Dyslipidemia in Type 2 Diabetes Mellitus Patients With Poor Glycemic Control: Relationship Between HbA1c and Lipid Profile.

Huiwen Xu
Yangzhou University
Shuang Qiu
Yangzhou Hospital of Traditional Chinese Medicine
Xiaodan Yuan
Jiangsu Province Academy of Traditional Chinese Medicine
Yan Zou
Yangzhou University
En Takashi
Nagano College of Nursing
Kitayama Akio
Nagano College of Nursing
Lin Liu (liulin163com@163.com)
Yangzhou University

Research Article

Keywords: Dyslipidemia, Type 2 diabetes mellitus, Glycosylated hemoglobin

Posted Date: March 3rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-258114/v1

The title of the paper:

Dyslipidemia in type 2 diabetes mellitus patients with poor glycemic control: relationship between HbA1c and lipid profile.

The full names of the authors:

Huiwen Xu[1,2], Shuang Qiu[3], Xiaodan Yuan[4] , Yan Zou[1], En Takashi[2], Kitayama Akio[2], Lin Liu[1*]

[1] School of Nursing, Yangzhou University, #136 Jiangyang Road, Yangzhou, China 225009

[2] Nagano College of Nursing, Komagane, Nagano, Japan 399-4117

[3] Department of Pharmacy, Yangzhou Hospital of Traditional Chinese Medicine, #557 Wenchang Middle Road, Yangzhou, China 225000

[4] Jiangsu Province Academy of Traditional Chinese Medicine, #100 Hongshan Road, Qixia District Nanjing, China 210028

***Corresponding Author**

E-mail:liulin163com@163.com

Abstract

Aims: This study identified the lipid profile across a full range of poor glycemic control and the association between lipid profiles with different specific glycated hemoglobin (HbA1c) cutoffs in patients with type 2 diabetes (T2DM).

Methods: A total of 1183 T2DM patients with poor glycemic control (HbA1c>7%) selected through convenience sampling in three hospitals of Jiangsu province were surveyed during April 2018 and July 2019. Dyslipidemia was defined according to criteria of the Third Report of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).

Results: The prevalence of dyslipidemia was 55.2 % overall. Of 1183 subjects, 13.0% had high total cholesterol (TC), 33.1% had low high density lipoprotein cholesterol (HDL-C), 9.9% had high low density lipoprotein cholesterol (LDL-C), and 28.4% had high triglycerides (TG) concentrations. There was an increase in frequency of dyslipidemia in patients with different cutoff values of HbA1c (P<0.05). The prevalence of high TC was closely related with different cutoff values of HbA1c (adjusted OR =1.77, 2.56 3.82, respectively). Patients with HbA1c values 9%≤HbA1c<11% and HbA1c≥13% had significantly higher prevalence of dyslipidemia compared with the patients who had 7≤HbA1c<9%.

Conclusion: T2DM patients with 9%≤HbA1c<11% and HbA1c≥13% tend to have moderate and severe dyslipidemia respectively, suggesting the importance of glycemic control in normalizing dyslipidemia.

Keywords: Dyslipidemia; Type 2 diabetes mellitus; Glycosylated hemoglobin

1. Introduction

Recent studies showed that type 2 diabetes mellitus was associated with an increased risk for cardiovascular disease (CVD) [1,2]. The United Kingdom Prospective Diabetes Study (UKPDS) showed that maintaining HbA1c around 7.0% played a causal role in development of cardiovascular disease in newly diagnosed T2D [3, 4]. Khaw K et al. [5] have estimated that reducing the HbA1c level by 0.2% could lower the mortality by 10% in diabetes. Elevated HbA1c has been regarded as an independent risk factor for cardiovascular disease, and the Diabetes

Complications and Control Trial (DCCT) established HbA1c as the gold standard of glycemic control, with levels≤7% deemed appropriate for reducing the risk of vascular complications [6]. Apart from HbA1c, there were also historical data suggesting abnormal lipid levels were established risk factors for CVD in T2DM [7,8].

Different mechanisms are responsible for the development of dyslipidemia in individuals with diabetes. Defects in insulin action and hyperglycemia could lead to dyslipidemia in patients with diabetes [9]. Lebovitz et al.[10] suggested that there was a lipotoxic mechanism by triglyceride which interferes with gastric or neural pathway which regulates glycemic control. Dyslipidemia interacts with glucose metabolism. One previous study have reported that HbA1c was associated with low HDL cholesterol in a J-shaped manner, and hyperglycemia defined as HbA1c≥7.0 % increased risk of high LDL cholesterol in T2DM [11]. Although compared with HbA1c<7% ,T2DM patients with HbA1c≥7% had significantly higher levels of lipid profile [12,13], it is unknown whether there was a linear and significant increase levels of lipid profile associated with HbA1c value of ≥7%. To our knowledge, there have been no studies describing differences in the lipid profile across a full range of poor glycemic control (HbA1c≥7.0%).

Due to the significant association between HbA1c as well as serum lipids, we conducted this study that aims to determine the prevalence of different types of dyslipidemia among T2DM patients with poor glycemic control and to identify the association between lipid profiles with different specific HbA1c cutoffs.

2. Materials and methods

2.1 Study subjects

A multicenter cross-sectional study was conducted using questionnaires and laboratory data. The enrolled patients came from tertiary hospitals that have more than 40 beds in their endocrinology department from Nanjing and Yangzhou. The eligibility criterion for the study was T2DM with poor glycemic control (HbA1c>7%). Exclusion criteria were: (i) women who were pregnant or breast feeding; (ii) crucial organ failure or other severe diseases, including myocardial infarction, serious neurological or mental disorders, severe infections, or disseminated intravascular coagulation. A total of 1194 patients with T2DM were enrolled from April 2018 to

July 2019 at the three hospitals. 1183 patients who completed the study were analyzed in our study. The study was approved by the Ethics Committee of the Hospital of Integrated Traditional Chinese and Western Medicine of Jiangsu Province. All methods were performed in accordance with the guiderlines of the Declaration of Helsinki. All patients enrolled in the study were in formed of the aims of the study, and written informed consent was obtained before participation.

2.2 Outcomes and Variables

Demographic data about age, gender, weight, height, duration of diabetes, blood pressure, and the status of diabetes complications were collected from patients' medical histories.

Body weight and height were measured in all subjects wearing light clothing and standing barefoot at 8 am before breakfast, and BMI was calculated by dividing weight (kg) by the square of height (m^2).

