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Lipid status and linear relationship between total cholesterol and triglycerides in glycogen storage disease type I

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Abstract. – OBJECTIVE: Glycogen storage disease type Ia (GSDIa) is a glucose metabolic disorder. GSDIa patients are characterized by hypoglycemia, hepatomegaly, hyperlipidemia, and hyperlactacidemia. This retrospective study aimed to review the lipid status, explore lipid treatment targets, and assess preferable lipid-lowering drugs.

PATIENTS AND METHODS: Clinical data on GSDIa patients' characteristics were collected. Most patients were followed-up once a year. Diet control and raw cornstarch treatment were used to maintain normal blood glucose and lipid levels. Some patients were given lipid-lowering drugs. We compared the lipid levels before and after each treatment.

RESULTS: A total of 163 GSDIa patients were enrolled in this study. After treatment with raw cornstarch, the total triglycerides (TG) level has significantly decreased by 30±50% (8.37±7.23 to 5.39±5.29 mmol/L, $p<0.001$). There was no change in the total cholesterol (TC) level. Fifteen patients regularly took atorvastatin, and 15 took fibrates for more than one year. The therapeutic effect of atorvastatin was better than fibrates. The TC was positively correlated with TG after treatment, resulting in the following linear equation: TG=1.63×TC-2.86. Using this equation and Chinese children's normal TC level of 5.18 mmol/L, we aimed to maintain the patients at TG < 5.58 mmol/L.

CONCLUSIONS: Patients with GSDIa have significant abnormalities in lipid metabolism. Because the complications of hyperlipidemia are caused mainly by TC, thereby, by maintaining it at a normal level, we could set a TG target by the linear equation that allowed a certain degree of hypertriglyceridemia. This study found that the therapeutic effect of atorvastatin was better than fibrates.

Key Words:
Glycogen storage disease type Ia, Lipid metabolism, Atorvastatin.

Abbreviations

ASCVD, Arteriosclerotic cardiovascular disease; G6Pase, Glucose-6-phosphatase; GSDIa, Glycogen storage disease type Ia; HDL-C, High density lipoprotein-cholesterol; LDL-C, Low density lipoprotein-cholesterol; NCEP, National Cholesterol Education Program; TC, Total cholesterol; TG, Total triglycerides; VLDL, Very-low-density lipoprotein.

Introduction

Glycogen storage disease type I (GSDI, OMIM 232200) is a glucose metabolic disorder caused by glucose-6-phosphatase (G6Pase) deficiency. The incidence of GSDI is about 1/100,000[1], of which GSDIa accounts for 80%[2]. Because the last step of glycogenolysis and gluconeogenesis is affected, GSDI patients present with severe hypoglycemia, hyperlipidemia, hyperuricemia, hyperlactacidemia, and growth and development retardation[3]. The main therapeutic approaches are dietary control and raw cornstarch treatment.

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Raw cornstarch can maintain a normal glucose production rate, thus avoiding hypoglycemia and reducing secondary metabolic complications.

G6Pase is mainly located in the liver. It is composed of the glucose-6-phosphatase catalytic subunit (G6PC) and glucose-6-phosphate transporter (G6PT)[4]. G6PT transports G6P to the endoplasmic reticulum, where G6PC hydrolyzes it into glucose and phosphate[5,6]. Mutations in G6PC are the cause of GSDIa.

Untreated GSDIa patients usually show significant lipid metabolism disorders, which include elevated total triglycerides (TG) and total cholesterol (TC), and decreased low- and high-density lipoprotein- cholesterol (LDL-C and HDL-C, respectively)[7]. Although hyperlipidemia in GSDIa patients is prevalent and severe, studies on the lipid status in GSDIa patients are extremely rare. Most published studies are case reports, in which treatment status and genotyping are ignored. Currently, there are neither recommended lipid-lowering drugs nor definite treatment targets for GSDIa patients.

To date, this is the most extensive retrospective single-center study of lipid metabolism in GSDIa patients. In this study, we reviewed the status of lipid metabolism in GSDIa patients, aiming to reveal their lipid status, explore the lipid treatment targets, and identify preferable lipid-lowering drugs.

