Glycative Stress Research

Online edition : ISSN 2188-3610
Print edition : ISSN 2188-3602
Received : August 26, 2016
Accepted : October 7, 2016
Published online : December 31, 2016

Original article

Low Carbohydrate Diet (LCD): Long and short-term effects and hyperketonemia

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Abstract

***Background*:** Discussion has continued concerning calorie restriction (CR) and low carbohydrate diet (LCD). LCD was developed by Bernstein, Atkins and others, and by our co-authors in Japan. In this study, we report and discuss long-term effects in 2,699 cases, and short-term effects and hyperketonemia in 51 cases.

***Subjects and Methods*:** Study 1 (long-term): Subjects were 2,699 cases with diabetes, metabolic syndrome, or both. Methods included continuing LCD and measuring weight reduction in six to twelve months. Study 2 (short-term): Twenty-four diabetics were compared on a CR diet (1,400 kcal/day, carbo-60%) and a super-LCD (1,400 kcal/day, carbo-12%). We recently tried insulinogenic index-carbo70 (IGI-carbo70) from glucose and immunoreactive insulin (IRI; 0, 30 min) for a meal of carbohydrates of 70 g. Study 3 (hyperketonemia): Blood ketone bodies and 3-hydroxybutylic acid (3-OHBA) were measured in 51 diabetics with super-LCDs.

***Results*:** Study 1: Weight reduction of more than 10% was observed in 25.6% of subjects, and more than 2.5% was observed in 78.8% of subjects. Study 2: Base data included HbA1c 7.7 ± 1.4 %, homeostasis model assessment (HOMA)-R 3.2 ± 1.9, and HOMA-β 44.5 ± 37.0. Responses of blood glucose to meals (0-120 min) were 156 → 236 mg/dL to CR and 116 → 141 mg/dL to LCD for ten days. Triglyceride value decreased from 143.4 ± 86.8 mg/dL to 93.9 ± 34.8 mg/dL on LCD for ten days. IGI-carbo70 showed less than 0.5 in 75% of cases. Study3: Total ketone bodies were measured in four groups, which were A (4 to 5 days), B (7 to 9 days), C (11 to 13 days), D (21 to 28 days), with an average value of 994 μmol/mL in C, 36 to 623 μmol/mL in A, B, and D. As 3-OHBA value increases from normal (<85 μmol/mL) to extremely high (3,577 μmol/mL), the ratio increases from 60% - 70% up to 90%.

***Conclusion*:** Long-term effects of LCD would be successful. Short-term effects revealed that the change from CR to LCD in only ten days caused a significant decrease of blood glucose and triglycerides. Similar to the 75 g oral glucose tolerance test (OGTT), intake of a meal with carbohydrates of 70 g would be clinically simple and useful as insulinogenic index (IGI)-carbo70. Super-LCD would increase blood ketone bodies about three fold of the standard level in four to five days. These findings would be the fundamental data in the LCD area and contribute the research of glycative changes.

***KEY WORDS*:** low carbohydrate diet (LCD), ketone bodies, 3-hydroxybutylic acid (3-OHBA), HOMA-R, HOMA-β, diabetes mellitus

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Introduction

Metabolic syndrome such as obesity and diabetes mellitus has recently increased, and Calorie Restriction (CR) and low carbohydrate diets (LCD) have been noted in medical and health fields. In Europe and the United States, Bernstein, Atkins and others [1,2] have developed LCD, which has been wide spread [3-8].

In Japan, the coauthors have successfully treated thousands of patients with obesity, metabolic syndrome and other diseases [9-12]. Ebe K first started in Japan in 1999 with many books, and Bando H developed this movement with medical presentations. We have developed a clinical study and research of LCD [13].

From our clinical experiences, we report 1) long-term effects of LCD on 2,699 cases, 2) short-term effects of LCD, and 3) hyperketonemia due to LCD. This report would contribute the pathophysiological role of ketone bodies and glucose to glycative changes in patients with diabetes mellitus and obesity.

Subjects and Methods

Study 1: Long effects of LCD

The subjects included 2,699 cases which were obese patients associated with diabetes, metabolic syndrome, or both. Methods included the treatment of a low carbohydrate diet for the patients, and we compared body weight before and after treatment; about six to twelve months at a stable weight.

Study 2: Short-term effects of LCD

Subjects included 24 patients with diabetes mellitus. Ten were male, 14 female; with an average age of 61.6 ± 9.7 years, median of 62.5 years, and a range of 40 to 78 years. They were admitted for further evaluation and treatment for 12 to 14 days, in which they had the same protocol for endocrine and metabolic examination. As for diet therapy, they were on a conventional calorie restriction (CR) from zero to two days, and a low carbohydrate diet (LCD) from three to 14 days. The former (CR) had 1,400 kcal/day, a 60 % calorie ratio from carbohydrates, with a breakfast of 450 kcal, 70 g of carbohydrates. The latter (LCD) (super LCD formula by Ebe) had 1,400 kcal/day, (breakfast 400 kcal, lunch 450 kcal, supper 550 kcal), a 12% calorie ratio from carbohydrates, with a breakfast of 400 kcal, and 12 g of carbohydrates.