Fasting venous blood samples were collected after a fast of at least 10 hours. Fasting blood glucose (FBG), HbA1c, TG, TC, HDL-C and LDL-C levels were tested following standard laboratory procedures. Plasma glucose was analyzed by a YSI 2700 Select Biochemistry Analyzer (YSI, Inc., Yellow Springs, OH). HbA_{1c} content was determined by high performance liquid chromatography (Bio-Rad Diamat, Munich, Germany). The serum concentrations of TC, HDL-C, LDL-C and TG were determined by colorimetric methods using commercial kits (Abbott, Abbott Park, IL) with an Architect c8000 analyzer (Abbott) according to the instructions of the manufacturer.

2.3 Definitions

The definition of dyslipidemia was referring to the Third Report of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [14] . Borderline high and high TC was defined as having TC levels of 200-239 mg/dL (5.18-6.21 mmol/L) and ≥240 mg/dL (≥6.22 mmol/L), respectively. Low HDL-C was defined as having HDL-C levels <40 mg/dL (<1.04 mmol/L). Borderline high, high, and very high LDL-C was defined as having LDL-C levels of 130-159 mg/dL (3.37-4.13mmol/L), 160-189 mg/dL (4.14-4.91 mmol/L), and ≥190mg/dL (≥4.92 mmol/L), respectively. Borderline high, high, and very high TG was defined as having triglyceride levels of 150-199 mg/dL (1.70-2.25 mmol/L), 200-499 mg/dL (2.26-5.64 mmol/L), and ≥500 mg/dL (≥5.65 mmol/L), respectively. Dyslipidemia was defined as any of the following: high TC,

high LDL-C, low HDL-C and high TG.

2.4 Statistical analysis

Characteristics of the study subject were summarized using descriptive statistical methods. HbA_{1c} was categorized in 4 groups with 2% increments from 7% to 13%, or higher. The normality of continuous data was calculated using the Kolmogorov-Smirnov test. If the distribution was normal, continuous variables were presented as mean± standard deviation (SD) when data were normally distributed. Those continuous data without normal distribution should be presented as median (interquartile range (IQR)). Mean differences in lipid profile among different categories of HbA1c were compared using analysis of covariance after adjusting for sex, BMI and age. The linear trend chi-square test was used between lipid profile and HbA1c. Pearson correlation was used between HbA_{1c} and the following variables: TC, TG, HDL-C and LDL-C. Hierarchical regression analysis was conducted using the prevalence of dyslipidemia as the dependent variable. To further analyze the impact of the level of HbA1c on the prevalence of dyslipidemia, predictors were entered in three blocks by three steps. Cardiovascular and cerebrovascular disease, BMI and level of HbA1c were fit as categorical variables. All *P* values were two-sided, and a $P < 0.05$ was considered statistically significant. All data were analyzed using SPSS 24.0 (IBM Corporation, New York, NY).

3. Results

3.1 Clinical characteristics of study participants

Out of all the participants, 11 (0.9%) patients were excluded due to the absence of lipid profile. The remaining 1183 T2DM were included in this analysis and their characteristics were described in Table 1. A total of 55.4% of T2DM had an admission HbA1c7%≤HbA1c<9% and 5.1% had an admission HbA1c higher than 13%. The age was significantly higher ($P<0.01$) in 7%≤HbA1c<9% (58.07±9.73), 9%≤HbA1c<11% (57.30±9.88) and 11%≤HbA1c<13% (54.16±10.87) than HbA1c≥13% (52.78±14.34). The level of TC was significantly higher ($P<0.01$) in HbA1c≥13% (211.49±58.78) as compared to 7%≤HbA1c<9% (188.67±42.62). There was a significant increase in HDL-C levels and TG levels in patients with 7%≤HbA1c<9% as compared to individuals with 11%≤HbA1c<13% and HbA1c≥13%. No significant differences were observed with regard to HDL-C.

Table 1. Clinical and biochemical characteristics of participants with type 2 diabetes (N=1183)

Participant's Characteristics	7%≤HbA1c<9% (n=655)	9%≤HbA1c<11% (n=315)	11%≤HbA1c<13% (n=153)	HbA1c≥13% (n=60)	*P* value
Age, years	58.07±9.73	57.30±9.88	54.16±10.87	52.78±14.34	<0.01
Male, n (%)	321 (49.0%)	166(52.7%)	73(47.7%)	30(50%)	0.685
BMI, kg/m^2	24.81±2.76	24.79±2.81	24.18±3.01	23.48±3.03	<0.01
BMI categories, n（%）					
BMI＜24 kg/m^2	301 (46.0%)	146 (46.3%)	82 (53.6%)	38 (63.3%)	0.174
BMI 24-28 kg/m^2	285 (43.5)	133 (42.2%)	55 (35.9%)	18 (30.0%)	
BMI ≥28 kg/m^2	69 (10.5%)	36(11.5%)	16 (10.5%)	4 (6.7%)	
SBP ,mmHg	129.09±13.58	129.54±14.59	127.87±15.88	121.95±13.99	<0.01
DBP, mmHg	78.26±8.77	78.26±8.98	78.58±9.30	73.73±7.17	<0.01
Duration of DM, years	8.08±5.48	7.98±5.26	6.25±5.07	4.66±4.04	<0.01
History of CVD, n (%)	54 (8.2%)	19 (6.0%)	7 (4.6%)	5 (8.3%)	0.332
History of stroke, n (%)	21 (3.2%)	7 (2.2%)	5 (3.3%)	1 (1.7%)	0.524
FBG, mmol/l	8.77±2.29	10.87±2.80	12.42±3.71	14.02±4.01	<0.01
TC, mg/dL	188.67±42.62	195.46±45.45	202.35±50.36	211.49±58.78	<0.01
LDL-C, mg/dL	113.43±34.79	116.39±36.06	122.69±39.68	129.46±40.35	<0.01
HDL-C, mg/dL	47.73±17.75	46.70±16.22	45.90±12.39	45.19±13.12	0.423
TG, mg/dL	176.13±145.07	196.59±134.68	205.77±196.19	221.27±208.11	<0.05

Mean values (SD) or percentages (%) are shown.

BMI= Body Mass Index; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; CVD= Cardiovascular Disease; HbA1c= Haemoglobin A1c; FBG=Fasting Blood Glucose; TC = Total Cholesterol; LDL-C=Low-Density Lipoprotein-Cholesterol; HDL-C=High-Density Lipoprotein – Cholesterol; TG=Triglyceride.