Patients and Methods

Patients

The study includes 163 GSDIa patients, referred to the Pediatric Department of Peking Union Medical College Hospital between July 1985 and April 2017. Most patients were followed-up once a year. All patients presented with development retardation, hepatomegaly, fasting hypoglycemia, hyperlipidemia, hyperlactacidemia, and elevated liver enzymes. According to the GSD medical guidelines published by the American College of Medical Genetics and Genomics in 2014[7], the diagnosis was confirmed when a mutation was found in the G6PC gene. Since analyzing G6Pase activity by liver biopsy is a traumatic operation, we did it only when the clinical diagnosis was not clear. Dietary control and raw cornstarch treatment were used to maintain normal blood glucose and lipid levels. The guidelines of raw cornstarch dosing are 1.6 g per kilogram of ideal body weight every 3-4 hours for young children, and 1.7-2.5 g per kg every 4-5 hours (sometimes six hours) for older children, adolescents, and adults. Some patients with severe hyperlipidemia were treated with lipid-lowering drugs. Fifteen of the study participants regularly took atorvastatin (Lipitor, Loughbeg, Ringaskiddy, Co. Cork, Ireland), and 15 took fibrates for more than one year. The fibrates include fenofibrate (Lipanthyl, Rue des Pres Potets, Fontaine les Dijon, France) or gemfibrozil (Jiezhi, Suzhou, Jiangsu, China). They were divided into an atorvastatin group and a fibrates group. According to the diagnostic criteria of hyperlipidemia by the American National Cholesterol Education Program (NCEP) Children's Experts Group[8], the data were divided based on five age groups: 0-4 y, 5-9 y, 10-14 y, 15-19 y, and over 20 y.

The participants' mean values in each age group were used as the outcome measure. The change in the patients' lipid value is relatively fast and becomes stable several months after treatment initiation. Therefore, each patient was counted as one case in each age group. This can be considered as reflecting on the level of the last one or two years. We focused on the control level of each age group, so the data of any patient in the different age groups are independent of each other.

General Examination

Trained examiners used standardized protocols. All participants were instructed to fast for five hours before venipuncture. Compliance was determined by an interview on the morning of the examination. Laboratory evaluations for all patients included TC, TG, HDL-C, and LDL-C.

Diagnostic Criteria of Hyperlipidemia

The blood lipid levels in our study were grouped by age, as indicated above. The normal range of TC, TG, HDL-C, and LDL-C in children was based on American NCEP Children's Expert Group guidelines[8] and adjusted for age and sex in our study (Table I). For patients older than 18 years, the diagnostic criteria followed the 2016 Chinese Guideline for the Management of Dyslipidemia in Adults[9].

Statistical Analysis

Data were divided into five groups by age: 0-4, 5-9, 10-14, 15-19 and greater than 20 years. The data were analyzed with SPSS version 24.0 (SPSS Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation ($\bar{x}$ ±

Table I. The normal range of TC, TG, LDL-C and HDL-C in patients of all ages in this study.

Sex		TC [mg/dl (mmol/L)]					TG [mg/dl (mmol/L)]				
Age (year-old)		0-4	5-9	10-14	15-19	> 20	0-4	5-9	10-14	15-19	> 20
Hyperlipidemia	M	> 209 (5.41)	> 209 (5.41)	> 208 (5.39)	> 203 (5.26)	≥ 240 (6.20)	> 102 (1.15)	> 104 (1.18)	> 129 (1.46)	> 152 (1.72)	≥ 200 (2.30)
	F	> 206 (5.34)	> 211 (5.46)	> 207 (5.36)	> 209 (5.41)		> 11 5 (1.30)	> 108 (1.22)	> 135 (1.53)	> 136 (1.54)	
Sex		**LDL-C [mg/dl (mmol/L)]**					**HDL-C [mg/dl (mmol/L)]**				
Age (year-old)		5-9	10-14	15-19	> 20	5-9	10-14	15-19	> 20		
Hyperlipidemia	M	> 133 (3.44)	> 136 (3.52)	> 134 (3.47)	≥ 160 (4.10)	< 39 (1.01)	< 38 (0.98)	< 31 (0.80)	< 40 (1.0)		
	F	> 144 (3.73)	> 140 (3.63)	> 141 (3.65)		< 37 (0.96)	< 38 (0.98)	< 36 (0.93)			

The normal range of TC, TG, LDL-C and HDL-C in children was based on American NCEP Children's Expert Group guidelines. For patients older than 18 years, the diagnostic criteria followed the 2016 Chinese Guideline for the Management of Dyslipidemia in Adults.

s). Medians and interquartile ranges (M±Q) were used to describe non-normally distributed quantitative variables. To avoid bias, each subject was weighted equally within each age group. The lipid levels of each patient in each age group were the average of multiple follow-ups data.