1) On admission, the patients had fundamental tests including blood glucose, HbA1c, immunoreactive insulin (IRI) and triglyceride (TG) associated with calculating a homeostasis model assessment (HOMA)-R and HOMA-β, and had measured TG value on day 12.

2) Blood glucose (0, 30, 120 min.)and IRI values (0, 30 min) for breakfast on CR (day 2), and glucose values (0, 120 min) for breakfast on LCD (day 12) were investigated. We calculated the increment of IRI (0 to 30 min)/increment of glucose (0 - 30min) for insulinogenic index-carbo70 (IGI-carbo70).

3) The concentration and components of blood ketone bodies were measured at four to five days (group A), seven to nine days (group B) and 11 to 13 days (group C). These data were inserted into Study 3.

Study 3: Elevated ketone bodies on LCD

We included 51 subjects with continuing LCD treatment. Twenty-one were male, 30 female, the average age was 59.5 ± 9.6 years, median age of 61.5 years, and a range of 34 to 78 years. They had continued super-LCD meals, which include 12% of carbohydrates in calories.

As ketone bodies, 3-hydroxybutylic acid (3-OHBA, β-hydroxybutylic acid) and acetoacetic acid (AcAc, acetoacetate) values were measured. In a clinical setting, a ketone bodies usually meant the value of 3-OHBA, and its standard range of 3-OHBA was less than 85 μmol/mL. The cases were classified into four groups according to the continuing days for LCD, in which group A was for four to five days, group B was for seven to nine days, group C was for 11 to 13 days and group D was 21 to 28 days. .

Statistical analysis

Data were shown as the mean ± standard deviation. As for the analysis of two groups, a t-test and Mann-Whitney U-test were used, and the Spearman method was adopted from the correlation of ketone body study. We used JMP (Version 8) statistical analysis software (JMP Japan Division of SAS Institute Japan Ltd., Minato-ku, Tokyo, Japan) and the Microsoft Excel analytical tool with a four step method. A significance level of less than 5% was obtained using the two-tailed test and was considered to indicate a significant difference.

Ethical considerations

The present study was conducted in compliance with the ethical principles of the Declaration of Helsinki and Japan's Act on the Protection of Personal Information, and with reference to the Ministerial Ordinance on Good Clinical Practice (GCP) for Drug (Ordinance of Ministry of Health and Welfare No. 28 of March 27, 1997). No ethics committee meeting was held. We obtained the informed consent from subjects concerning this questionnaire.

Results

Study1 showed the weight reduction rate in 2,699 cases, in which 567 subjects (21.2%) had weight reduction of 2.5% to 4.9%, 854 (32.0%) reduced 5.0% to 9.9%, 683 (25.6 %) reduced 10% and more than 10% (***Fig. 1***). Thus, 2,104 subjects (78.8%) showed weight reduction of 2.5% and more than 2.5%.

Study2 showed the following data.

1) Fundamental data on admission is in ***Table 1***, and the data of HOMA-R and HOMA-β are in ***Fig. 2***, in which 18, and six cases in 24 cases, respectively, showed ranges outside of the normal ranges.

2) Blood glucose values of zero and 120 min on day two (CR) and day12 (LCD) were shown in ***Fig. 3***, in which the value of the latter was decreased from the former.

Serum levels of triglyceride (TG) were measured on day two with CR, and day 12 with LCD, and showed 143.4 ± 86.8 mg/dL, and 110.3 ± 69.3 mg/dL, respectively, with a significant difference ($p<0.05$, $n = 22$) (***Fig. 4***). These data were calculated without two cases with extremely high TG values on day two.

3) The values of blood glucose and IRI (0, 30 min) were increased in response to breakfast of CR including 70 g of carbohydrate (***Fig. 5***). Simultaneously, we have recently tried to calculate for insulinogenic index (IGI) for 70 g of carbohydrates, similar to the 75 g oral glucose tolerance test (OGTT) and the insulinogenic index (***Fig. 6***). They showed less than 0.5 in 75% of the cases.

4) Several correlations among multiple markers were shown in ***Fig. 7***. HbA1c values had a significant negative correlation with HOMA-β, and not a significant correlation with HOMA-R (***Figs. 7a, b***). IRI values had a significant negative correlation with fasting glucose, and a positive correlation with HOMA-β (***Figs. 7c, d***). IRI increments for 70 g of carbohydrates showed significant positive correlation with HOMA-β, and not a significant correlation with HOMA-R (***Figs. 7e, f***). In contrast, the IRI value in 30 minutes had a significant correlation with both HOMA-R and HOMA-β (***Figs. 7g, h***).