3.2 Prevalence rates of abnormal lipid levels by HbA1c and gender group.

Table 2 showed the prevalence rates of abnormal lipid levels by HbA1c and gender group. Of

1183 subjects, 13.0% had high TC, 33.1% had low HDL-C, 9.9% had high LDL-C, and 28.4% had high TG concentrations. The HbA1c-specific prevalence of borderline high and high TC increased with HbA1c (P = 0.001) and only in men (P = 0.002). The prevalence of low-HDL was significantly higher in men than women (P < 0.05). The prevalence of borderline high, high, and very high LDL-C was 21.2%, 6.9% and 3.0%, respectively. Differences between men and women were not significant in LDL-C and HDL-C .The prevalence of borderline high, high, and very high TG was 20.2%, 24.3% and 4.1%, respectively. And the HbA1c-specific prevalence of borderline high, high, and very high TG increased with HbA1c (P = 0.017). The prevalence of dyslipidemia increased significantly with HbA1c (49.3% vs. 59.4% vs. 58.8% vs. 68.3%; P <0.05) (Fig 1).

There was significant correlation between HbA1c and TC, TG and LDL-C (P=0.000; P=0.019; P=0.000) (Fig 2). Additionally, no significant correlation was found between HDL-C and HbA1c (P = 0.399).

Table 2. Prevalence of different types of dyslipidemia categorized by patients' HbA_{1c} and gender group (N=1183)

	TC mg/dL (mmol/L)		HDL mg/dL (mmol/L)	LDL mg/dL (mmol/L)			TG mg/dL (mmol/L)		
	200-239 (5.18-6.21)	≥240 (≥6.22)	<40 (<1.04)	130-159 (3.37-4.13)	160-189 (4.14-4.91)	≥190 (≥4.92)	150-199 (1.70-2.25)	200-499 (2.26-5.64)	≥500 (≥5.65)
All (n=1183)									
Total	327 (27.6%)	154 (13.0%)	392 (33.1%)	251(21.2%)	82 (6.9%)	36 (3.0%)	239 (20.2%)	287 (24.3%)	48 (4.1%)
7%≤HbA_{1C}<9%	176 (74.6%)	60 (25.4%)	201 (30.7%)	123 (68.0%)	43 (23.8%)	15 (8.3%)	137 (45.2%)	149 (49.2%)	17 (5.6%)
9%≤HbA_{1C}<11%	85 (64.4%)	47 (35.6%)	117 (37.1%)	73 (72.3%)	16 (15.8%)	12 (11.9%)	63 (38.2%)	85 (51.5%)	17 (10.3%)
11%≤HbA1C<13%	49 (61.3%)	31 (38.8%)	51 (33.3%)	39 (63.9%)	16 (26.2%)	6 (9.8%)	26 (34.7%)	40 (53.3%)	9 (12.0%)
HbA1C≥13%	17 (51.5%)	16 (48.5%)	23 (38.3%)	16 (61.5%)	7 (26.9%)	3 (11.5%)	13 (41.9%)	13 (41.9%)	5 (16.1%)
P for trend	0.001		0.115	0.438			0.017		
Men (n=590)									
Total	149 (25.3%)	63 (10.7%)	233 (39.5%)	112 (19.0%)	36 (6.1%)	15 (2.5%)	119 (20.2%)	128 (21.7%)	29 (4.9%)
7%≤HbA_{1C}<9%	78 (77.2%)	23 (22.8%)	119 (37.1%)	54 (67.5%)	20 (25.0%)	6 (7.5%)	68 (47.9%)	63 (44.4%)	11 (7.7%)

9%≤HbA$_{1C}$<11%	43 (74.1%)	15 (25.9%)	73 (44.0%)	36 (83.7%)	3 (7.0%)	4 (9.3%)	34 (40.0%)	40 (47.1%)	11 (12.9%)
11%≤HbA1C<13%	21 (53.8%)	18 (46.2%)	27 (37.0%)	15 (53.6%)	11 (39.3%)	2 (7.1%)	9 (26.5%)	19 (55.9%)	6 (17.6%)
HbA1C≥13%	7 (50.0%)	7 (50.0%)	14 (46.7%)	7 (58.3%)	2 (16.7%)	3 (25%)	8 (53.3%)	6 (40.0%)	1 (6.7%)
P for trend	0.002		0.325	0.199			0.130		
Women (n=593)									
Total	178 (30.0%)	91 (15.3%)	159 (26.8%)	139 (23.4%)	46 (7.8%)	21 (3.5%)	120 (20.2%)	159 (26.8%)	19 (3.2%)
7%≤HbA$_{1C}$<9%	98 (72.6%)	37 (27.4%)	82 (24.6%)	69 (68.3%)	23 (22.8%)	9 (8.9%)	69 (42.9%)	86 (53.4%)	6 (3.7%)
9%≤HbA$_{1C}$<11%	42 (56.8%)	32 (43.2%)	44 (29.5%)	37 (63.8%)	13 (22.4%)	8 (13.8%)	29 (36.3%)	45 (56.3%)	6 (7.5%)
11%≤HbA1C<13%	28 (68.3%)	13 (31.7%)	24 (30.0%)	24 (72.7%)	5 (15.2%)	4 (12.1%)	17 (41.5%)	21 (51.2%)	3 (7.3%)
HbA1C≥13%	10 (52.6%)	9 (47.4%)	9 (30.0%)	9 (64.3%)	5 (36.7%)	0 (0%)	5 (31.3%)	7 (43.8%)	4 (25%)
P for trend	0.078		0.211	0.920			0.062		