Since the normal distribution was not confirmed, the lipids' levels before and after treatment were analyzed by Wilcoxon signed-rank test. We analyzed the correlations between TC and TG by Pearson's correlation coefficient. The linear regression equation was computed by the SPSS program. Differences with a p-value <0.05 were considered statistically significant.

Results

General Characteristics

A total of 163 GSDIa patients from 160 families were included in this study. These included 98 males and 65 females, with a male to female ratio of 1:0.66. All patients were from China. The age at first hospital visit was between four months and 38 years (8.1± 7.2 years). The follow-up time was 0-29 years (5.7± 5.4 years). The age at last follow-up visit was between four months and 43 years (13.8± 8.2 years). All patients were treated with raw cornstarch. Lipid levels were assessed 773 times, of which the assessment was performed after the raw cornstarch treatment 624 times. TG level was within the normal range in only 13 assessments performed in ten patients (2%). Patients with severe hyperlipidemia were treated with lipid-lowering drugs. Fifteen patients regularly took atorvastatin, and 15 took fibrates (fenofibrate or gemfibrozil) for more than one year. Lipid levels were assessed 109 times after treatment by atorvastatin or fibrates.

Lipid Levels in GSDIa Patients Before Treatment With Lipid-Lowering Drugs

The lipid levels in GSDIa patients before and after the raw cornstarch treatment, including TC, TG, HDL-C, and LDL-C and the normal percentage, are presented in Table II.

Lipid Levels in GSDIa Patients After Treatment With Lipid-Lowering Drugs

Fifteen patients were treated with fibrates for 1-3 years, and 15 were treated with atorvastatin for 1-6 years. TC, TG, HDL-C, and LDL-C levels after treatment with fibrates or atorvastatin are presented in Table III.

Comparison of Lipid Levels Between Treatments

Comparison of Lipid Levels Before and After Raw Cornstarch Treatment

The comparison of lipid levels before and after raw cornstarch treatment is shown in Table IV. The TG level has decreased by 30±50% (8.37± 7.23 to 5.39± 5.29 mmol/L. p<0.001) after treatment. There was no change in the TC level.

Comparison of Lipid Levels Before and After Lipid-Lowering Drugs Treatment

The comparison of lipid levels in patients before and after treatment with fibrates are shown in Table V, and those after treatment with ator-

Table II. The lipid levels in GSDIa patients before and after the raw cornstarch treatment.

Lipid levels in GSDIa patients before the raw cornstarch treatment				
	M ± Q (mmol/L)	Range (mmol/L)	Normal percentage	N
TC	5.78 ± 3.07	2.78~18.77	41.7%	133
TG	8.32 ± 8.51	1.81~73.96	1.4%	142
HDL-C	0.92 ± 0.59	0.29~5.39	42.4%	92
LDL-C	2.42 ± 1.36	0.68~6.26	88.9%	92
Lipid levels in GSDIa patients after the raw cornstarch treatment				
TC	5.84 ± 2.18	1.71~22.79	41.9%	289
TG	5.83 ± 5.63	0.57~ 34.32	2.0%	293
HDL-C	1.03 ± 0.30	0.24~2.28	57.7%	253
LDL-C	3.19 ± 1.14	0.80~7.32	68%	253

N represents the number of assessment times.

Table III. The lipid levels in GSDIa patients after treatment with fibrates or atorvastatin.

	Fibrates M ± Q (mmol/L)	Atorvastatin M ± Q (mmol/L)	N
TC	6.27 ± 2.64	4.87 ± 1.41	15
TG	6.33 ± 6.04	5.05 ± 5.50	15
HDL-C	0.87 ± 0.55	1.01 ± 0.27	9
LDL-C	3.54 ± 2.48	2.69 ± 1.03	9

N represents the number of patients.

Table IV. The comparison of lipid levels before and after raw cornstarch treatment (M ± Q).

Index	Number of patients	Before M ± Q (mmol/L)	After M ± Q (mmol/L)	Decrease ratio (Before minus After)	*p*-value
TC	97	5.92 ± 2.98	5.82 ± 1.97	0 ± 30%	0.39
TG	101	8.37 ± 7.23	5.39 ± 5.29	30 ± 50 %	< 0.01
HDL-C	65	0.96 ± 0.63	1.10 ± 0.34	-6 ± 49%	0.32
LDL-C	64	2.40 ± 1.36	2.96 ± 1.38	-21 ± 54%	< 0.01

The lipid levels before and after raw cornstarch treatment were non-normal distribution, and the Wilcoxon signed-rank test was performed.

