Clinical Efficacy of Low Carbohydrate Diet (LCD) with Investigation of Lipid Metabolism

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Abstract

Carbohydrate and lipid metabolism were studied. Subjects were 121 patients with type 2 diabetes mellitus (T2DM), and provided Calorie restriction (CR) on day 1,2 and Low Carbohydrate Diet (LCD) from 3 to 14 days. Basal biomarkers, daily glucose profile on day 2, 4, and lipids including remnant-like particle cholesterol (RLP-C) were measured, subjects were classified into 4 groups due to average glucose with mean HbA1c 6.3%, 6.9%, 7.9%, 9.2%, respectively. Average glucose from day 2 to 4 in each group was significantly decreased. M value considerably decreased in group 2, 3, 4, indicating useful M value. Correlations were investigated among glucose, HbA1c, urinary C-Peptide and M value.

As for lipids, Triglyceride from day 2 to 14 decreased considerably. RLP-C levels showed significant correlation with Triglyceride, LDL-C, atherogenic index (T-C − HDL / HDL) and TG/HDL value. These results would suggest that RLP-C may be involved in the development of arteriosclerosis of T2DM, and may have the role of further research direction in the future.

In current study, our results would become the fundamental data for the further development of LCD therapy in various counties and districts, and suggest the research direction for patients with T2DM from the combined point of glucose and lipid metabolism in the future.

Keywords: Remnant-like particle cholesterol; Low carbohydrate diet; Morbus value; Type 2 diabetes mellitus; Lipid metabolism

Abbreviations

LCD: Low-Carbohydrate Diet; CR: Calorie Restriction; T2DM: Type 2 Diabetes Mellitus; RLP-C: Remnant-Like Particle Cholesterol; M value: Morbus value; IRI: Immuno-Reative Insulin; CPR: C-peptide Immunoreactivity; HOMA-R: Homeostasis Model Assessment-Insulin Resistance; HOMA-β: Homeostasis Model Assessment of β-Cell Function; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol

Introduction

The discussion concerning Calorie Restriction (CR) and low carbohydrate diet (LCD) has been continued for years. Several significant reports indicating predominance of LCD were published [1-6]. Consequently, LCD has been estimated to have clinical efficacy in nutritional therapy for the patients with type 2 diabetes mellitus (T2DM) and metabolic syndrome. Authors and colleagues have lots of experience of LCD for T2DM, and reported

clinical studies [7-10]. Our recent study includes blood glucose variability in diabetic patients, using Morbus (M) value, which is one of the index of blood sugar level and mean amplitude of glycemic excursions (MAGE) [11-14].

On the other hand, lipid metabolism in metabolic syndrome has been also in discussion, and recent studies include remnant-like particle cholesterol (RLP-C) [15-18]. Combined these aspects, we investigated blood glucose variability for the M-value in diabetic patients, and lipid metabolism including RLP-C in this study.

Materials and Methods

The subjects were 121 patients with Type 2 diabetes mellitus (T2DM), which were 52 males and 69 females, with age groups

ranging between 28-84 years old, 60.8 ± 11.0 (mean ± SD) years old in average, 63 years old in the median value. They were admitted for 14-15 days, and received endocrine and metabolic evaluation with lipid analysis.

Methods included a controlled diet for the patients. On day 1 and 2, Calorie Restriction (CR) diet was provided which had 60% carbohydrates, 25% lipids and 15% protein with 1400 kcal/day. From day 3 to 14 days, Low Carbohydrate Diet (LCD) was provided, which had 12% carbohydrates, 64% lipids and 24% protein with 1400 kcal/day. This has been called super-LCD formula in our nutritional investigation for LCD [7,9,10,19].

The examination protocol was as follows: 1) basal biomarkers and daily profile of blood glucose on day 2, 2) daily profile of blood glucose on day 4, 3) several biomarkers such as triglyceride and uric acid on day 14.

Analysis method and M value

A daily profile of blood glucose was measured 7 times a day, and data were calculated for average glucose level and Morbus (M) value. According to the average glucose level, subjects were classified into 4 groups, namely, group 1,2,3,4.

Morbus (M) value has been proposed for analyzing blood glucose variability. It is a logarithmic transformation of the deviation of blood glucose from an arbitrary assigned "ideal" glucose value, with an expression of both the mean glucose value and the effect of glucose swings [11-14,20].