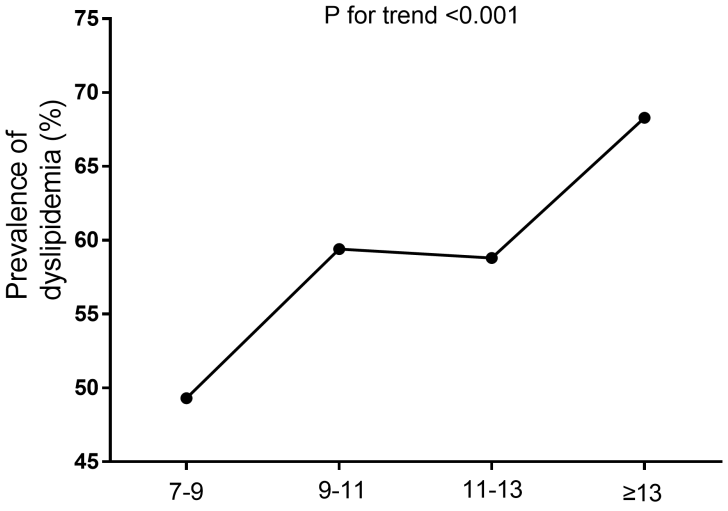

Figure 1. Prevalance of dyslipidemia by category of HbA_{1c}

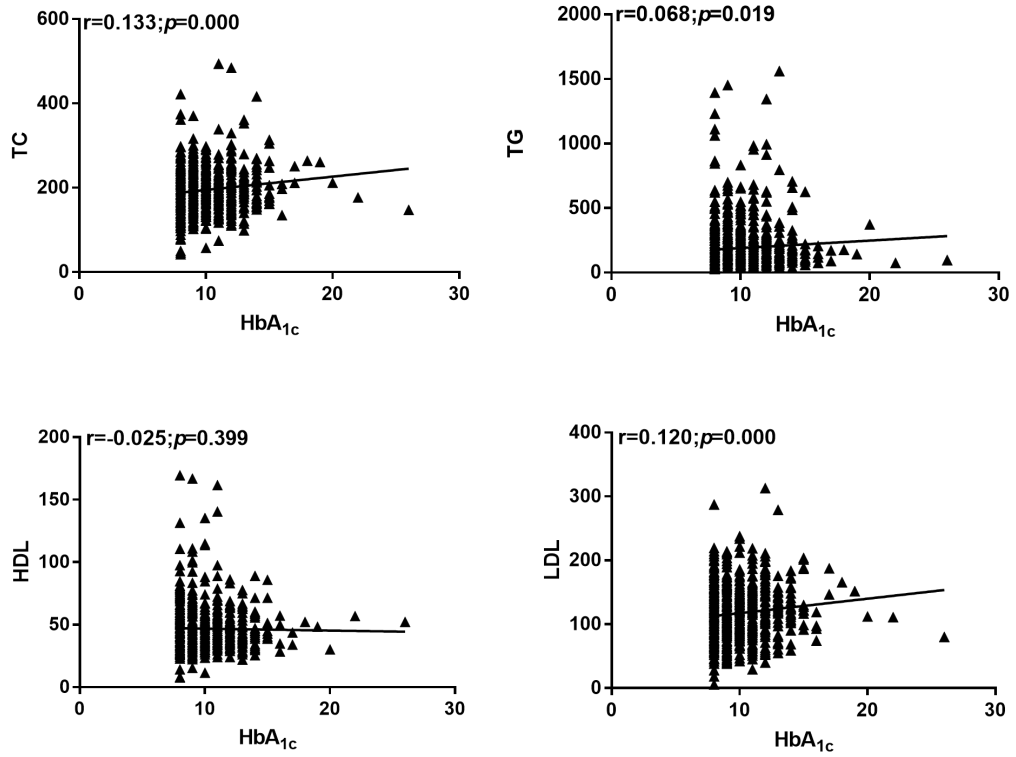

Figure2. Corrleation between TC,TG,HDL, LDL and HbA_{1c} in type 2 patients with poor glycemic control

3.3 Comparisons of lipid profile by different cutoff values of HbA1c

The 7%≤HbA1c<9% had a mean of 13.5 and 22.90 less TC (95%CI, -24.37 to -2.62; 95%CI, -39.26 to -6.55) compared with 11≤HbA1C<13% and HbA1C≥13%. There was no significant difference in lipid profile between 7%≤HbA1c<9% and 9%≤HbA1C<11% group. Significant differences in LDL-C were respectively found between 7%≤HbA1c<9% and 11≤HbA1c<13%, 7%≤HbA1c<9% and HbA1C≥13%. No significant difference between HbA1c levels in lipid profile was noted in men. Compared with HbA1C≥13%, 7%≤HbA1c<9% had a mean of 30.09 less TC, 18.37 less LDL-C and 95.83 less TG in women group (Table 3).

Table 3. Mean difference in lipid profile among different levels of HbA_{1c} (N=1183)

	7%≤HbA1C<9% vs 9%≤HbA_{1C}<11%	7%≤HbA1C<9% vs 11≤HbA1C<13%	7%≤HbA1C<9% vs HbA1C≥13%	9%≤HbA_{1C}<11% vs 11%≤HbA1C<13%	9%≤HbA_{1C}<11% vs HbA1C≥13%	11%≤HbA1C<13% vs HbA1C≥13%
All						

TC, mg/dL	-6.69 (-14.90 to 1.53)	-13.50 (-24.37 to -2.62)**	-22.90(-39.26 to -6.55) **	-6.81(-18.66 to 5.04)	-16.22(-33.20 to 0.77)	-9.41(-27.63 to 8.81)
HDL, mg/dL	1.06(-1.91 to 4,03)	2.37(-1.57 to 6.30)	3.62(-2.30 to 9.53)	1.31(-2.99 to 5.60)	2.55(-3.61 to 8.71)	1.25(-5.36 to 7.86)
LDL, mg/dL	-2.87(-9.40 to 3.65)	-8.86(-17.49 to -0.22)*	-15.53(-28.52 to -2.53)**	-5.98(-15.42 to 3.45)	-12.65(-26.18 to 0.88)	-6.67(-21.18 to7.84)
TG, mg/dL	-19.01(-46.33 to 8.32)	-26.64(-62.81 to 9.52)	-45.32(-99.72 to 9.07)	-7.63(-47.15 to 31.88)	-26.32(-82.96 to 30.33)	-18.68(-79.45 to 42.09)
Men						
TC, mg/dL	-4.13(-16.05 to 7.80)	-13.07(-29.53 to 3.39)	-14.39(-38.62 to 9.83)	-8.95(-26.69 to 8.80)	-10.27(-35.38 to 14.85)	-1.32(-28.42 to 25.77)
HDL, mg/dL	1.32(-3.06 to 5.71)	2.29(-3.76 to 8.34)	2.69(6.22 to 11.59)	0.96(-5.56 to 7.49)	1.36(-7.87 to 10.59)	0.40(-9.56 to 10.36)
LDL, mg/dL	0.03(-9.03 to 9.09)	-6.79(-19.29 to 5.71)	-12.10(-30.50 to 6.31)	-6.82(-20.31 to 6.66)	-12.13(-31.20 to 6.95)	-5.30(-25.89 to 15.28)
TG, mg/dL	-17.16(-58.66 to 24.24)	-32.45(-89.59 to 24.69)	6.74(-77.38 to 90.85)	-15.29(-76.91 to 46.33)	23.90(-63.29 to 111.09)	39.19(-54.89 to 133.26)
Women						
TC, mg/dL	-10.27(-21.38 to 0.84)	-12.56(-26.67 to 1,56)	-30.09(-51.74 to -8.44) **	-2.29(-17.95 to 13.37)	-19.82(-42.29 to 2.85)	-17.53(-41.68 to 6.61)
HDL, mg/dL	0.61(-3.39 to 4.62)	2.64(-2.45 to 7.73)	4.68(-3.12 to 12.48)	2.23(-3.62 to 7.67)	4.07(-4.10 to 12.34)	2.04(-6.66 to 10.74)
LDL, mg/dL	-6.35(-15.76 to 3.06)	-10.17(-22.12 to 1.79)	-18.37(-36.71 to -0.03) *	-3.81(-17.08 to 9.45)	-12.02(-31.22 to 7.19)	-8.20(-28.66 to 12.25)
TG, mg/dL	-22.21(-57.62 to 13.19)	-19.46(-64.45 to 25.53)	-95.83(-164.84 to -26.82) **	2.75(-47.16 to 52.67)	-73.62(-145.88 to -1.36)*	-76.43(-153.51 to 0.65)