Table V. The comparison of lipid levels in patients before and after treatment with fibrates (M ± Q).

Index	Number of patients	Before M ± Q (mmol/L)	After M ± Q (mmol/L)	Decrease ratio (Before minus After)	*p*-value
TC	15	6.66 ± 3.65	6.27 ± 2.64	-6 ± 48%	0.36
TG	15	7.96 ± 6.60	6.33 ± 6.04	21 ± 101%	0.41
HDL-C	8	0.95 ± 0.23	0.87 ± 0.55	10 ± 17%	0.14
LDL-C	8	2.39 ± 1.66	3.54v ± 2.48	-30 ± 83%	0.07

The lipid levels before and after fibrates treatment were non-normal distribution, and the Wilcoxon signed-rank test was performed.

vastatin are shown in Table VI. TC and TG levels have slightly but insignificantly decreased after the fibrates treatment. TC in 5/15 patients (33.3%) and TG in 1/15 patients (6.7%) have returned to the normal level after treatment with fibrates.

After treatment with atorvastatin, TC, TG, and LDL-C have significantly improved (p<0.05). The TC level in 11/15 patients (73.3%) returned to normal. The TG level did not return to normal in any of the patients.

Linear Correlation Analysis and Linear Regression Equation Between TC and TG

In our study, a total of 452 data of TC and TG levels were collected in patients with dietary control combined with raw cornstarch treatment. Pearson's correlation coefficient test was performed on the TC and TG levels. The TC and TG were positively correlated, with r = 0.514 (p<0.001).

Table VI. The comparison of lipid levels in patients before and after treatment with atorvastatin(M ± Q).

Index	Number of patients	Before M ± Q (mmol/L)	After M ± Q (mmol/L)	Decrease ratio (Before minus After)	*p*-value
TC	15	6.96 ± 1.61	4.87 ±1.41	35 ± 26 %	< 0.01
TG	15	8.80 ± 5.37	5.05 ± 5.50	33 ± 48 %	0.02
HDL-C	9	0.96 ± 0.27	1.01 ± 0.27	3 ± 26 %	0.89
LDL-C	9	3.42 ± 1.42	2.69 ± 1.03	40 ± 32 %	0.01

The lipid levels before and after atorvastatin treatment were non-normal distribution, and the Wilcoxon signed-rank test was performed.

A linear regression equation was established for TC and TG, and the regression standard error S_Y was recorded. The 95% predicted interval for TC level was represented by $Y \pm t_{0.05/2,\ (452-2)} S_Y$. Based on this, the regression equation was Y=1.63X-2.86, where Y represented the TG level, and X represented the TC level in mmol/L. The F-regression test was performed on the overall regression coefficient, resulting in $p<0.01$; the decision coefficient was $R^2=0.264$, and the standard error $S_Y=4.48$ (Figure 1).

Patients' Prognosis Following Treatment

Acute pancreatitis, derived from severe hypertriglyceridemia, was diagnosed in one patient (male, 29y), with TG maintained at 10.37- 19.78 mmol/L for five years. Pancreatitis occurred despite treatment with fibrates.

None of these patients was diagnosed with coronary heart disease, peripheral artery disease, or atherosclerotic aortic disease that are known to be associated with mild to moderately elevated TC and TG levels.

Gene Mutation Test Results

At least one mutation was found in the G6PC gene in all 163 patients. Forty-two mutation types were detected. These included 28 missenses, nine deletions, four nonsenses, and one splicing. The most common mutations were p.Leu216Leu (58.2%) and p.Arg83His (10%).

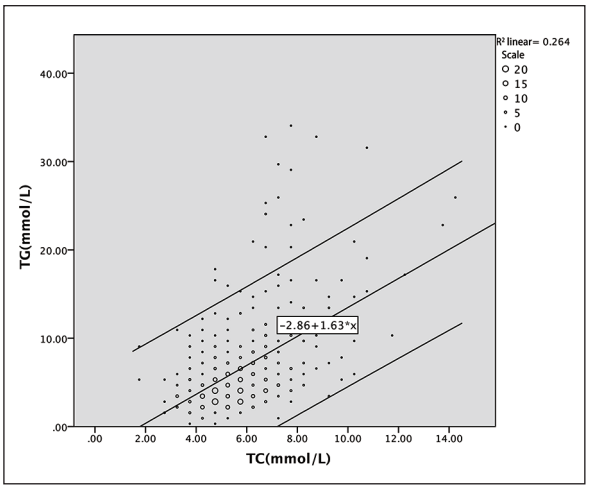

Figure 1. TC and TG linear relationship (n= 452, R^2= 0.264, $p<0.01$). The size of the scale represents the number of cases.

