specific protein autoanalyzer (Biosystems S.A., Barcelona, Spain). Skeletal muscle mass was assessed by bioelectrical impedance detection technology via the InBody 720 (Biospace, Korea). Vibration perception threshold (VPT) was assessed using a digital biothesiometer (Laxons Technology, Beijing, China), and the mean values of five measurements for each foot were calculated. VPT values < 15V were regarded as normal and values ≥ 15V for at least one foot were regarded as abnormal.

Statistical analysis

The Kolmogorov-Smirnov test was used to test the normality of all datasets. Normally distributed continuous data are represented as the mean ± SD, whereas non-normally distributed continuous data are represented as the median and interquartile range. Categorical variables are expressed as percentages. To analyze differences between the two groups, data with a normal distribution were analyzed using the unpaired Student's *t*-test and skewed data were analyzed using the Mann-Whitney U-Test. Categorical variables were analyzed using the chi-square test. Pearson, Spearman, and partial correlation analyses were used to identify factors that were associated with sdLDL-C levels. Multivariate logistic regression was performed to determine the relationship between sdLDL-C levels and DPN. Furthermore, receiver operating characteristic (ROC) analysis was conducted to identify a threshold value of sdLDL-C that would suggest the presence of DPN. All *P* values are two-tailed and *P* < 0.05 was considered to represent statistical significance. SPSS version 24.0 (IBM Inc., Armonk, NY, USA) was used for the analyses.

Results

Clinical characteristics of the two groups

We first analyzed the clinical characteristics of the T2DM patients with and without DPN (Table 1). We found that the DPN group was older than the non-DPN group (*P* < 0.001). The duration of diabetes in the DPN group was longer than that in the non-DPN group (*P* < 0.001), and the DPN group had a higher VPT than the non-DPN group (*P* < 0.001). The circulating sdLDL-C (*P* < 0.001), HDL-C (*P* < 0.001), LDL-C (*P* = 0.009), and TC (*P* = 0.013) levels significantly differed between the groups. Furthermore, significant differences in sex (*P* < 0.001), SBP (*P* < 0.05), uACR (*P* < 0.05), uMALB (*P* = 0.026), and diabetic retinopathy (*P* < 0.001) were found between the DPN and non-DPN groups. Finally, the skeletal muscle mass and DBP were significantly lower in the DPN group (*P* < 0.001, *P* = 0.001, respectively). However, no

significant differences in FPG, HbA1c, TG, UA, or BMI were observed between the DPN and non-DPN groups.

Table 1
Clinical characteristics of the DPN and non-DPN groups

	DPN (n = 702)	Non-DPN (n = 780)	P
Males,n(%)	409(58.3)	517(66.3)	0.001*
Age(years)	60(53,65)	50(38,59)	< 0.001*
Diabetes duration(years)	10(6,16)	4(0.58,10)	< 0.001*
SBP(mmHg)	138(125,151)	133(122,145)	< 0.001*
DBP(mmHg)	84(77,93)	83(74,90)	0.001*
FPG(mmol/L)	8.41(6.52,10.63)	8.27(6.88,10.71)	0.463
HbA1c(%)	8.9(7.6,10.2)	8.9(7.4,10.8)	0.359
TC(mmol/L)	5.03(4.32,5.82)	4.89(4.22,5.63)	0.013*
TG(mmol/L)	1.55(1.13,2.21)	1.54(1.03,2.47)	0.892
HDL-C(mmol/L)	1.08(0.92,1.29)	1.15(0.98,1.32)	< 0.001*
LDL-C(mmol/L)	3.12(2.59,3.69)	3.02(2.45,3.58)	0.009*
sdLDL-C(mmol/L)	1.13(0.86,1.37)	1.01(0.76,1.29)	< 0.001*
UA(mmol/L)	308.5(261,369)	319.5(260,388)	0.103
uACR(mg/mmol)	1.52(0.72,5.82)	1.09(0.56,2.76)	< 0.001*
uMALB(mg/L)	10.63(4.8,39.91)	9.4(4.75,24.99)	0.026*
BMI(kg/m ²)	25.8(23.7,27.8)	25.95(23.5,28.6)	0.185
Skeletal muscle mass(kg)	27.95(23.1,31.7)	29.7(23.95,33.4)	< 0.001*
VPT(v)	18(13.3,24.3)	8.2(6.2,10.7)	< 0.001*
DR,n(%)	269(38.3)	115(14.7)	< 0.001*
The Mann-Whitney U Test and χ^2 tests were used. Median (interquartile range) and N (%) are shown. * $P < 0.05$. SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; HbA1C: glycated hemoglobin; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; sdLDL-C: small dense low-density lipoprotein-cholesterol; UA: uric acid; uACR: urine albumin/creatinine ratio; uMALB: urine microalbumin; BMI: body mass index; VPT: vibration perception threshold; DR: diabetic retinopathy.			