As for Study3, the value of blood ketone bodies (3-OHBA + AcAc) in 51 cases on LCD is shown in ***Fig. 8***. In four groups, cases with extremely high values were observed in group C, and the levels were almost same in groups A, B and D.

Fig. 9 shows the value and ratio of 3-OHBA. Its value was from normal values to 3,577 µmol/mL, and the ratio was around 60% to 70% when the values were within the standard and three fold levels (less than 85 µmol/mL and 255 µmol/mL). As 3-OHBA level increases, its ratio increases approximately up to 90%.

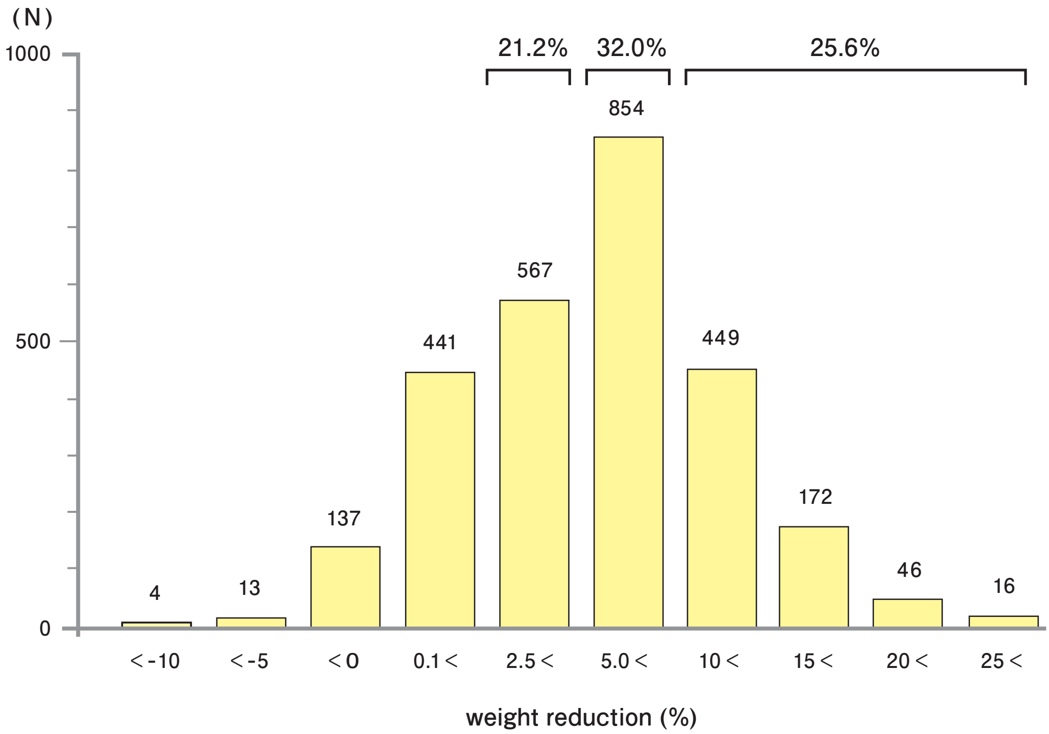

Fig. 1. **Weight reduction rate in 2,699 cases.**
Five hundred sixty-seven subjects (21.2%) had a weight reduction of 2.5% to 4.9%, 854 (32.0%) had 5.0% to 9.9%, 683 (25.6 %) had 10% and more than 10%. Thus, 2,104 subjects (78.8%) showed weight reduction of 2.5% and more than 2.5 %.

Table 1. Base data of the patients.

1) Fasting values	
Fasting glucose	156.4 ± 55.4 mg/dL
HbA1c	7.7 ± 1.4 %
IRI	8.5 ± 4.9 μU/mL
Triglyceride	143.4 ± 86.8 mg/dL
HOMA-R	3.2 ± 1.9
HOMA-β	44.5 ± 37.0
2) Meal loading (carbohydrate 70 g)	
Glucose (0 min)	161.7 ± 51.6 mg/dL
Glucose (30 min)	212.4 ± 60.9 mg/dL
Glucose (increase)	50.8 ± 25.8 mg/dL
IRI (0 min)	8.5 ± 4.9 μU/mL
IRI (30 min)	22.7 ± 15.0 μU/mL
IRI (increase)	14.2 ± 12.7 μU/mL
IGI-carbo70	0.39 ± 0.38

IRI, immunoreactive insulin; HOMA, homeostasis model assessment; IGI-carbo70, insulinogenic index-70 g of carbohydrate in calorie-restricted (CR) diet. Data are shown in mean ± standard deviation.