The formula of M value is as follows: M=MBS + MW, where MW=(maximum blood glucose – minimum glucose)/20; MBS=the mean of MBSBS; MBSBS=individual M-value for each blood glucose value calculated as (absolute value of [10 × log (blood glucose value/120)]) [3].

For the interpretation of M value, the standard range is <180, borderline is 180-320 and abnormal is >320. There were discussions concerning how many times of sampling per day is necessary. It was reported that multiple sampling and a 7-point glycemic trial per day would have yielded similar results [14,21].

Statistical analyses

In current study, data was represented as the mean ± standard deviation. For statistical analyses, correlation coefficients (Pearson) were calculated using the JMP (Version 8) statistical analysis software (JMP Japan Division of SAS Institute Japan Ltd., Minato-ku, Tokyo, Japan) and Microsoft Excel analytical tool.

Intergroup comparisons were made using the Wilcoxon rank sum test or the Bonferroni multiple comparison (Lambert method). A significance level of less than 5% obtained using a two-tailed test was considered to be statistically significant.

Ethical considerations

Current study was conducted in compliance with the ethical principles of the Declaration of Helsinki and Japan's Act on the Protection of Personal Information along with the Ministerial Ordinance on Good Clinical Practice (GCP) for Drug (Ordinance of Ministry of Health and Welfare No. 28 of March 27, 1997).

No ethical committee meeting was held. Informed consent was obtained from the subjects concerning this questionnaire. The study was registered with UMIN #R000031211.

Results

Fundamental data

Summarized data of 121 subjects were shown in **Table 1**. They were categorized for 4 groups due to the average glucose level. The mean HbA1c in each group was 6.3%, 6.9%, 7.9%, 9.2%, respectively. Blood glucose level on day 4 was significantly decreased compared with those on day 2 in each group. Triglyceride level on day 14 was significantly decreased compared with those on day 2 in each group.

Correlation for HbA1c, glucose and M value

There were significant correlation between average glucose and HbA1c **(Figure 1)**, and for the urinary C-peptide excretion between day 2 and 4 **(Figure 2)**.

Average glucose on day 2 and 4 revealed significant correlation (p<0.01), and M value on day 2 and 4 revealed significant correlation (p<0.01) **(Figure 3).**

Average glucose and M value on day 2 and 4 showed significant correlation (p<0.01) **(Figure 4)**.

Compared with both figures, average glucose and M value on day 4 decreased apparently. The change of M value in each group from day 2 to day 4 were shown in **(Figure 5)**.

Analyses among lipid biomarkers

The change of TG levels from day 2 to day 14 were shown in **Figure 6**. In response to LCD for 12 days, Triglyceride level was significantly decreased (p<0.05). The regression curve (y=0.3738x + 44.072) reveled the degree of decreased TG.

RLP-C levels showed significant correlation with Triglyceride on day 2 (p<0.01) and LDL-C on day 2(p<0.05) **(Figure 7)**.

RLP-C showed significant correlation with atherogenic index (T-C–HDL/HDL) (p<0.05), and TG/HDL value (p<0.01) **(Figure 8).**

