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Analysis of serum lipid profile and apolipoprotein in patients with concurrent gallbladder stone disease and type 2 diabetes mellitus: a population-based study in China

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Abstract

Background

Gallbladder stone diseases being common disorder, prior studies have identified an association between gallstones and abnormal lipids, type 2 diabetics have higher rates of significant abnormalities in lipid metabolism, so the prevalence of dyslipidemia may be higher in gallstone disease patients with type 2 diabetes mellitus (T2DM) than in the general population. The aim of this study was to compare the serum lipid and lipoprotein abnormalities between gallbladder stone patients who have T2DM and controls in China.

Methods

Retrospective analysis of serum lipid and apolipoprotein levels in patients aged 40 years and older with gallbladder stone combined with T2DM, T2DM, gallbladder stone and normal group of 407 individuals in four groups. 135 cases with gallbladder stones combined with T2DM were compared with 102 cases with T2DM, 119 cases with gallbladder stone and 51 normal individuals respectively among four groups. Triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), very low-density lipoprotein (VLDL), serum apolipoprotein (apo) AI (ApoAI), apolipoprotein (apo) B (ApoB) and their ratio (ApoAI/ApoB) were collected from the four groups and compared. One-way ANOVA and nonparametric tests (Kruskal-Wallis tests) were used to compare groups. $P < 0.05$ was considered statistically significant.

Results

Compared to three control groups, the patients over 40 years old with gallbladder stone combined with T2DM had significant abnormal changes in lipids: the LDL and APoB levels were significantly raised in patients with gallbladder stones combined with T2DM ($P < 0.05$), and in males LDL levels were significantly higher in gallbladder stones patients with concomitant T2DM ($P < 0.05$).

Conclusions

The study showed that LDL and APoB levels were statistically significant in patients over 40 years of age with concurrent gallbladder stone disease and T2DM, with male patients having significantly higher LDL levels but no statistically significant parameters were found in female patients.

Background

Gallstone disease (GSD) is one of the most common diseases of digestive tract worldwide with a substantial financial burden on the global health-care system, according to the reported estimates that

the prevalence of GSD increased up to 15%[1]. The possible risk factors associated with the disease include gender, age, obesity, diabetes, dyslipidemias, rapid appetite loss, hepatitis C and cirrhosis[2–5]. There was a strong association between diabetes mellitus with gallstone events[6–8]. Type 2 diabetes mellitus (T2DM) and prediabetes is commonly associated with dyslipidemia and hypertension[9]. The coexistence of these risk factors for type 2 diabetes might be the reason that patients with GSD had an increased diabetes risk. A growing number of studies suggested that lipid disorder is a common risk factor for both gallstone disease and T2DM[10–13], which can increase the risk of developing coronary heart disease and stroke. Although retrospective clinical studies have showed that the changes in lipid profiles occur not only in cholelithiasis cases but also in patients who underwent laparoscopic cholecystectomy[14–16], there are few data regarding the compare of the serum lipid abnormalities in gallbladder stones patients with concomitant T2DM with controls, this study is aimed to analyze the level of the serum lipid profile and apolipoprotein in patients over 40 years with gallstones combined with T2DM in China.

Methods

The study was carried in the Department of General Surgery of Lu'An People's Hospital attached to Anhui Medical University, retrospectively from July 2016 to June 2018.

The study was approved by the ethical committee of Lu'an People's Hospital.
Written informed consent for the use of these people's detection results and personal information in this study was obtained from themselves or guardians. T2DM combined with gallbladder stones, gallbladder stones, T2DM and normal controls were respectively selected in four groups of 407 individuals. T2DM combined with gallbladder stones was classified as the diabetic stones group, with ages ranging from 40 to 84 years and mean age of (58.92 ± 9.59) years; T2DM without gallbladder stones was classified as the diabetic group, with ages ranging from 40 to 76 years with mean age of (56.74 ± 9.35) years; gallbladder stone group was classified as the gallstone group, with ages ranging from 40 to 91 years with mean age of (58.03 ± 12.04) years, and in normal group, the age ranged from 40 to 84 years with mean age of (57.21 ± 10.40) years. The group with diabetes mellitus combined with gallbladder stones is abbreviated as GD group and used as the case group. The diabetic group, the gallbladder stone group and the normal group were abbreviated as D group, G group and N group, respectively and they were all set as the control group.