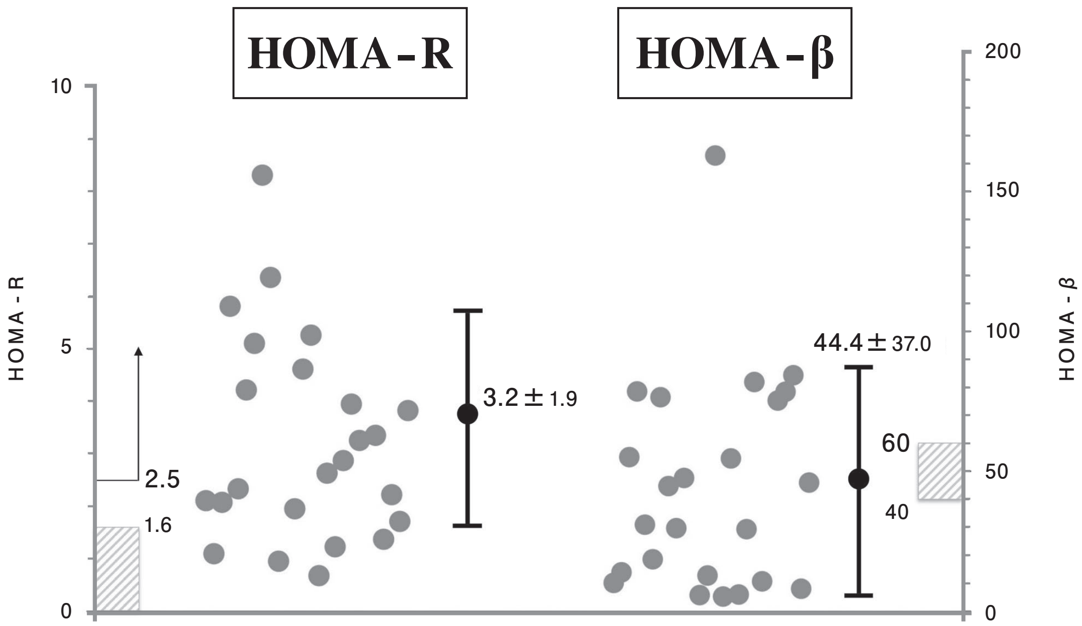

Fig. 2. **HOMA-R and HOMA-β of the patients.**
As for HOMA-R, the normal range is usually under 1.6 and a value more than 2.5 suggests the presence of insulin resistance (n = 24). As for HOMA-β, the normal range is from 40 to 60 (n = 24). Bar indicates standard deviation. HOMA, homeostasis model assessment.

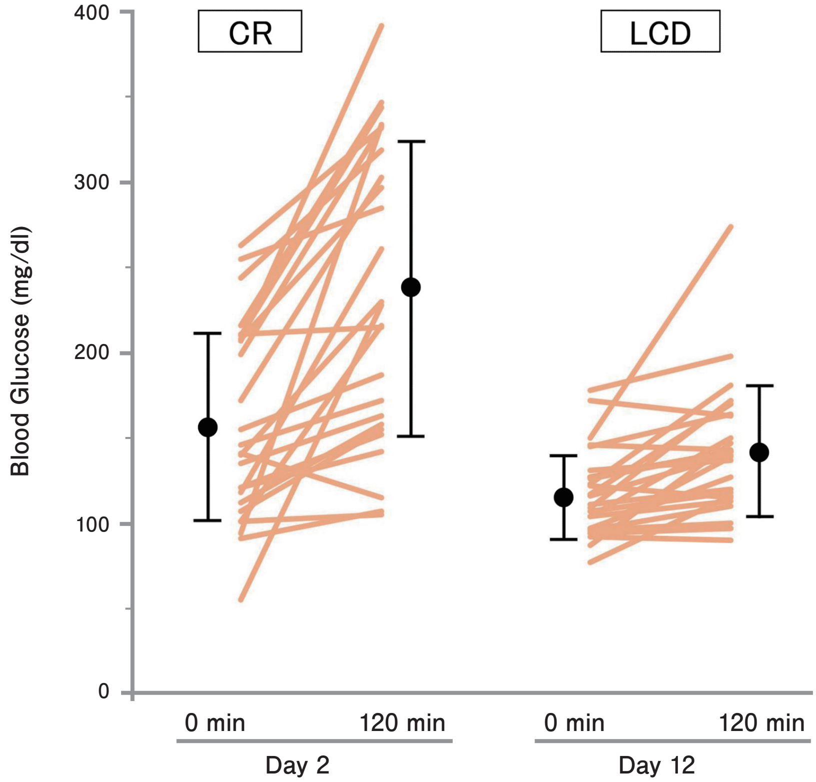

Fig. 3. **Blood glucose values after zero min and 120 min for breakfast on day two and day 12.**
The subjects were on a calorie restriction diet (CR) on days zero to two (n = 24), and on a low carbohydrate diet (LCD) on day three to13 (n = 24). Both regimen had same calories of 450 kcal. Bar indicates standard deviation.