Data is mean difference (95% CI); *P<0.05; **P<0.01

3.4 Predicators of abnormal lipid profile

Table 4 illustrated that increasing HbA_{1c} was significantly associated with the prevalence of high TC (adjusted OR =1.77, 2.56 3.82, respectively). The prevalence of borderline high, high, and very high LDL-C was not closely related with different cutoff values of HbA_{1c}. Subjects with HbA1C≥13% tended to have more prevalence of high TG compared with 9%≤HbA1C<11% (adjusted OR = 2.08, 2.51, respectively) (Table 4).

Table 4. Adjusted odds ratio (95%CI) of dyslipidemia prevalence among different levels of HbA_{1c}

	TC mg/dL (mmol/L)		HDL mg/dL (mmol/L)		LDL mg/dL (mmol/L)		TG mg/dL (mmol/L)		
	200-239 (5.18-6.21)	≥240 (≥6.22)	<40 (<1.04)	130-159 (3.37-4.13)	160-189 (4.14-4.91)	≥190 (≥4.92)	150-199 (1.70-2.25)	200-499 (2.26-5.64)	≥500 (≥5.65)
7%≤HbA_{1C}<9%	1	1	1	1	1	1	1	1	1
9%≤HbA_{1C}<11%	1.01(0.75 to	1.77(1.18 to	1.31(0.99 to	1.32(0.95 to	0.77(0.43 to	1.70(0.79	0.95(0.68 to	1.27(0.93 to	2.08(1.04 to

	1.37)	2.67)**	1.75)	1.83)	1.39)	to 3.68)	1.32)	1.74)	4.18)*			
11%≤HbA1C<13%	1.22(0.83 to	2.56(1.58 to	1.16(0.79 to	1.44(0.94 to	1.68(0.91 to	1.65(0.62	0.79(0.50 to	1.25(0.83 to	1.93(0.81 to			
	1.80)	4.15)**	1.70)	2.18)	3.11)	to 4.39)	1.26)	1.89)	4.56)			
HbA1C≥13%	1.02(0.56 to	3.82(2.01 to	1.49(0.85 to	1.53(0.82 to	1.96(0.83 to	2.10(0.57	1.11(0.58 to	1.05(0.54 to	2.51(1.80 to			
	1.85)	7.31)**	2.61)	2.82)	4.64)	to 7.67)	2.14)	2.01)	7.83)			

Data is odd ration (95% CI); *P<0.05; **P<0.01

Hierarchical regression analysis results showed that the R^2 was 0.019 after the first-block control variable was included in step 1. The R^2 changed from 0.019–0.048 after inclusion of the second-block variable in the equation in step 2. After inclusion of the third-block variable, the R^2 value increased to 0.069, which implied that the different cutoff values of HbA_{1c} was a remarkable predictor of the prevalence of dyslipidemia (P < 0.05). Compared with 7≤HbA1c<9%, subject with 9%≤HbA1c<11% and HbA1c≥13% were more likely to have dyslipidemia (OR=1.43 95%CI: 1.07-1.92; OR=2.10 95%CI: 1.12-3.94) (Table 5).

Table 5. Hierarchical regression analysis of dyslipidemia

Variable	**Model 1**		**Model 2**		**Model 3**	
Independent variable	OR	95% CI	OR	95% CI	OR	95% CI
Age (years)	0.98	(0.97 to 0.99) **	0.98	(0.97 to 0.99) **	0.98	(0.97 to 0.99) **
Gender (male vs. female)	0.84	(0.66 to 1.06)	0.86	(0.68 to 1.09)	0.86	(0.68 to 1.10)
BMI						
BMI<24kg/m^2			Ref.		Ref.	
24≤BMI<28kg/m^2			1.85	(1.45 to 2.38) **	1.93	(1.50 to 2.49) **
BMI≥28kg/m^2			1.57	(1.05 to 2.34) *	1.63	(1.09 to 2.43) *
Duration of DM (years)			0.99	(0.97 to 1.02)	0.99	(0.97 to 1.02)
Cardiovascular and cerebrovascular disease						
None			Ref.		Ref.	
History of CVD			1.24	(0.78 to 1.96)	1.25	(0.79 to 1.20)
History of stroke			1.95	(0.92 to 4.15)	2.08	(0.97 to 4.44)
FBG (mmol/l)					1.03	(0.99 to 1.08)

level of HbA_{1c}				
7≤HbA1C<9%			Ref.	
9%≤HbA_{1C}<11%			1.43	(1.07 to 1.92)*
11%≤HbA1C<13%			1.35	(0.90 to 2.01)
HbA1C≥13%			2.10	(1.12 to 3.94)*
p value	<0.01	<0.01		<0.01
R^2	0.019	0.048		0.069

*P<0.05; **P<0.01

4. Discussion

To our knowledge, this is the first study to describe the relationship between impaired glycaemic control as defined by 4 different cutoff values of HbA1c and prevalence of dyslipidemia. Using these data, we were able to identify the 9%≤HbA1c<11% and HbA1c≥13% in which the prevalence of dyslipidemia was significantly higher than 7≤HbA1c<9%.