Relationship between sdLDL-C and clinical parameters

Spearman correlation analysis showed that sdLDL-C positively correlated with SBP, DBP, TC, LDL-C, uACR, and uMALB ($P=0.017$, $P<0.001$, $P<0.001$, $P<0.001$, $P=0.005$, and $P=0.002$, respectively; Table 2), and negatively correlated with HDL-C ($P=0.01$, Table 2).

Table 2
Correlations between sdLDL-C and clinical parameters

Parameters	sdLDL-C	
	r	p
SBP(mmHg)	0.062	0.017*
DBP(mmHg)	0.134	< 0.001*
TC(mmol/L)	0.730	< 0.001*
HDL-C(mmol/L)	-0.067	0.010*
LDL-C(mmol/L)	0.814	< 0.001*
uACR(mg/mmol)	0.073	0.005*
uMALB(mg/L)	0.082	0.002*
VPT(v)	-0.050	0.054
DR,n(%)	0.011	0.685
Pearson and Spearman analyses were used. * $P<0.05$. SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; uACR: urine albumin/creatinine ratio; uMALB: urine microalbumin; VPT: vibration perception threshold; DR: diabetic retinopathy.		

Relationship between sdLDL-C levels and the presence of DPN in patients with T2DM

Table 3 shows the results of the multiple logistic regression analysis that was performed to identify the relationship between sdLDL-C levels and the presence or absence of DPN in T2DM patients. The independent variables included in the equation were sex, age, duration of diabetes, SBP, DBP, TC, LDL-C, HDL-C, sdLDL-C, uACR, uMALB, skeletal muscle mass, and VPT. sdLDL-C, duration of diabetes, and VPT were found to be independent risk factors of the presence of DPN in T2DM patients (odds ratio [OR] = 5.86, 95% confidence interval [CI]: 2.60–13.20, $P<0.001$; OR = 1.07, 95% CI: 1.04–1.09, $P<0.001$; and OR = 1.21, 95% CI: 1.16–1.26, $P<0.001$, respectively), whereas HDL-C was independent protective factor(OR = 0.281, 95% CI: 0.099–0.799, $P=0.017$; Table 3). ROC analysis was performed to identify the optimal cut-off value of sdLDL-C for the prediction of DPN and showed that the area under the curve (AUC) for

sdLDL-C was statistically significant. The most appropriate cut-off value for sdLDL-C was 0.985 mmol/L (AUC = 0.571; 95% CI: 0.541–0.600; sensitivity, 64.8%; specificity, 47.7%, $P < 0.001$) (Fig. 1).

Table 3

Results of the multivariate regression analysis of factors that were independently associated with DPN in T2DM patients

Parameters	P	OR	95% CI
Age	0.280	0.988	0.965–1.010
Diabetes duration	< 0.001*	1.065	1.039–1.091
sdLDL-C	< 0.001*	5.857	2.599–13.203
LDL-C	0.179	0.652	0.350–1.217
HDL-C	0.017*	0.281	0.099–0.799
VPT	< 0.001*	1.209	1.163–1.257
* $P < 0.05$. sdLDL-C: small dense low-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; VPT: vibration perception threshold.			

Discussion

In the present study, we investigated the relationship of sdLDL-C and other conventional risk factors to DPN in T2DM patients. We found that the circulating sdLDL-C level is high in T2DM patients with DPN and that high sdLDL-C is independently associated with the presence of DPN in these patients. To our knowledge, we have not seen any report describing the association of sdLDL-C with DPN in T2DM patients. In this retrospective study, we tried to investigate the prognostic value of sdLDL-C in T2DM patients with DPN.

A high circulating concentration of sdLDL-C is one of the key features of diabetic dyslipidemia [11]. Hyperglycemia and insulin resistance are associated with greater hepatic lipogenesis and adipose tissue fatty acid metabolism, which leads to dyslipidemia in both type 1 diabetes and T2DM [13, 14]. A high sdLDL-C concentration is more common among patients with insulin resistance and lipid profiles consistent with mixed dyslipidemia or hypertriglyceridemia [15]. Recent studies have shown associations between sdLDL-C and cardiovascular risk, metabolic dysregulation, and several pathophysiological processes [16–18]. The mechanism may depend on the fact that sdLDL-C particles are smaller than other LDL types and have a longer plasma half-life, rendering them more susceptible to glycation and oxidative stress, and therefore highly atherogenic [19]. Vascular risk factors have been identified to also be potential risk factors for neuropathy in diabetic and non-diabetic individuals [20]. It has also been previously reported that DPN is associated with a higher risk of a first cardiovascular event [12].