**Table 1** Subjects classified for 4 groups due to average glucose level.

| Categorization				
group	Group 1	Group 2	Group 3	Group 4
Subjects				
number	30	30	30	31
sex (male/female)	13/17	13/17	10/20	16/15
age (y.o.)	60 (54-65)	64 (51-70)	65 (55-72)	64 (56-68)
average glucose (mg/dL)	123 (115-128)	161 (141-168)	198 (184-212)	259 (248-294)
Glucose (basal)				
HbA1c (%)	6.3 (5.9-7.1)	6.9 (6.3-7.4)	72 (7.4-9.1)	22 (8.5-10.2)
Fasting Glucose (mg/dL)	111 (102-135)	132 (118-141)	170 (151-205)	210 (186-235)
IRI (μU/mL)	7.4 (6.0-12)	7.5 (3.9-10.4)	5.3 (3.6-10.1)	5.4 (3.1-7.8)
HOMA-R	2.4 (1.3-4.0)	2.4 (1.2-3.8)	2.1 (1.3-4.3)	23 (1.5-4.2)
HOMA-β	60 (30-85)	41 (24-58)	21 (11-40)	11 (7.7-17)
Glucose (M value related)				
average glucose on day 2 (mg/dL)	123 (115-128)	161 (150-179)	198 (184-212)	259 (248-294)
average glucose on day 4 (mg/dL)	101 (97-113)	125 (112-137)	152 (143-164)	185 (166-205)
M value on day 2	8.9 (5.7 - 21.7)	42.9 (33.1 -52.0)	120 (96.8 - 151)	325 (269 - 509)
M value on day 4	8.5 (4.2 - 14.8)	5.4 (3.2 - 9.5)	14.8 (7.6 - 28.1)	60.1 (32.8 -105)
Glucose (CPR excretion in urine)				
urinary CPR on day 2 (mg/day)	67.3 (27.3-105)	56.5 (36.5-86.8)	59.4 (38.5-66.2)	74.0 (50.5-89.7)
urinary CPR on day 4 (mg/day)	56.0 (34.1-73.0)	40.8 (25.5-52.1)	43.3 (33.8-83.4)	64.0 (51.0-73.0)
Lipid Metabolism				
Triglyceride on day 2 (mg/dL)	113 (71-143)	94 (67.5-157)	96 (73.5-125)	114 (70-175)
Triglyceride on day 14 (mg/dL)	93 (59-111)	88 (61.5-99)	69 (56-89)	88 (71-113)
HDL-C on day 2 (mg/dL)	57 (49-72)	57 (48-68)	65 (58.3-76)	63 (53-89)
HDL-C on day 14 (mg/dL)	47.5 (42-68)	50 (44-62)	58 (52-74)	59 (46-70)
LDL-C on day 2 (mg/dL)	109 (97-137)	132 (102-1551)	126 (104-158)	145 (103-171)
LDL-C on day 14 (mg/dL)	120 (110-141)	138 (115-175)	137 (113-160)	155 (114-180)
RLP-C on day 2 (mg/dL)	4.4 (3.3-6.7)	4.1 (3.0-7.5)	4.8 (4.0-6.0)	4.7 (4.0-6.4)
The results were expressed by the data of median (25%- 75%).				

$$y = 0.0179x + 4.4583$$
$$R^2 = 0.4139$$
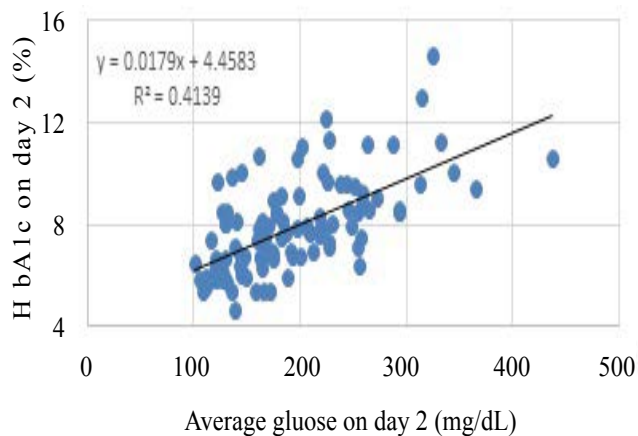
Figure 1 Correlation between average glucose and HbA1c. Both factors revealed significant correlation (p<0.01).