All patients obtained fasting blood samples by venipuncture under aseptic conditions before receiving treatment. Patients with intrahepatic calculi, undergoing cholecystectomy, patients on antilipidemic drugs or patients with renal failure, nephrotic syndrome, pancreatitis, cardiac failure, morbid obesity, hypothyroidism, sickle cell disease, hemoglobinopathies, and pregnancy were excluded from the study.

The fasting serum lipid profile sample was collected along with the preoperative investigations. Blood samples drawn from the case and controls were analyzed for serum lipid profile and apolipoprotein. The serum lipid profile and apolipoprotein parameters included total cholesterol(TC), triglycerides (TG), high-

density lipoproteins (HDL), low-density lipoproteins(LDL), very low-density lipoproteins (VLDL) as well as serum apolipoprotein(apo)AI (ApoAI), apolipoprotein(apo)B (ApoB) and their ratio(ApoAI/ApoB) of the patients.

The statistical analyses were conducted using SPSS software, version 25.0 for Windows (SPSS, Chicago, IL) and the figures were generated using GraphPad Prism software (v 5.01; GraphPad Software, La Jolla, CA, USA). If numerical variables were normally distributed, they are presented as mean ± standard deviation(SD),the quantitative data were compared by one-way analysis of variance (ANOVA) followed by the Bonferroni test when the variances were homogenous or the Tamhane's T2 test when the variances were not homogenous for pair-wise comparison; if numerical variables were non-normally distributed, they are expressed as median(interquartile range [IQR])，Kruskal–Wallis test with Bonferroni correction were used for multiple comparisons. $P < 0.05$ was considered statistically significant.

Results

Of the individuals in four groups who underwent serum lipid profile and apolipoprotein analysis from July 2016 to June 2018, all respondents are 40 years old or older, the population with concurrent gallbladder stone disease and type 2 diabetes mellitus aged below 40 was small, so patients aged below 40 years. were excluded. The mean age of GD group, G group，D group and N group was 58.92 years,58.03 years，56.74 years，57.21 years, respectively. GD group consisted of 86 females and 49 males with female to male ratio of 1.76:1, N group had 28 females and 23 males with ratio of 1.22:1, D group had 36 females and 66 males with ratio of 0.55:1, and G group had 84 females and 35 males with ratio of 2.4:1 (Table 1).

The mean serum lipid and apolipoprotein including TC, TG, LDL, HDL, VLDL, APOAI, ApoB and APOAI/APOB in patients aged 40 years and above was shown in Table 2. The comparison of total lipid serum profile in GD group showed that the mean serum levels of TCH, TG and VLDL were high but not statistically significant ($P > 0.05$), compared with other three groups, however LDL level and ApoB level showed statistically significantly difference ($P < 0.05$) (Table 3). The mean levels of APoAI/B were lower in in a gallstone with diabetic patients, but the decrease was not statistically significant. The serum HDL, ApoB level in patients with gallbladder stones combined with T2DM was observed to be not statistically significant ($P > 0.05$) with other groups (Table 2). The extracted data was represented using a violin plot with quartiles indicated by dotted lines and median indicated by full lines(Fig. 1). This analysis showed the significant difference about the level of LDL(Fig. 1a) and ApoB(Fig. 1b) in the GD group showing the higher figures than the other three groups.

In patients aged over 40 years, we further analyzed the serum lipid profile and apolipoprotein of male and female patients separately. In males the serum LDL level in GD group was observed to be higher than three control groups which was statistically significant ($P < 0.05$) (Table 4, Table 5), the data were used to plot a bar graph as mean ± SD in four separate groups(Fig. 2),but no statistically significant parameters were found in female patients of GD group.

Table 1
Age and gender distribution of patients > 40 years in the case and three control groups

Physical Parameter	N	D	G	GD	P
Age (mean ± SD) years	57.21 ± 10.40	56.74 ± 9.35	58.03 ± 12.04	58.92 ± 9.59	0.36*
Gender (n,%)					
Females	28(12.00%)	36(15.4%)	84(35.9%)	86(36.8%)	
Males	23(13.3%)	66(38.2%)	35(20.2%)	49(28.3%)	
The age in mean ± SD. SD: standard deviation;*One-way analysis of variance (ANOVA).					