Among the major diabetic complications, DPN, diabetic nephropathy, and diabetic retinopathy are considered microvascular complications [21]. DPN is a highly prevalent complication of T2DM, and in

addition to the well-characterized axonal injury [22], diabetes affects Schwann cells and the vascular endothelium, as demonstrated by segmental demyelination and endoneurial microangiopathy [23]. These complications account for the majority of morbidity and mortality associated with diabetes. The fact that the risk of diabetic complications persists despite improvements in glycemic control in patients with T2DM suggests that other components of the metabolic syndrome may play a role in the onset and progression of these complications [24]. Emerging evidence indicates that dyslipidemia is important in the pathogenesis of diabetic neuropathy [20]. The study demonstrated that high plasma triacylglycerol concentration is associated with the progression of neuropathy in T2DM, and that obesity and dyslipidemia are independently associated with a higher risk of developing neuropathy [25].

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, the use of lipid-lowering therapy was associated with a lower risk of lower limb amputation, which suggests that lipid lowering may have beneficial effects on DPN [26]. Gordon et al.[24]. reported that hypertriglyceridemia significantly correlates with small nerve fiber integrity, whereas glucose control more closely correlates with large myelinated fiber function. The exact mechanism underlying triglyceride-mediated injury has yet to be elucidated, but it may involve the dysregulation of lipid metabolism within motor and/or sensory neurons [25]. Previous studies have shown that dyslipidemia is a risk factor for DPN, along with high TG, LDL-C concentrations [26]. In the present study, we found that the circulating sdLDL-C, LDL-C, and TC levels were higher in T2DM patients with DPN ($P < 0.001$, $P = 0.009$, and $P = 0.013$, respectively). The TG concentration of T2DM patients with DPN was higher than that of T2DM patients without DPN, but no significant difference was observed between the two groups ($P = 0.892$). A high LDL-C concentration was associated with the presence of DPN, consistent with the results of previous studies [27]. Interestingly, we found that sdLDL-C is an independent risk factor for the presence of DPN in T2DM patients, whereas LDL-C was not. This implies that the circulating concentration of sdLDL-C may be more useful for the prediction of DPN than LDL-C. Several potential underlying mechanisms may be implicated. First, free fatty acids have been shown to directly damage Schwann cells *in vitro* and to promote inflammatory cytokine release from adipocytes and macrophages [28]. Second, cholesterol can be oxidized to oxysterols, which have been shown to cause neuronal apoptosis [29].

In the present study, we also aimed to identify links between other conventional risk factors and DPN in T2DM patients. Increasing age, sex, and the presence of other microvascular complications were found to be significantly associated with DPN. Previous studies have shown that age is risk factor [30], few studies have shown no association [31], and we found that increasing age was associated with DPN (Table 1). In a retrospective study, no sex difference was identified, but we found that sex was significantly associated with DPN in patients with T2DM, the males in DPN group were less than non-DPN group [32]. Other microvascular complications, such as nephropathy or retinopathy, are risk factors for DPN, which shows that these complications go hand-in-hand in diabetic patients [33]. In the present study, we found that the prevalence of retinopathy, uACR, and uMALB concentration significantly differed between T2DM patients with or without DPN ($P < 0.01$, $P < 0.01$, and $P = 0.026$, respectively; Table 1). Patients with diabetic nephropathy tend to be more insulin resistant and have poorer lipid profiles [34], and we found that uACR

and uMALB positively correlated with sdLDL-C ($P = 0.005$ and $P = 0.002$, respectively; Table 2). Additionally, high uACR and uMALB were associated with DPN and dyslipidemia.

Previous cross-sectional studies have shown significant differences in HbA1c between T2DM patients with or without DPN [35]. On the contrary, Liu et al. [32]. showed that HbA1c was not associated with a difference in the significance of the outcomes. In the present study, we found that HbA1c and FPG did not significantly differ between T2DM patients with or without DPN. Early treatment with hypoglycemic agents might explain the results in HbA1c and FPG between the DPN and non-DPN groups. Furthermore, we found that SBP and DBP significantly differed between the DPN and non-DPN groups. The oxidative stress, endothelial dysfunction, and the abnormal production of cytokines that characterize T2DM patients with DPN are likely to be the explanation for this [36]. High SBP has previously been shown to be a risk factor for DPN in European patients [37]. Finally, we found that the skeletal muscle mass of T2DM patients with DPN was lower than that of T2DM patients without DPN ($P < 0.001$). Oh et al. [38]. suggest that DPN may be directly associated with muscle dysfunction because muscles are directly innervated by peripheral nerves and their function is controlled by nerve activity. Additionally, longer durations of diabetes and dyslipidemia are associated with low skeletal muscle mass [39].