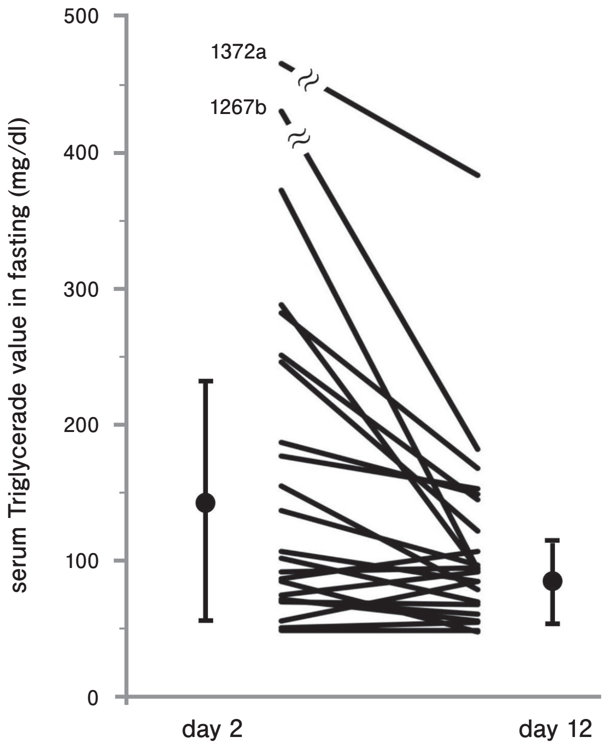

Fig. 4. **Serum triglyceride level in fasting on day two and day 12.**
The patients were on calorie-restricted diet (CR) with carbohydrate ratio 60% 1,400 kcal/day in day zero to two, and on low carbohydrate diet (LCD) with carbohydrate ratio 12%, 1,400 kcal/day on day three to13. The average value of TG decreased from 233.9 ± 324.6 mg/dL to 110.3 ± 69.3 mg/dL (mean ± SD), with a significant difference ($p < 0.01$), when two cases were included (a: n = 1,372, b: n = 1,267). When we exclude two cases, TG value decreased from 143.4 ± 86.8 mg/dL to 93.9 ± 34.8 mg/dL (mean ± SD), with significant difference (＊ : $p < 0.01$). TG, triglyceride; SD, standard deviation.