$$y = 0.7394x + 6.2123$$
$$R^2 = 0.7404$$
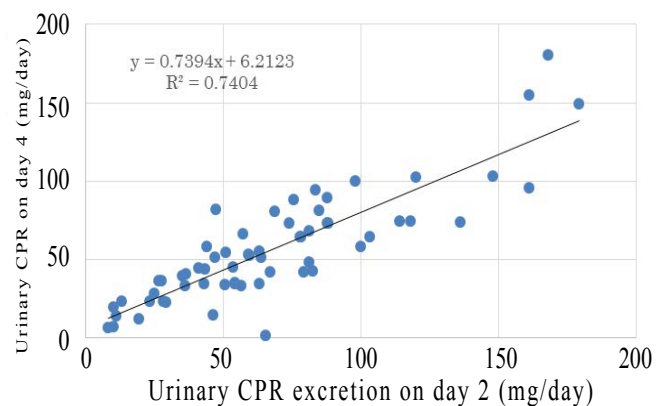
Figure 2 Correlation of urinary C-peptide excretion between day 2 and 4. CR diet was provided on day 1 and 2, and LCD was provided from day 3 to 14. Urinary C-peptide excretion was measured for 24 hours during the formula diet which is CR or LCD.
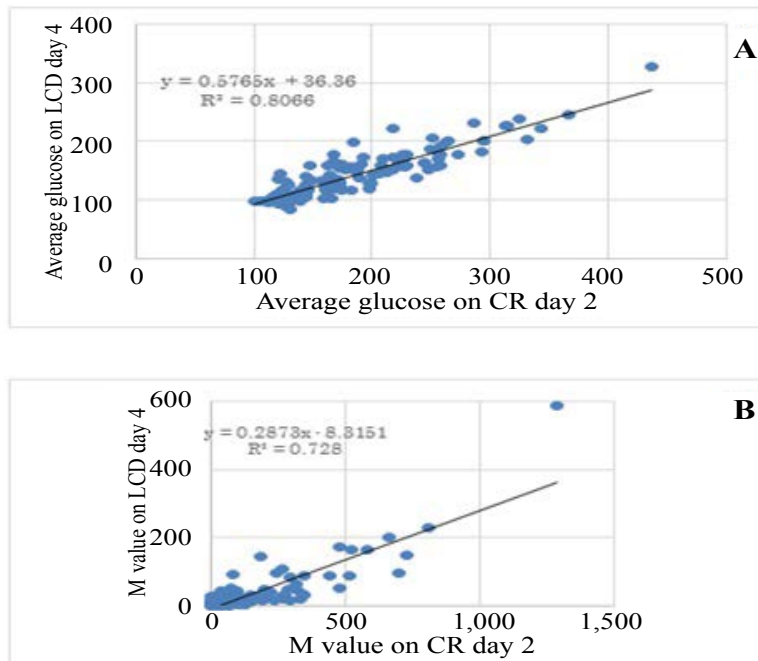
Figure 3 Comparison of average glucose and M value between CR and LCD. **A)** Average glucose on day 2 and 4 revealed significant correlation (p<0.01) and glucose level decreased according to the regression curve (y = 0.5765x + 36.36). **B)** M value on day 2 and 4 revealed significant correlation (p<0.01) and M value decreased according to the regression curve (y = 0.2873x - 8.3151).
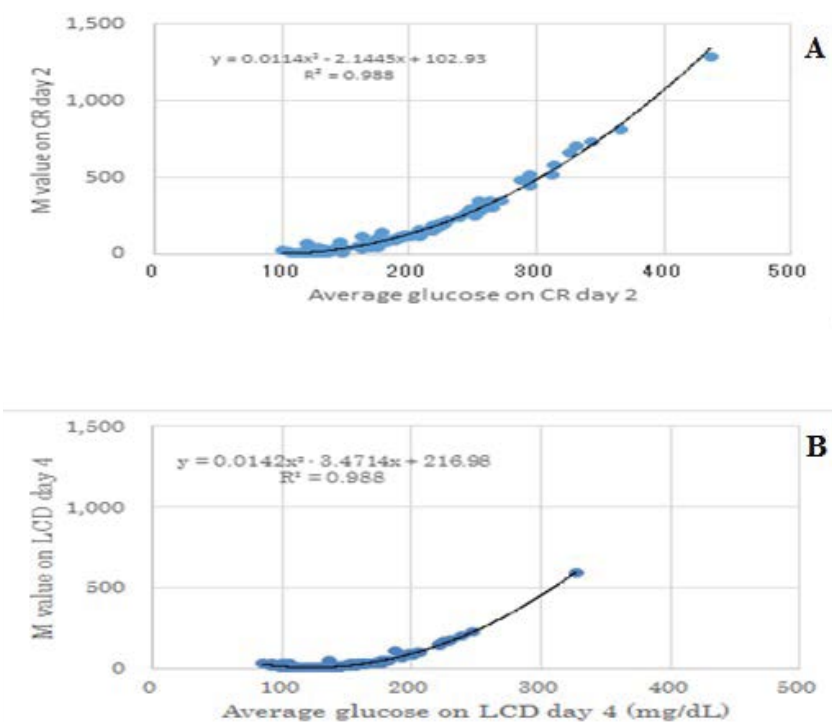