Discussion

GSDIa is a hereditary disease caused by G6Pase catalytic subunit mutation. The typical manifestation of this metabolic disorder includes hypoglycemia, hyperlipemia, hyperuricemia, and hyperlactacidemia. Blood lipid characteristics of GSDIa are high TC, TG, and LDL-C, and low HDL-C. Hyperlipidemia in GSDIa patients is caused mainly by increased levels of acetyl-CoA and very-low-density lipoprotein (VLDL)[10]. Hyperlipemia is an important risk factor of cardiovascular and cerebrovascular diseases.

Previous studies[1,7] lack large epidemiological data on lipid levels in patients with GSDIa. Furthermore, there is no large-scale study on lipid levels after using lipid-lowering drugs in GSDIa patients.

Lipid Levels in GSDIa Patients Before the Intervention

The TC and TG levels in normal newborns are 1.7 mmol/L and 0.4 mmol/L, respectively. They both increase gradually after birth[11]. The normal values of lipid levels vary with age. The normal range values of TC, TG, HDL-C, and LDL-C used in this study were based on the American NCEP Children's Expert Group report[8].

The mean level of TC in our study was 5.78±3.07 mmol/L in 133 GSDIa patients, with 58.3% of them having hypercholesteremia. The mean level of TG was 8.32±8.51 mmol/L in 142 GSDIa patients, with 98.6% of them having hypertriglyceridemia.

The incidence of hyperlipidemia is high in GSDIa patients. A previous study on 62 GSDI patients (53 GSDIa and nine GSDIb) found TC and TG mean levels of 6.18± 2.47 mmol/L and 11.17± 9.85 mmol/L, respectively, before treatment[12]. Another study, on 11 GSDIa patients, found TC and TG levels to range between 4.31-6.89 mmol/L and 16.26-69.09 mmol/L, respectively. However, the incidence of hyperlipemia was not reported in this study[13].

Thus, the level of hyperlipemia before treatment in our study is similar to that previously reported. The incidence of hypertriglyceridemia is significantly higher than that of hypercholesteremia.

Lipid Levels in GSDIa Patients After Raw Cornstarch Treatment

Despite raw cornstarch treatment in our study, 58.1% had hypercholesterolemia, and 98% had hypertriglyceridemia. In the European Study

on Glycogen Storage Disease Type I (ESGSDI), 41.3% of 233 GSDIa patients had hypercholesterolemia, and 72.7% had hypertriglyceridemia[2]. Two other investigations, on 37 and 41 GSDIa patients, respectively, found the incidence of hypercholesterolemia range between 76 and 81.6 %, and the incidence of hypertriglyceridemia range between 85.3 and 100 %[14,15]. As in our study, the incidence of hypertriglyceridemia was higher than that of hypercholesterolemia.

In a previous study, TC and TG had significantly decreased after raw cornstarch treatment in 62 GSDI patients (including 53 GSDIa patients)[12]. TC had decreased from 6.18±2.47 mmol/L to 5.61± 1.84 mmol/L (p= 0.02) and TG had decreased from 11.17±9.85 mmol/L to 6.81±5.97 mmol/L (p= 0.01). In another report[16] on 19 GSDI patients treated with nocturnal gastric tube infusion since they were one year old, lipid levels decreased significantly but did not return to the normal level.

In our study, after treatment with raw cornstarch, the TG level had significantly decreased by 30 ± 50 % (8.37±7.23 to 5.39±5.29 mmol/L, p<0.05), while the TC level did not change. Like these previous researches, we found that the TG level could be decreased significantly by raw cornstarch treatment.

Comparison of Lipid Levels After Treatment With Lipid-Lowering Drugs

The lipid-lowering drugs used in this study were fibrates (fenofibrate and gemfibrozil) and atorvastatin. A previous study[17] showed a normal secretion of VLDL but decreased VLDL degradation rate in two GSDIa patients. This might reflect a decrease in lipoprotein lipase activity. In these two patients, TG had decreased by 50 % following treatment with fibrates.

It has been showed that dyslipidemia in GSDIa patients was characterized by an increase in VLDL level and a decrease in LDL-receptor metabolism. Furthermore, statins were shown to have a strong effect on lipid-lowering treatment in multiple studies, mainly on lowering VLDL remnants through the uptake of LDL receptors. Thus, lipid levels could be substantially decreased by statins[18].