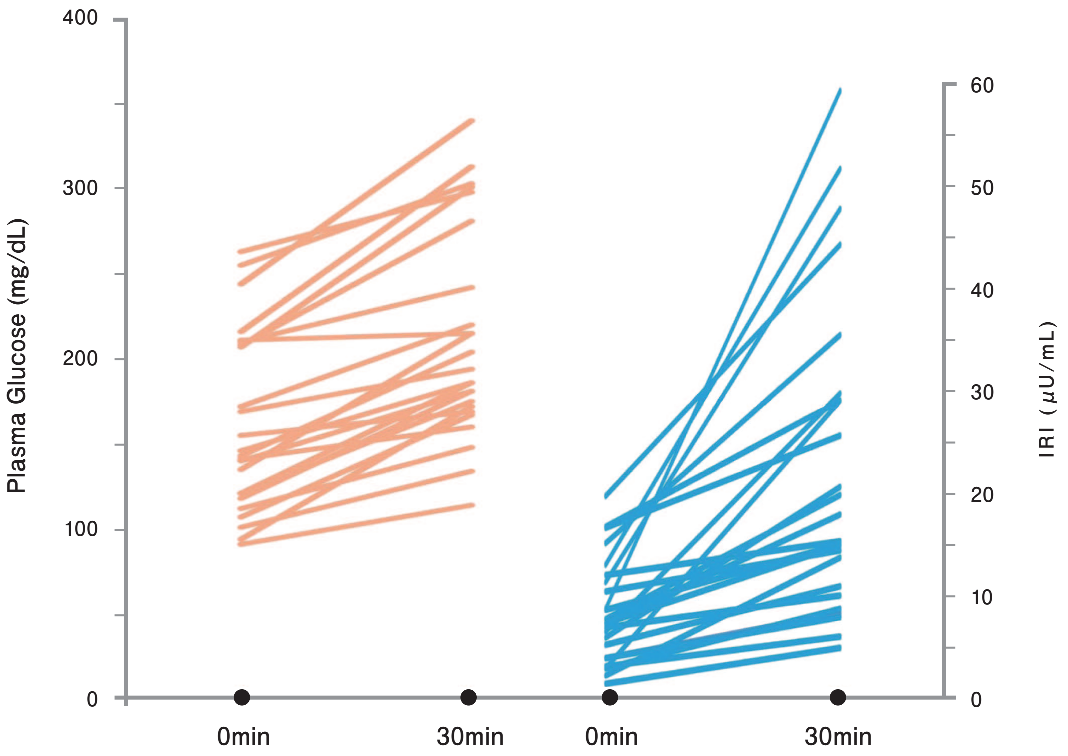

Fig. 5. **Responses of glucose against meals including 70 g of carbohydrate.**
The responses of glucose and IRI were from 161.7 ± 51.6 mg/dL to 212.4 ± 60.9 mg/dL, and from 8.5 ± 4.9 μU/mL to 22.7 ± 15.0 μU/mL, respectively (n = 22). IRI, immunoreactive insulin.

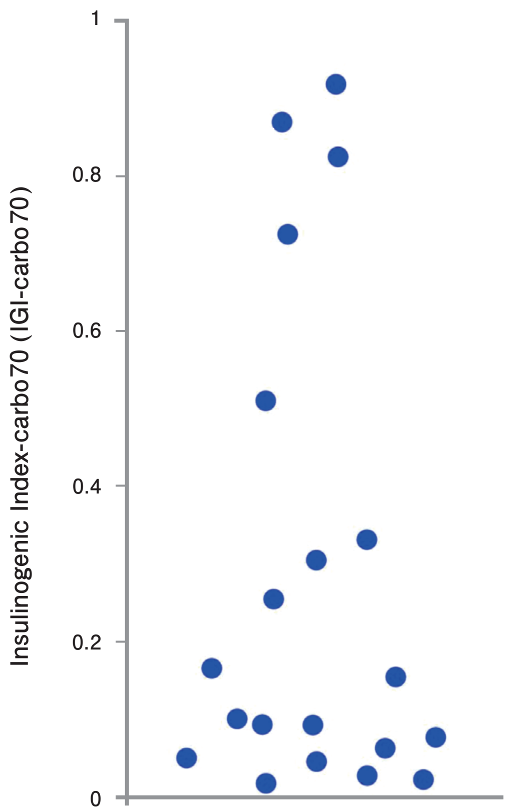

Fig. 6. **A trial for calculating insulinogenic index (IGI) for meals including 70g of carbohydrate.**
As the same concept for IGI in 75 g oral glucose tolerance tests (75g OGTT), insulinogenic index-carbo70 (IGI-carbo70) is calculated in order to speculate the ability of insulin. IGI-carbo70 was 0.39 ± 0.38 in mean ± SD, and 0.39 ± 0.08 in mean ± SEM (n = 20). OGTT, oral glucose tolerance test; SD, standard deviation; SEM, standard error mean.