Figure 4 Correlation of average glucose and M value on CR and LCD. **A)** Average glucose and M value on day 2 revealed significant correlation (p<0.01). **B)** Similarly, both factors had significant correlation (p<0.01). Compared with both figures, average glucose and M value on day 4 decreased apparently.
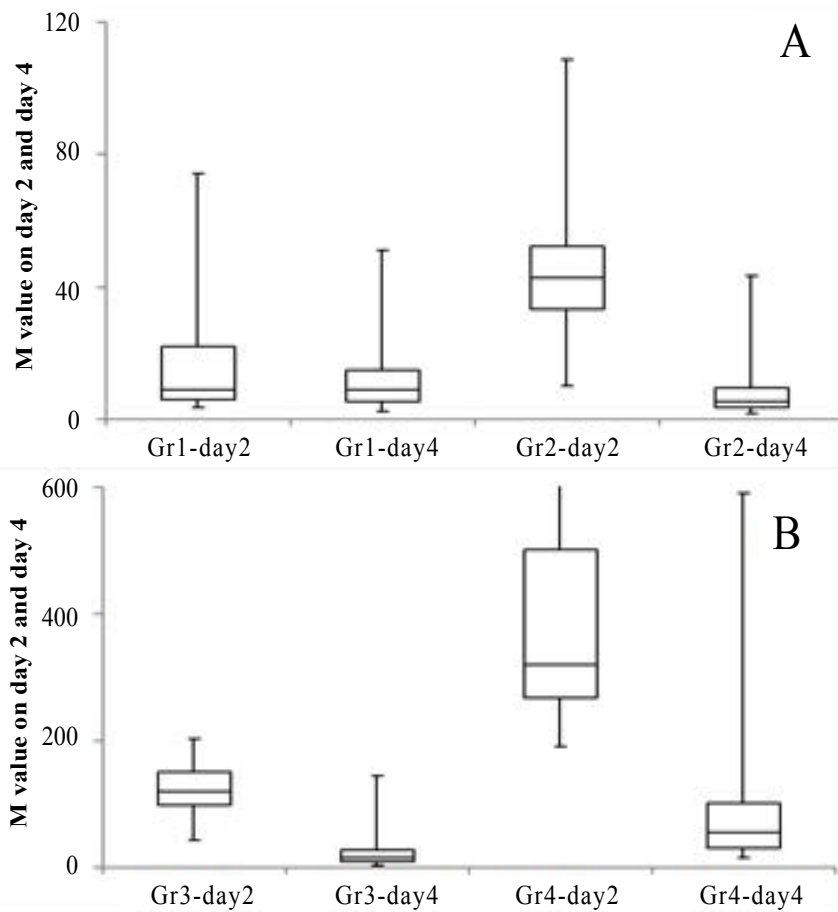
Figure 5 The change of M value in each group from day 2 to day 4. **A)** Group 1 revealed almost same median value, and group 2 revealed decreased median values. **B)** Group 3 and 4 revealed decreased median levels from day 2 to day 4. Boxplot shows 5 components, which are median. 25% quartile, 75% quartile, maximum and minimum.
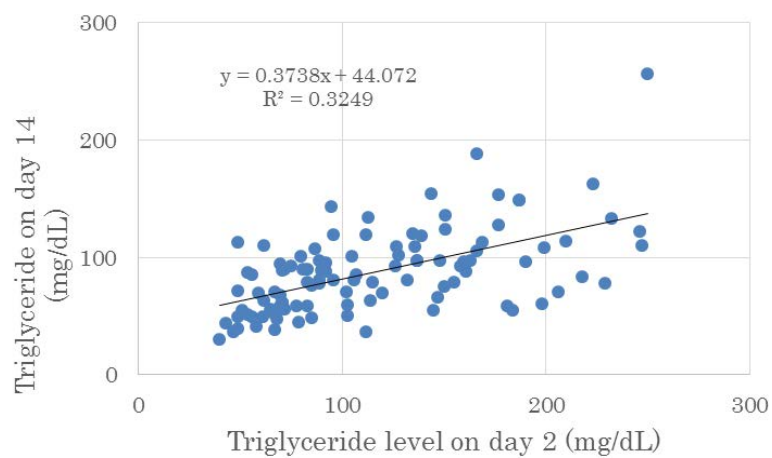