In our study the prevalence of dyslipidemia was 55.2% in poor glycemic control of T2DM patients. A recently study conducted in Indonesia revealed that 80.8% of patients suffered from dyslipidemia in poor glycemic control group (HbA_{1c}>7) [15], which was much higher than our study. The levels of TC and TG in our study were lower than the study conducted by A Hussain et al. [16] in T2DM with HbA1c>7. As compared to a another study by Artha IMJR et al. [17] involving 56 poor glycemic control patients (HbA1c>7), the level of TG in our study was higher, and the level of TG was similar. Although the level of lipid profile in these studies was inconsistency, diabetic patients with poor and worse glycemic control had significantly higher levels of TC, TG, LDL-C and low level of HDL-C than group with good glycemic control [18,19]. One of the causes is the decreased level of insulin with poor glycemic control. The insulin level is related to the synthesis, secretion and activity of lipoprotein lipase (LPL), which is the main enzyme responsible for the hydrolysis of TG. Other study has shown that long-term hyperglycemia increases the supply of raw materials for liver synthesis of TG and promotes the liver's ability to release TG, leading to higher levels of TG and TC [20].

It is worth noting that the prevalence of high TC and TG increased significantly with level of HbA1c. However, the prevalence of low HDL-C increased at first and then declined along with

increasing HbA1c, with the lowest prevalence being observed among the 11%≤HbA1c<13% group. A similar trend of lipid distribution was found in the China lipid study, with highest prevalence of low HDL-C among the HbA1c 8% group [11].

Age is strongly associated with dyslipidemia. Many studies have reported that the prevalence of dyslipidemia increased with age [21,22]. In our study, the OR for the dyslipidemia significantly decreased with age. It was not difficult to find patients with low value of HbA1c were older than high value of HbA1c (58.07±9.73 vs.52.78±14.34 year). Age is protective factor for dyslipidemia in T2DM with poor glycemic control.

A significant finding of this study was 9%≤HbA1c<11% and HbA1c≥13% were the risk factors for the prevalence of dyslipidemia. We did not find that HbA1c at 11-13% increased prevalence of dyslipidemia among T2DM with poor glycemic control compared with 7%≤HbA1c<9%. Some data have indicated that the prevalence of dyslipidemia has increased dramatically in diabetes with poor glycemic control [16,23]. Recent studies suggested that HbA1c was positively correlated with high blood lipid and it can be as an indicator of dyslipidemia in the adults of Afghani [23] and Pakistan [24] patients. Another study focusing on the poorly-controlled T2DM patients (HbA1c>7%) found that small, dense HDL-C particles in patients was affected by the level of glycemic control [25] . However, there is paucity of data on which specific HbA1c cutoffs is most relevant with the extent of dyslipidemia. Mechanisms underlying HbA1c cutoff values related trend of prevalence in dyslipidemia are not completely clear. Possible explanations may be due to interrelationship between carbohydrate metabolism and lipid metabolism [26]. T2DM was characterized by the defect of islet function, and insulin resistance is a primary defect in T2DM. Several studies revealed that insulin had impact on the liver apolipoprotein production and regulated the related enzymatic and protein activity of lipid metabolism, which leaded to dyslipidemia in diabetes mellitus [27].

It is worth noting that the prevalence of dyslipidemia increased significantly with advancing BMI. The DYSIS Belgian study also indicated that obese participants were more susceptible to have high TG than slim ones [28]. It is well known that atherogenic dyslipidemia, involving hypertriglyceridemia and low HDL, is a key component of excess CVD risk in insulin-resistant states, and notably in T2DM. One study indicated that obese subjects were more susceptible to predispose to cardiovascular health risks than slim individuals [29]. There was a U-shaped

relationship between BMI and the mortality of CVD and patients whose BMI was greater than 25kg/m^2 had an increased risk of cardiovascular death [30]. Our study confirmed that patients with 28≤BMI <24 kg/m^2 had a twice risk of dyslipidemia than BMI＜24 kg/m^2.

This study also has several limitations. Because it is based on a cross-sectional design, it is difficult to assess any temporal risk factors for dyslipidemia. Due to limited information and lack of data on lifestyle such as dietary patterns, physical activity and so on, we can't analyze their contribution to dyslipidemia. Moreover, the lack of data about medication use is an important limitation of the study.

4. Conclusions

In this study, the prevalence of dyslipidemia with poor glycemic control in type 2 diabetes was high. T2DM patients with 9%≤HbA1C<11% and HbA1C≥13% tended to have moderate and severe dyslipidemia compared with 7%≤HbA1C<9%.

Funding

This research was supported by "Huxin Fund" project of Jiangsu Key Laboratory of Zoonotic Diseases (NO.HX2005).

Conflicts of Interest

The authors declare that they have no competing interests.

Author Contributions

En Takashi and Kitayama Akio contributed to the conception and design of the study. Huiwen Xu and Xiaodan Yuan contributed to the collection data of the study. Yan Zou and Shuang Qiu contributed to the analysis and interpretation of the data. Liu lin and Huiwen Xu drafted the manuscript. All of the authors have read and approved the final manuscript.

References

[1] Beckman, J.A, Creager, M.A. & Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 287(19): 2570-2581. https://doi.org/10.1001/jama.287.19.2570 (2002)

[2] Haffner, S.M, Lehto, S., Ronnemaa, T., Pyorala, K. & Laakso, M. Mortality from coronary heart disease in subjects with type 2 diabetes and in non diabetic subjects with and without prior

myocardial infarction. *N Engl J Med* 339: 229–234. https://doi.org/10.1056/NEJM199807233390404 (1998)

[3] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853 (1998;).