Table 2
The median and the quartile range of lipid profile and apolipoprotein in case and three control groups

Physical Parameter	N	D	G	GD	P*
TC	3.98(3.71 ~ 4.99)	4.34(3.56 ~ 4.88)	4.49(4 ~ 4.95)	4.66(3.91 ~ 5.34)	0.014
TG	1.03(0.86 ~ 1.39)	1.23(0.87 ~ 1.63)	1.19(0.91 ~ 1.78)	1.38(1.05 ~ 1.94)	< 0.01
HDL	1.26(1.06 ~ 1.42)	1.23(0.99 ~ 1.46)	1.2(0.98 ~ 1.41)	1.27(1.07 ~ 1.51)	0.246
LDL	1.98(1.69 ~ 2.42)	2.19(1.8 ~ 2.659)	2.07(1.85 ~ 2.46)	2.49(2.06 ~ 3.02)	< 0.01
VLDL	0.49(0.39 ~ 0.65)	0.55(0.39 ~ 0.73)	0.54(0.41 ~ 0.8)	0.62(0.47 ~ 0.87)	0.001
APoAI	1.25(1.14 ~ 1.34)	1.19(0.99 ~ 1.35)	1.23(1.07 ~ 1.38)	1.22(1.03 ~ 1.42)	0.257
APoB	0.78(0.66 ~ 0.95)	0.88(0.68 ~ 1.01)	0.8(0.68 ~ 0.93)	0.94(0.76 ~ 1.15)	< 0.01
ApoAI/ApoB	1.6(1.33 ~ 1.89)	1.34(1.09 ~ 1.82)	1.49(1.24 ~ 1.86)	1.27(1.08 ~ 1.53)	< 0.01
*Kruskal–Wallis non-parametric test; Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride. Units of TC, TG, HDL and LDL are mmol/L, Units of Apo A1 and Apo B are g/L.					

Table 3
Multiple comparisons of LDL and ApoB in patients over 40 years among case and three control groups

physical parameter	Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	P[a]
LDL	GD-N	-92.451	19.334	-4.782	< 0.01
	GD-G	-75.041	14.791	-5.073	< 0.01
	GD-D	-58.657	15.432	-3.801	0.001
ApoB	GD-N	-71.026	19.332	-3.674	0.001
	GD-G	-69.661	14.789	-4.71	< 0.01
	GD-D	-41.169	15.431	-2.668	0.046

a. Significance values have been adjusted by the Bonferroni correction for multiple tests.

Figure 1 The median and interquartile range(IQR) of the LDL(Fig. 1a) and ApoB(Fig. 1b) levels for the case(GD group) and three control groups(N, D, G groups), the median, upper and lower quartiles, the range were shown as a violin plot

Table 4
Showing median and mean values of lipid profile and apolipoprotein in case and three control groups

Physical Parameter	N	D	G	GD	P
TC	3.77(3.65 ~ 4.91)	4.32(3.43 ~ 4.82)	4.46(3.73 ~ 4.93)	4.37(3.57 ~ 5.3)	0.398**
TG	1.08(0.76 ~ 1.39)	1.22(0.76 ~ 1.63)	1.19(0.84 ~ 1.94)	1.43(0.96 ~ 1.99)	0.046**
HDL	1.22(1 ~ 1.41)	1.24(0.97 ~ 1.4)	1.09(0.85 ~ 1.26)	1.19(0.94 ~ 1.35)	0.13**
LDL	1.96 ± 0.5	2.16 ± 0.63	2.11 ± 0.48	2.54 ± 0.75	0.002*
VLDL	0.5(0.34 ~ 0.68)	0.55(0.34 ~ 0.73)	0.54(0.38 ~ 0.87)	0.64(0.43 ~ 0.9)	0.109**
APoAI	1.21(1.08 ~ 1.32)	1.15(0.97 ~ 1.28)	1.07(1 ~ 1.27)	1.13(0.93 ~ 1.33)	0.169**
APoB	0.75(0.6 ~ 0.9)	0.86(0.66 ~ 0.98)	0.79(0.69 ~ 0.89)	0.91(0.76 ~ 1.12)	0.015**
ApoAI/ApoB	1.66(1.33 ~ 1.94)	1.37(1.09 ~ 1.87)	1.34(1.2 ~ 1.61)	1.19(0.98 ~ 1.46)	0.002**

* One-way analysis of variance (ANOVA); ** Kruskal–Wallis non-parametric test.