Figure 6 The change of triglyceride level from day 2 to day 14. In response to LCD for 12 days, triglyceride level was significantly decreased (p<0.05). The regression curve (y=0.3738x+44.072) reveled the degree of decreased TG.
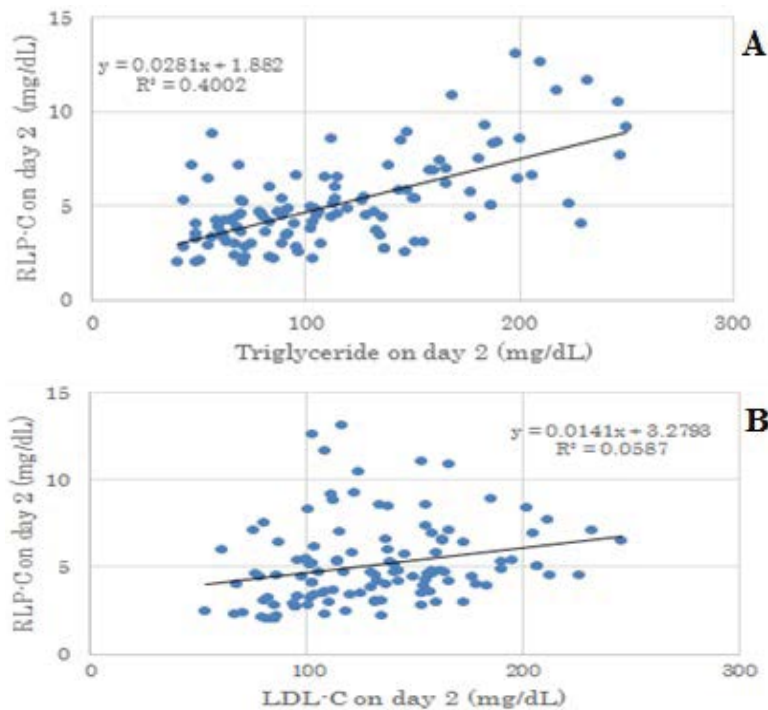
Figure 7 Correlation of RLP-C and triglyceride / LDL-C on day 2. **A)** RLP and triglyceride levels revealed significant correlation (p<0.01). **B)** RLP and LDL-C levels revealed significant correlation (p<0.05).
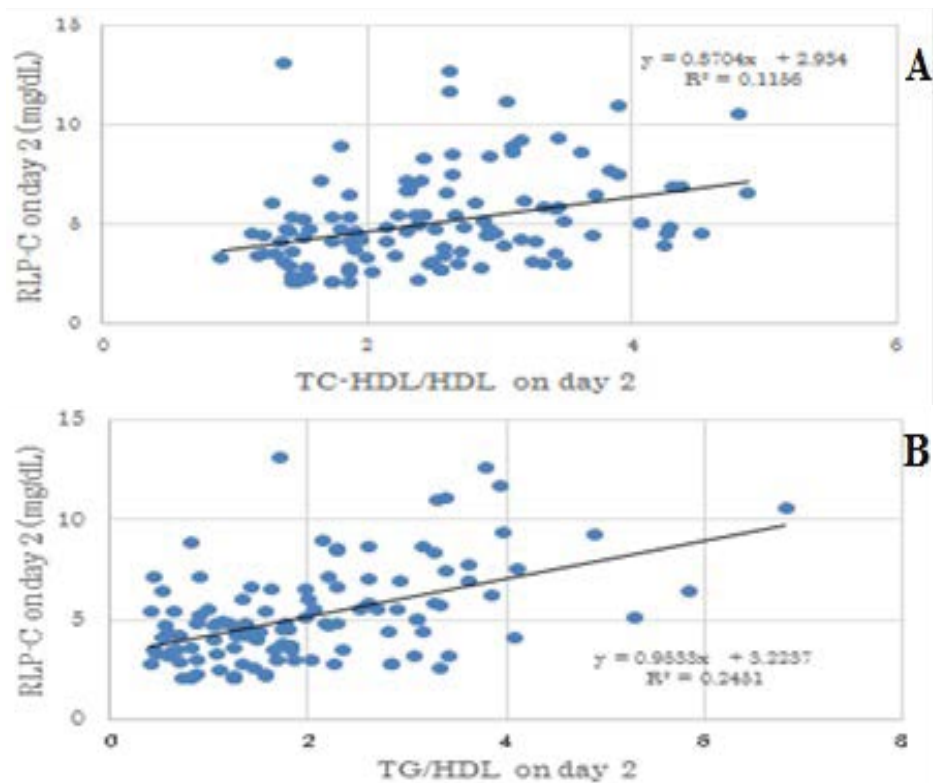
Figure 8 Correlation of RLP-C and biomarkers. **A)** Significant correlation was shown between RLP-C and atherogenic index which is calculated by T-C −HDL / HDL (p<0.05). **B)** Significant correlation was shown between RLP-C and TG/HDL value (p<0.01).