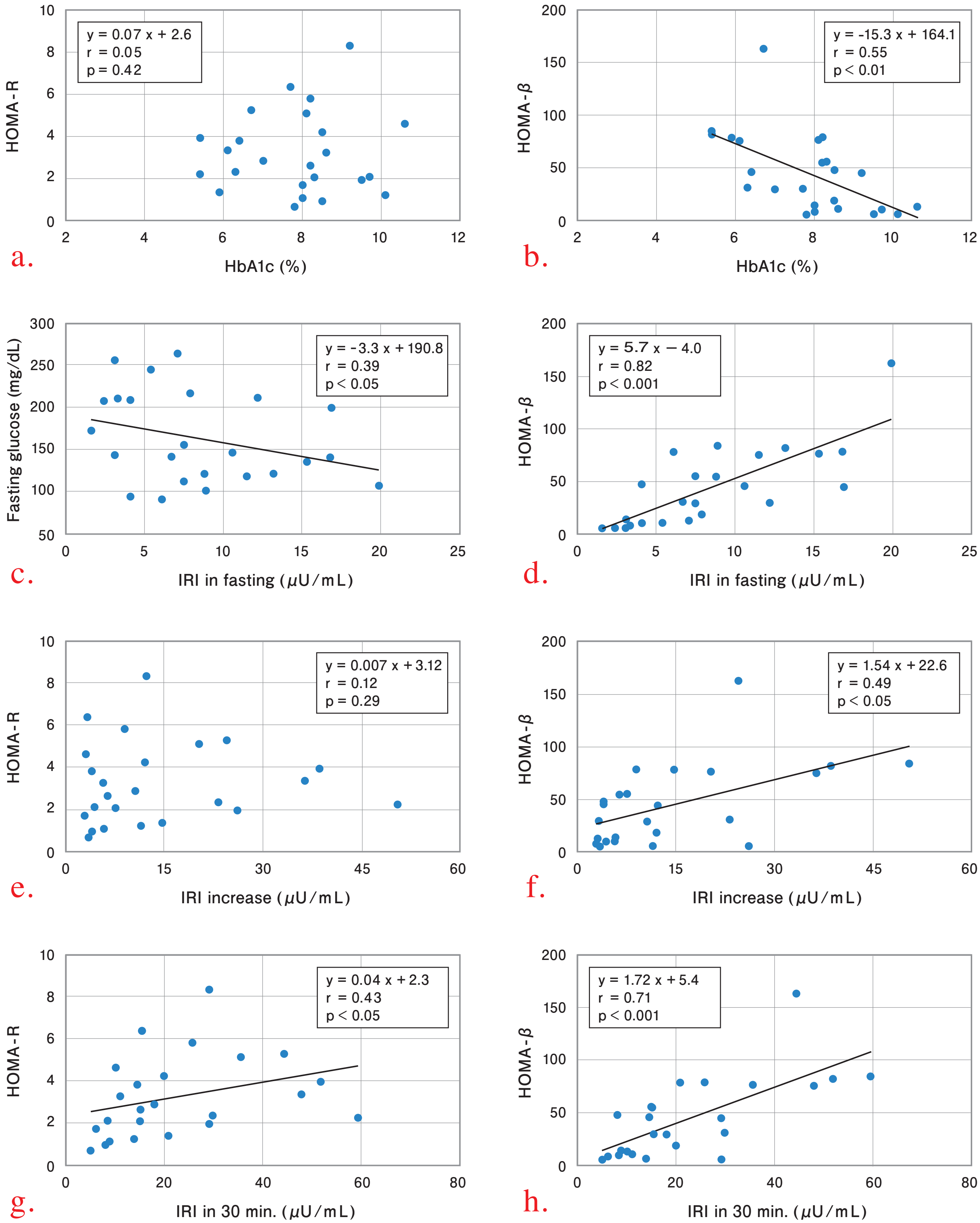

Fig. 7. **Correlation among HbA1c, HOMA-R, HOMA-β, IRI (fasting, increase, 30 min) and blood glucose (n = 24).**

a: Correlation between HbA1c and HOMA-R, not significant.
b: Correlation between HbA1c and HOMA-β, significant, $p<0.01$.
c: Correlation between fasting IRI and fasting glucose, significant, $p<0.05$.
d: Correlation between fasting IRI and HOMA-β, significant, $p<0.01$.
e: Correlation between IRI increase and HOMA-R, not significant.
f: Correlation between IRI increase and HOMA-β, significant, $p<0.05$.
g: Correlation between IRI in 30 min. and HOMA-R, significant, $p<0.05$.
h: Correlation between IRI in 30 min. and HOMA-β, significant, $p<0.001$.
HOMA, homeostasis model assessment; IRI, immunoreactive insulin.