Table 5
Multiple comparisons of LDL and ApoB in males aged over 40 years among case and three control groups.

physical parameter	Sample 1(I)-Sample 2(J)	Mean Difference (I-J)	Std. Error	95% Confidence Interval		P[a]
				Lower Bound	Upper Bound	
LDL	GD-N	0.58	0.15	0.18	0.99	0.001
	GD-G	0.38	0.13	0.02	0.74	0.030
	GD-D	0.43	0.13	0.07	0.80	0.011

a. Significance values have been adjusted by the Bonferroni correction for multiple tests.

Figure 2 The mean and standard deviation(SD) of the LDL level for the case(GD group) and three control groups(N, D, G groups), the mean and SD were shown as a bar chart.

Discussion

Gallstone disease remains one of the most common and most costly diseases of all digestive disorders requiring hospitalizations. It is a widely accepted idea that the gallstone formation is closely related to a disorder in the lipid and apolipoprotein metabolism[17, 18]. Diabetes mellitus is a metabolic disease with high prevalence among the population, 90% of whom are diagnosed with T2DM[19], type 2 diabetes seemed to prevail more frequently in those with hyperglyceridemia or those with hypercholesterolemia[20]. Serum lipid change in diabetics may lead to impairing gallbladder emptying[21], so patients with T2DM may suffer from a higher risk of gallbladder stone disease. Previous studies have found diabetes and GSD share some common risk factors, especially the dyslipidemia[22], abnormal blood lipid metabolism is closely related to the morbidity of T2DM and gallstone disease.

In this study, the type of gallbladder stones was not determined because we used sonographic findings, it was estimated to be mostly cholesterol gallstones as a result of improved living standards and changes in dietary habits in China recently. Aging is associated with significant changes in lipid profile and contributes to the development of gallstone. High incidence of GSD is observed in elderly population as the cumulative incidence had an increasing trend with age of up to 75 years old in participants, especially after 40 years old[23]. Age is also an important factor for diabetes mellitus and age distribution of diabetes in China increases with age[24]. In this study, we selected patients over 40 years of age with diabetes mellitus combined with gallbladder stones as the number of patients younger than 40 years was low.

Four group patients were collected from July 2016 to June 2018 and the changes in their serum profiles and apolipoprotein were evaluated over time using the LMM. The mean serum TC and TG were high in gallbladder stones patients with T2DM, but not statistically significant. We observed higher

concentrations of LDL and VLDL in the GD group than other three control groups. In detail, the differences of LDL between GD group and other control groups were statistically significant, and the ones for VLDL were not statistically significant.

ApoAI and ApoB are the major apolipoproteins for HDL and LDL, respectively. It was reported that serum apolipoprotein is likely more sensitive to change than serum lipid in distinguishing patients with gallbladder stones from those without stones, despite the lack of changes in lipid levels[25]. In this present study, we have found that increased concentrations of serum ApoB in GD group, and the difference for ApoB was statistically significant.

The main role of ApoAI and ApoB in the pathogenesis of gallbladder disease may be related to transport of cholesterol and nucleation of bile cholesterol. Our results suggested that serum concentration of LDL and HDL and their respective ApoB and ApoAI follow a similar pattern of association, presenting the same-directional changes in terms of serum concentration characterized by increased LDL and ApoB levels, reduced HDL and ApoAI levels, in agreement with other studies[26]. Meanwhile we observed higher concentrations of ApoB in GD group than control subjects, and the difference for ApoB was statistically significant. Our results suggested no correlation between GSD and HDL cholesterol concentration, which was consistent with other studies [27]. The current finding further illustrates the significant role of serum LDL and ApoB in the gallstone formation and the occurrence of diabetes for diabetic patients with gallbladder stone diseases.

Our study also showed that in males aged over 40 years we found medians of LDL and ApoB were higher in gallbladder stone patients with T2DM than other three groups, and the difference for LDL was statistically significant. However, in female patients above 40 years of age with diabetes combined with gallbladder stones, we did not find statistically significant differences in these parameters. The prevalence of dyslipidemia depends on the gender where males have a higher incidence. Lifestyle can be considered as a possible reason for such observation, as there may be more risk factors of dyslipidemia for men in lifestyle such as smoking, drinking alcohol and so on. There also could be more complex factors that would influence the changes of serum lipid profile and apolipoprotein in women. Perhaps, further studies are needed to verify our conjectures.