DPN is associated with higher prevalence of disability and mortality in patients with diabetes. Therefore, the identification of risk factors for DPN in T2DM patients is of great significance for the prevention and early diagnosis and treatment of DPN. In addition to sdLDL-C, the duration of diabetes, HDL-C level, and VPT values were found to be independently associated with DPN in T2DM patients in the present study. In our study, longer duration of diabetes was a risk factor of DPN between the DPN and non-DPN groups. ($P < 0.001$) Moreover, the duration of diabetes has been shown to be independently associated with the incidence of microvascular complications [40]. In the final logistic regression analysis, the number of years a participant had T2DM remained associated with the prevalence of DPN, in agreement with previous findings. The HDL-C concentration was lower in T2DM patients with DPN ($P < 0.001$), and multivariate logistic regression analysis (Table 3) confirmed that HDL-C is independently associated with the absence of DPN in T2DM patients, which might imply that it has a protective effect. VPT presented a fairly good performance to detect DPN. Santos et al. [41]. demonstrated an independent association between VPT and long-term hyperglycemia, which suggests that abnormal VPT might occur early in the development of DPN. Consistent with these studies, we found that T2DM patients with DPN had significantly higher VPT than those without DPN (18 vu [interquartile range (IQR): 13.3–24.3 vu] vs. 8.2 vu [IQR: 6.2–10.7 vu], $P < 0.001$). Moreover, VPT was independently associated with DPN in T2DM patients.

We also found that sdLDL-C positively correlated with SBP, DBP, TC, and LDL-C in T2DM patients with DPN, and negatively correlated with HDL-C (Table 2). Dyslipidemia accelerates atherosclerosis, increasing the thickness of blood vessel walls and flow resistance, and thereby blood pressure. Therefore, hypertension and hyperlipidemia are frequent comorbidities [42]. Furthermore, previous studies have shown that lipid-lowering treatments can also reduce blood pressure [43]. As shown in Table 2, we found that HDL-C negatively correlated with sdLDL-C. Furthermore, the multivariate logistic regression analysis

(Table 3) showed that HDL-C was independently protective factor for the T2DM patients with DPN, whereas sdLDL-C was the independent risk factor for DPN in these patients. The AUC for sdLDL-C (0.571, $P < 0.001$) indicated that sdLDL-C is suitable for use as a predictor of DPN. Thus, we have demonstrated significant independent associations in T2DM patients between circulating lipids and the risk of microangiopathy.

The present study had several limitations. First, the data were collected at a single hospital, which would have introduced some selection bias. Therefore, multicenter studies are required to corroborate our findings. Second, we collected the data retrospectively. To more fully understand the importance of sdLDL-C in T2DM patients with DPN, large-scale prospective studies should be conducted.

Conclusions

In summary, we have shown that sdLDL-C is high in T2DM patients with DPN and that it is an independent predictor of DPN in T2DM patients. These results should encourage further investigation of sdLDL-C as a potential biomarker of peripheral neuropathy in T2DM.

Declarations

Acknowledgments

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Authors' Contributions

Chao Sun and Xinli Zhou were involved in the study design; Qing Chen, Xu Zhang and Chao Sun performed the statistical analysis; Chao Sun drafted the manuscript; Junqiao Wang, Xinzhe Wang, Yiping Cheng, Wendi Zhang, Yuanyuan Fan and Chao Sun conducted data collection and explanation; Xinli Zhou and Chao Sun conceived of the study. All authors read and approved the manuscript to be published, and all authors agreed to be responsible for all aspects of the work to make sure that questions related to the accuracy or integrity of the work will be solved.

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Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics approval and consent to participate

The retrospective study was approved by the Ethics Committee of Shandong Provincial Hospital, Shandong University (Jinan, China), and conducted following the ethical principles of the Declaration of Helsinki (as revised in Brazil in 2013). The informed consent of the participants was not required because of the retrospective study design and the use of anonymized data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflicts of interest.

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Figures

Diagonal segments are produced by ties

Figure 1

Receiver operating characteristic curve of sdLDL-C for the diagnosis of DPN. The most appropriate cut-off value of sdLDL-C value was 0.985 mmol/L (area under the curve=0.571; 95% confidence interval: 0.541–0.600; sensitivity, 64.8%; specificity, 47.7%, $P<0.001$).