[4] Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R., & Neil, H. A. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 359 (15):1577–1589. https://doi.org/10.1056/NEJMoa0806470 (2008;)

[5] Khaw, K. T. *et al*. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of european prospective investigation of cancer and nutrition (EPIC-Norfolk). *BMJ*. 322(7277):15-18. https://doi.org/10.1136/bmj.322.7277.15 (2001)

[6] Rohlfing, C. L., *et al*. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. Diabetes care, 25(2), 275 – 278. https://doi.org/10.2337/diacare.25.2.275 (2002)

[7] Leiter, L. A. *et al*. Persistent lipid abnormalities in statin-treated patients with diabetes mellitus in Europe and Canada: results of the Dyslipidemia International Study. *Diabet Med* 28 (11):1343-1351. https://doi.org/10.1111/j.1464-5491.2011.03360.x (2011)

[8] Yang, W. *et al*. Prevalence of diabetes among men and women in China. *N Engl J Med* 362 (12):1090-1010. https://doi.org/10.1056/NEJMoa0908292 (2010)

[9] Bjornstad, P., & Eckel, R. H Pathogenesis of Lipid Disorders in Insulin Resistance: a Brief Review. *Curr Diab Rep*, 18(12), 127. https://doi.org/10.1007/s11892-018-1101-6 (2018)

[10] Lebovitz, H. E. et al. Fasting plasma triglycerides predict the glycaemic response to treatment of type 2 diabetes by gastric electrical stimulation. A novel lipotoxicity paradigm. *Diabetic Med* 30(6):687–693. https://doi.org/10.1111/dme.12132 (2013)

[11] Ji, L, *et al*. Hyperglycemia and duration of diabetes as risk factors for abnormal lipids: a cross sectional survey of 19,757 patients with type 2 diabetes in China. *J Endocrinol Invest* 37(9):843-52. https://doi.org/10.1007/s40618-014-0115-4 (2014)

[12] Ahmad Khan H. Clinical significance of HbA1c as a marker of circulating lipids in male and female type 2 diabetic patients. *Acta Diabetol* 44(4):193-200. https://doi.org/10.1007/s00592-007-0003-x (2007)

[13] Khan, H. A., Sobki, S. H., & Khan, S. A. Association between glycaemic control and serum lipids profile in type 2 diabetic patients: HbA1c predicts dyslipidaemia. Clin Exp Med 7(1):24-29. https://doi.org/10.1007/s10238-007-0121-3 (2007)

[14] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 285(19):2486-2497. https://doi.org/10.1001/jama.285.19.2486 (2001)

[15] Sunjaya, A. P., & Sunjaya, A. F. Glycated hemoglobin targets and glycemic control: Link with lipid, uric acid and kidney profile. *Diabetes Metab Syndr* 12(5):743-748. https://doi.org/10.1016/j.dsx.2018.04.039 (2018)

[16] Hussain, A., Ali, I., Ijaz, M., & Rahim, A. Correlation between hemoglobin A1c and serum lipid profile in Afghani patients with type 2 diabetes: hemoglobin A1c prognosticates dyslipidemia. *Ther Adv Endocrinol Metab* 2017;8(4):51-57. https://doi.org/10.1177/2042018817692296 (2017)

[17] Artha, I., *et al*. High level of individual lipid profile and lipid ratio as a predictive marker of poor glycemic control in type-2 diabetes mellitus. *Vasc Health Risk Manag* 15: 149-157. https://doi.org/10.2147/VHRM.S209830 (2019)

[18] Mullugeta, Y., Chawla, R., Kebede, T., & Worku, Y. Dyslipidemia associated with poor glycemic control in type 2 diabetes mellitus and the protective effect of metformin supplementation. *Indian J Clin Biochem* 27(4):363-369. https://doi.org/10.1007/s12291-012-0225-8 (2012)

[19] K, P., Kunikullaya U, K., & Goturu, J. Glycosylated Haemoglobin (HbA1c) - A Marker of Circulating Lipids in Type 2 Diabetic Patients. *J Clin Diagn Res* 8(2):20-23. https://doi.org/10.7860/JCDR/2014/7742.3996 (2014)

[20] Dickson-Humphries, T., Bottenberg, B., & Kuntz, S. Lipoprotein abnormalities in patients with type 2 diabetes and metabolic syndrome. *JAAPA* 26(7): 13-18 https://doi.org/10.1097/01.jaa.0000431506.00627 (2013)

[21] Li, Z., Yang, R., Xu, G., & Xia, T. Serum lipid concentrations and prevalence of dyslipidemia in a large professional population in Beijing. *Clin Chem* 51(1):144-150. https://doi.org/10.1373/clinchem.2004.038646 (2005)

[22] Bayram, F. *et al*. Prevalence of dyslipidemia and associated risk factors in Turkish adults. *J Clin Lipidol* 8(2):206-216. https://doi.org/10.1016/j.jacl.2013.12.011 (2014)

[23] Shahwan, M. J., Jairoun, A. A., Farajallah, A., & Shanabli, S. Prevalence of dyslipidemia and factors affecting lipid profile in patients with type 2 diabetes. *Diabetes Metab Syndr* 13(4):2387-2392. https://doi.org/10.1016/j.dsx.2019.06.009 (2019)

[24] Sarfraz, M., Sajid, S., & Ashraf, M. A. Prevalence and pattern of dyslipidemia in hyperglycemic patients and its associated factors among Pakistani population. *Saudi J Biol Sci*. 23(6):761-766. https://doi.org/10.1016/j.sjbs.2016.03.001 (2016)

[25] Gomez Rosso, L. *et al*. Poor glycemic control in type 2 diabetes enhances functional and compositional alterations of small, dense HDL3c. *Biochim Biophys Acta Mol Cell Biol Lipids*. 1862(2):188-195. https://doi.org/10.1016/j.bbalip.2016.10.014 (2017)

[26] Abou-Seif, M. A., & Youssef, A. A. Evaluation of some biochemical changes in diabetic patients. *Clin Chim Acta* 346(2):161-170.https://doi.org/10.1016/j.cccn.2004.03.030 (2004)

[27] Brunham, L. R., Kruit, J. K., Verchere, C. B., & Hayden, M. R. Cholesterol in islet dysfunction and type 2 diabetes. *J Clin Invest* 118(2):403-408. https://doi.org/10.1172/JCI33296 (2008)

[28]Devroey, D., Radermecker, R. P., Van der Schueren, B. J., Torbeyns, B., & Jaken, R. J. Prevalence of persistent lipid abnormalities in statin-treated patients: Belgian results of the Dyslipidaemia International Study (DYSIS). *Int J Clin Pract* 68(2):180-187. https://doi.org/10.1111/ijcp.12315 (2014)

[29]Alkerwi, A., Pagny, S., Lair, M. L., Delagardelle, C., & Beissel, J. Level of unawareness and management of diabetes, hypertension, and dyslipidemia among adults in Luxembourg: findings from ORISCAV-LUX study. *PLoS One* 2013;8(3):e57920. https://doi.org/10.1371/journal.pone.0057920 (2013)

[30] Chen, Y. *et al*. Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium. *BMJ* 347: f5446. https://doi.org/10.1136/bmj.f5446 (2013)