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Discussion

In north American and European countries, LCD has been more prevalent as Bernstein, Atkins and others have continued clinical research for years [1-6,22-25]. In Japan, author and colleagues have developed LCD, and investigated studies for metabolic syndrome with 2699 cases, T2DM, elevated ketone bodies and glucose variability as M value [7-10,26].

In this study, we adopted super-LCD including 12% carbohydrate, which is equivalent to VLCKD. Our formula diet contains 1400 kcal/day, which has 168 kcal of carbohydrate (1400 kcal × 0.12), and 42 g of carbohydrate per day [7,9,19] which is one of the very low-carbohydrate ketogenic diet (VLCKD) by the definitions of LCD [5].

Daily glucose profile can be estimated by MAGE and M (Morbus) values [11,12], and the latter would be more practical. There were similar results on 7 times or 20 times of sampling per day [11,13,21], showing similar result in comparison with continuous glucose monitoring (CGM) [27-30].

Average blood glucose in 4 groups decreased, indicating the short effect of LCD only for 2 days from CR to LCD. M value also significantly decreased in group 2,3 and 4. M value is characterized for its larger numerical change than that of glucose, and for better evaluation of relieving status. On contrast, M value in group 1 was not so changed from day 2 to 4, which seemed to be the characteristic point of M value. If the average blood glucose decrease from 100 mg/dl to 80 mg/dL, M value would increase because M value becomes minimum level when blood glucose is 100 mg/dL.

For only 2 days of formular LCD, there were considerable decrease of average glucose, urinary C-peptide excretion and M value. Obtained linear regression curve would become the reference data for this area of research. The decrease ratio of M value is larger than that of glucose, because M value represents both average glucose and MAGE.

Recently, the research of LCD have focused to less influence to cardiovascular risk factors, and research the relationship between glucose and lipids metabolism [31-33].

Isolation of remnant-like particles (RLPs) was performed and investigated, which are thought to be atherogenic agent [15]. RLP-C was supposed to be an independent risk factor for CVD in women, and provides significantly more information than do triglycerides [16,34]. After that, Epidemiologic studies have shown associations between RLP concentrations and atherosclerosis, cardiovascular disease (CVD), and chronic heart disease (CHD) [17,35].

Elevated RLP-C were observed in T2DM [16,34,36]. Diabetes Atherosclerosis Intervention Study (DAIS) had measured RLP-C and TG levels, which were significantly higher in diabetic CAD group than non-diabetic CAD group [37]. Furthermore, The AUCs of TG or RLP-C showed a correlation with the AUCs of plasma insulin, with the correlation with the insulin resistance index [37,38].

In metabolic syndrome, obesity and insulin resistance, ratio of triglycerides to high-density lipoprotein cholesterol (TG/HDL-C) would be high [39]. By the data from 1.35 million US individuals, median TG/HDL-C ratio was 2.2, and increasing TG/HDL-C ratios would accompany increasing levels of RLP-C, non-HDL-C and LDL density, with the highest relative increase of RLP-C and LDL-C [39].

In our study, TG/HDL-C ratio was 1.73(1.08-2.85). As to current research protocol with lipid investigation, we enrolled the patients whose triglyceride was less than 250 mg/dL, because extremely high value of triglyceride would not be adequate for statistical analyses. For future study, we will analyze those patients in the combined research of glucose and lipid metabolism.

As to correlation of RLP-C with 4 biomarkers which are TG, LDL-C, TC-HDL/HDL and TG/HDL, the linear regression curve and coefficient value could become the reference for the research of lipid metabolism.

Different dietary approaches on glycemic control has been in research, including 9 kinds of diet, namely, control, low-carbohydrate, low-fat, Mediterranean, high-protein, vegetarian, DASH, Paleo, low-glycemic index/load [40-42]. Our current study would be useful for selecting applicable method. Furthermore, interrelationship research between glucose and lipid metabolism would develop for decreasing diabetic complication in the future.

Conclusion

- By LCD nutritional therapy, average glucose and M value had considerably decreased, suggesting the efficacy of LCD and the clinical useful marker of LCD for the patients with T2DM.

- Investigation of lipid metabolism showed considerable TG decrease for LCD and the significant relationship between RLP-C and triglyceride, LDL-C, TC-HDL/HDL, TG/HDL.

- Current study would become fundamental data for the field of T2DM, LCD and research direction for glucose/lipid metabolism in the future.

Acknowledgement

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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