Conclusions

In conclusion, the present study demonstrates that LDL and ApoB levels of gallbladder stone disease patients with T2DM (GD group) were found to be statistically significantly high in cases > 40 years of age. There were no statistically significant differences in other parameters. Further analysis revealed that the male patients aged over 40 years in GD group had significantly higher LDL levels than three control groups, with statistically significant differences, and no statistically significant differences in these parameters were found in the female patients of GD group. From the study, it can be concluded that LDL and APoB levels have been shown to be significantly elevated in GD group and thus can be helpful in helping the subsequent development of gallbladder stone in T2DM patients. Considering the major role of

LDL in coronary artery disease, it would be prudent to screen all T2DM patients with cholelithiasis for dyslipidemia, which might help in instituting primary preventive measures; however, additional studies are required to confirm these findings.

Abbreviations

HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride; GSD ,Gallbladder stone diseases; type 2 diabetes mellitus, T2DM.

Declarations

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Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contribution

Xin-An Fang and Yong-Kang Liang collected and analyzed all the included data. LS designed this study and drafted the manuscript. All of the authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Lu'an People's Hospital. Informed consent was obtained from all the participants or their guardians.

Consent for publication

Informed consent for publication was obtained from all the participants or their guardians.

Competing interests

The authors declare that they have no competing interests.

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Figures

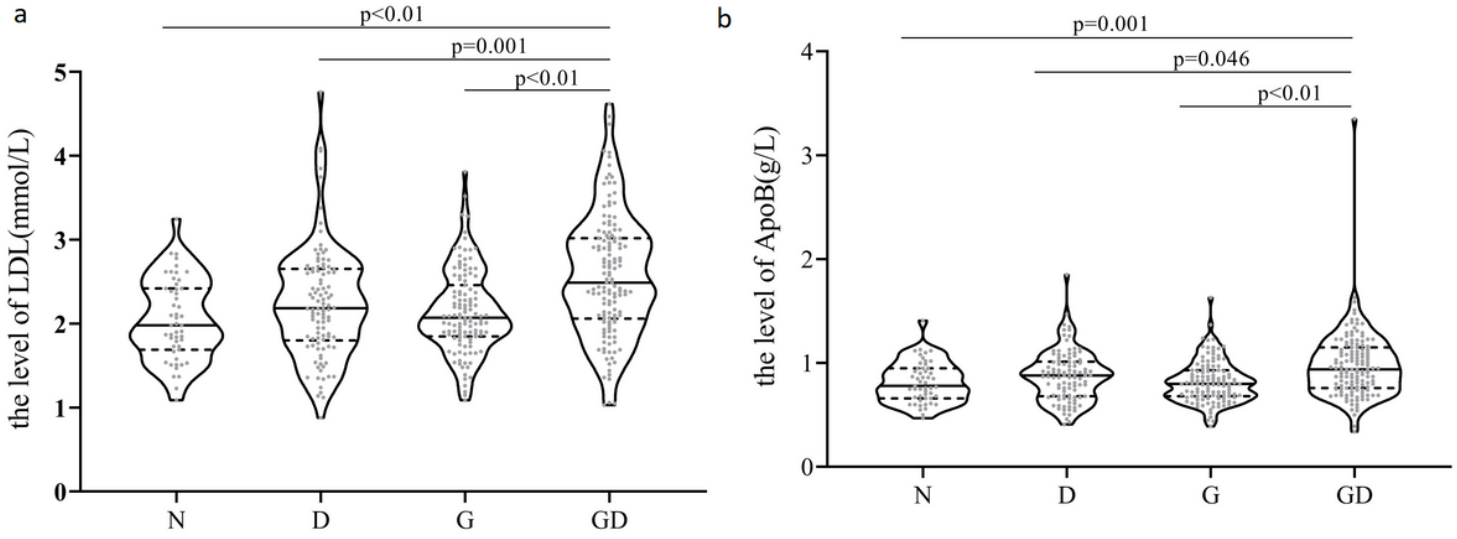

Figure 1

The median and interquartile range(IQR) of the LDL(Figure 1a) and ApoB(Figure 1b) levels for the case(GD group) and three control groups(N, D, G groups), the median, upper and lower quartiles, the range were shown as a violin plot