Figures

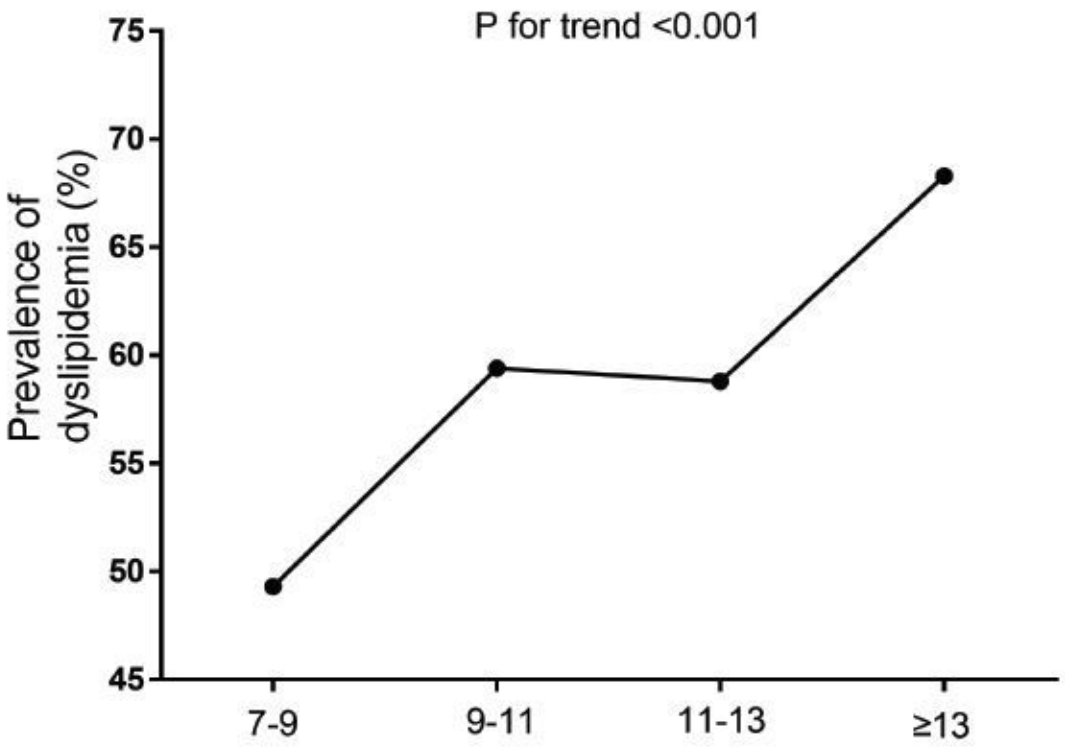

Figure 1

Prevalance of dyslipidemia by category of HbA1c

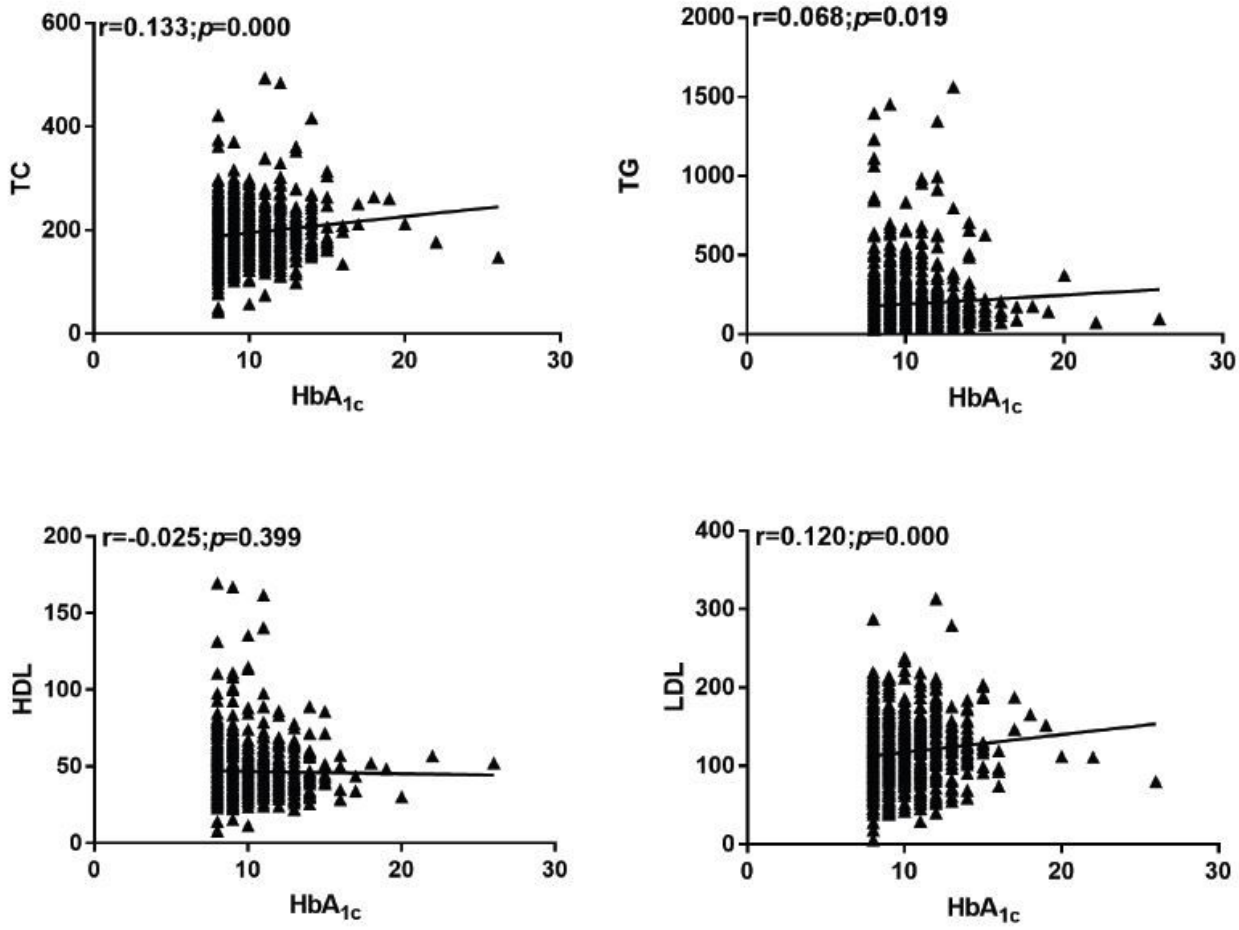

Figure 2

Corrleation between TC,TG,HDL, LDL and HbA1c in type 2 patients with poor glycemic control