In this study, lipid metabolism analysis was done in 30 GSDIa patients. The levels of TC and TG had improved after fibrates treatment, but changes did not reach the statistical significance level. TC and TG levels, however, had significantly improved following atorvastatin treatment. TC had decreased back to a normal level in 11/15 patients (73.3%). It was suggested that lipid metabolism could be improved following treatment with atorvastatin. We found that the therapeutic effect of atorvastatin was better than that of fibrates. TC could achieve a normal level in most patients following dietary control and treatment with raw cornstarch and atorvastatin.

The Linear Regression Equation Between TC and TG, and Blood Lipid Control Target

It was previously reported[19] that there was a correlation between TC and TG. A multiple linear regression equation for TC and TG had been established for some diseases[20]. Even though hyperlipidemia is prevalent among GSDIa patients, there is neither widely accepted diagnostic criteria nor realistic lipid control target for this patient group. The evidence of cardiovascular complications is rare, possibly due to a lack of long-term follow-up data. However, it is well established that hyperlipidemia is associated with an increased incidence of arteriosclerotic cardiovascular disease (ASCVD). The evidence of complications might accumulate over time. Future clinical trials might demonstrate a link between blood lipid levels and cardiovascular changes among GSDIa patients. Considering these side effects are mostly fatal or disabling, realistic treatment objectives and schedules are in dire need to prevent ASCVD from happening.

The cholesterol is the key factor leading to ASCVD. When the goal of maintaining blood lipids within the normal range is hard to achieve, a second-best solution would be normal TC to avert ASCVD and acute pancreatitis. The correlation between TG and TC could help fulfill this purpose. Pearson's correlation coefficient suggested a moderate positive correlation between TC and TG. A regression equation was established for this relationship, TG= 1.63 × TC- 2.86.

The American College of Medical Genetics and Genomics GSDI guidelines recommended maintaining a normal blood lipids range to reduce the risk of ASCVD and pancreatitis[7]. However, previous scholars[14] shown that hyperlipidemia in GSDI patients could be improved but not resolved. The incidence rate of hypertriglyceridemia is obviously higher than that of hypercholesteremia, but the incidence of pancreatitis, the main complication of hypertriglyceridemia, is low. So, it is important to decrease the level of TC as a key factor leading to ASCVD[21]. After treat-

ment with lipid-lowering drugs, TC decreased to normal in most patients, but it was difficult to decrease TG to a normal level.

Because the complications of hyperlipidemia are caused mainly by TC, its level should be the main target of lipid control in GSD patients. If TC is maintained at a normal level, TG does not have to be maintained normal and a certain degree of hypertriglyceridemia could be allowed. Thereby, as long as the TC remains normal, we could set a TG target while allowing a certain degree of hypertriglyceridemia. The lower bound of the normal TC level in Chinese children (5.18 mmol/L[22]) was inserted into the established regression equation, resulting in TG=5.58 mmol/L (95% confidence interval, -3.28 to 14.37 mmol/L). We, therefore, aimed to keep the TG level below 5.58 mmol/L. When this was achieved, a normal TC level could be maintained with no need for a further increase in lipid-lowering drug dosage.

If TC could be maintained at a normal level, the TG level derived from this regression equation could be used as a reference during clinical treatment. The blood lipid levels in the NCEP standard are grouped by age[8]. If we insert the normal values of TC into the regression equation, we could get the respective acceptable hypertriglyceridemia levels for the different age groups.

Moreover, this is a retrospective study. A long follow-ups time is needed to observe differences in atherosclerosis incidence between patients with TG> 5.58 mmol/L and those with TG≤ 5.58 mmol/L. Long-term treatment research is needed to confirm the feasibility of this control target.

Conclusions

Patients with GSDIa have significant abnormalities in lipid metabolism. We demonstrated a linear correlation between TC and TG, described as TG=1.63×TC-2.86. Because hyperlipidemia complications are caused mainly by TC, its level should be the main lipid control target in GSDIa patients. We suggest that if the TC can be maintained at a normal level, a certain degree of hypertriglyceridemia could be tolerated. We also suggest that the aim should be to keep TG level under 5.58 mmol/L after treatment, with no need for a further increase in lipid-lowering drug dosage to maintain TC at a normal level. We showed that lipid metabolism could be improved by atorvastatin, with the therapeutic effect of atorvastatin being better than fibrates.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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