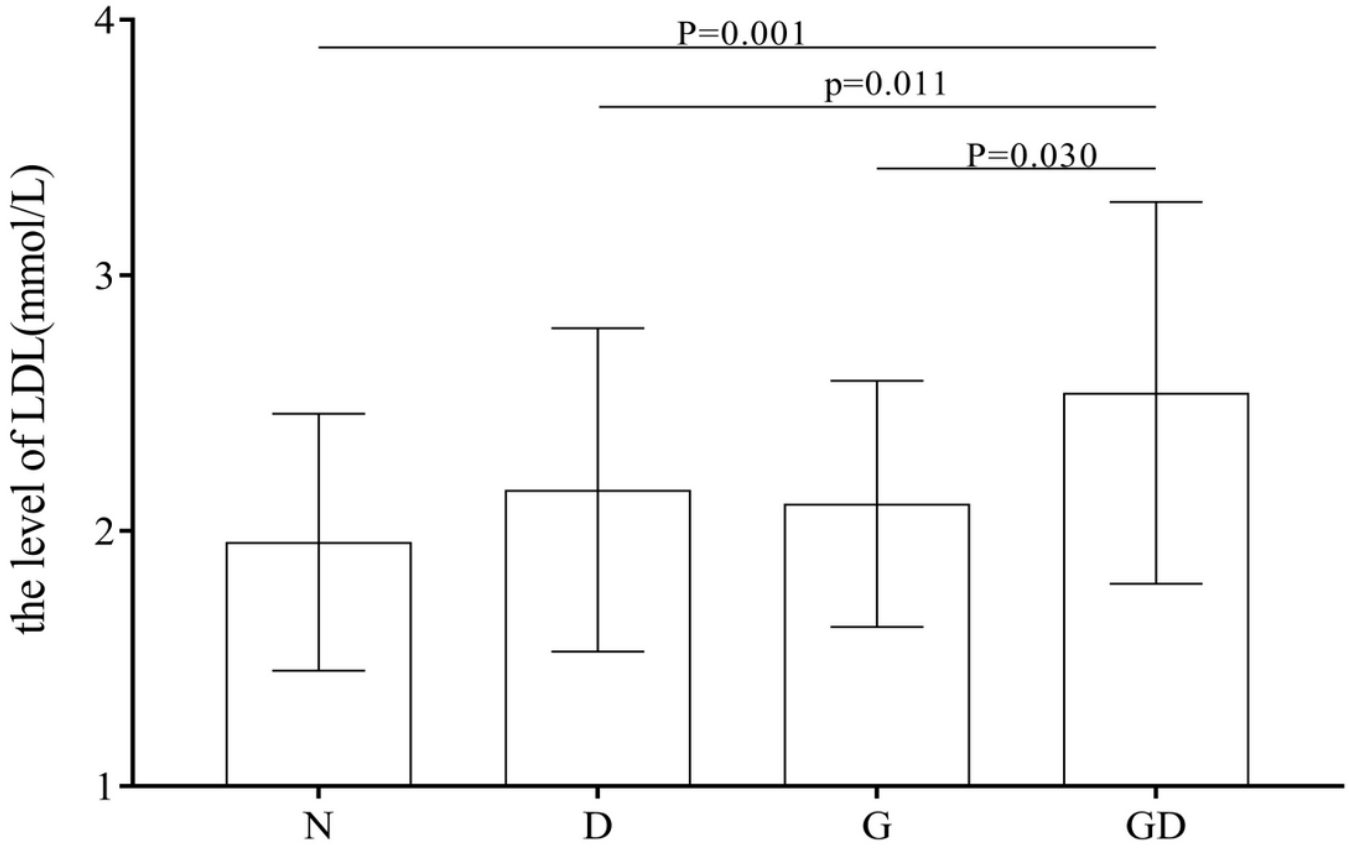

Figure 2

The mean and standard deviation(SD) of the LDL level for the case(GD group) and three control groups(N, D, G groups), the mean and SD were shown as a bar chart.