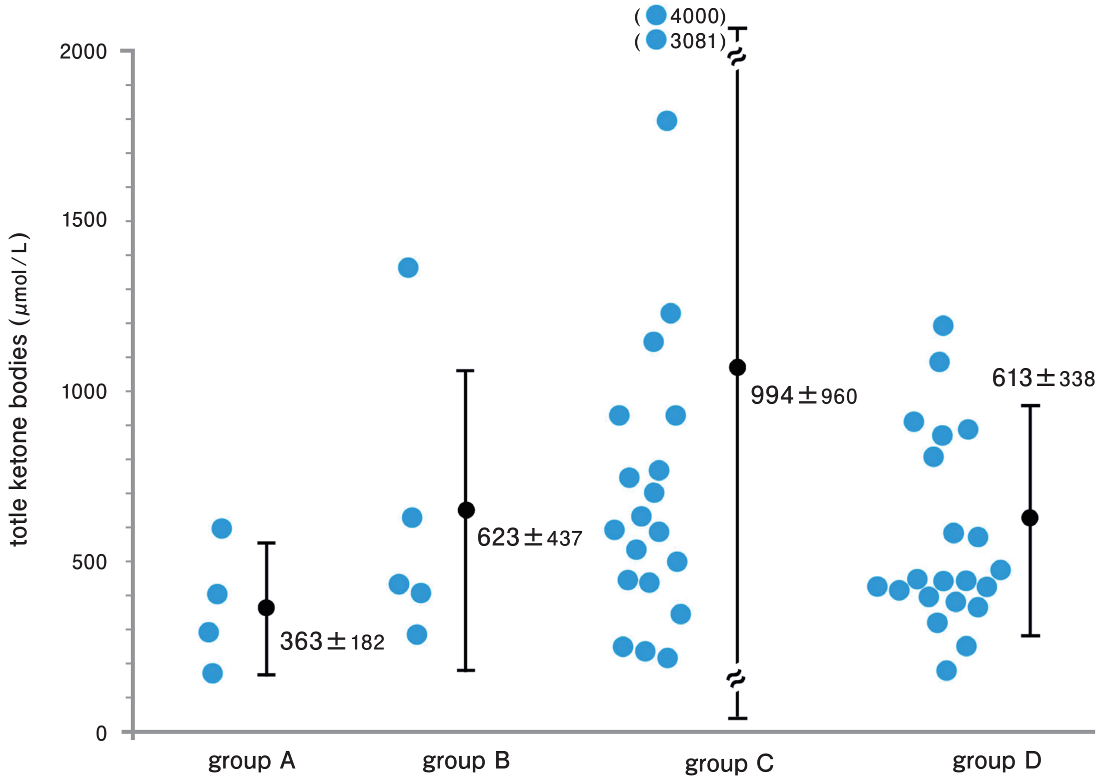

Fig. 8. **The value of blood ketone bodies in 51 cases on LCD.**
According to continuing days on LCD, we classified four groups, in which group A is four to five days (n = 4), B is seven to nine days (n = 5), C is 11 to 13 days (n = 21), D is 21 to 28 days (n = 21). Cases with extremely high value were observed in group C, and the levels were almost same in group A, B and D. LCD, low carbohydrate diet. Bar indicates standard deviation.

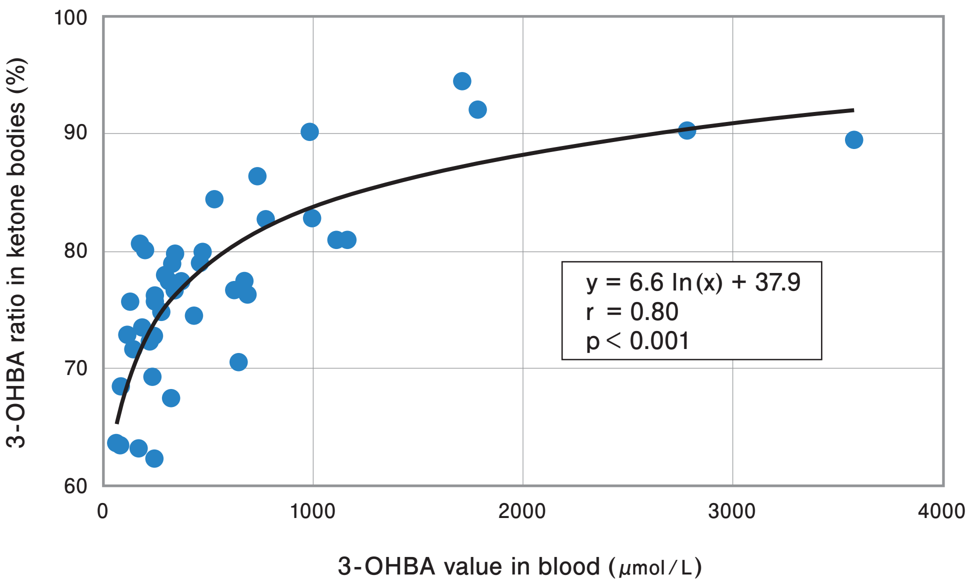

Fig. 9. **Correlation between 3-OHBA value in blood and 3-OHBA ratio in ketone bodies (n = 39).**
When 3-OHBA value is within the standard level and its three fold level (less than 85 μmol/mL and 255 μmol/mL) the 3-OHBA ratio in ketone bodies are around 60% to 70%. As 3-OHBA values increase, the ratio of 3-OHBA increases up to approximately 90%. 3-OHBA, 3-hydroxybutylic acid.

Discussion

1) Long effects of LCD

Our coworkers and we have continued to develop clinical studies and research of LCD for many years [9-13].

The degree of weight reduction seemed to be satisfactory (***Fig. 1***). Weight check-up after LCD intervention was measured when the weight became stable in six to 12 months. The diet protocol was started on super-LCD (carbohydrate 12%, avoiding staple food such as rice and bread in three meals), and after the standard-LCD (carbohydrate 24%, avoiding staple food in two meals) and petit-LCD (carbohydrate 36%, avoiding staple food in one meal) were applied, depending on the situation of the patients, which can reduce the weight gain rebound [9-12]. Reports with more than 2,000 cases have been rare, and our results would be fundamental data in light of ordinary outpatient care.

Through our investigation, we can suggest several characteristic aspects, such as 1) adequate education of meals and daily life, 2) behavioral changes in the most patients, 3) spontaneous continuation of LCD after the research protocol, 4) wide spread of LCD by recommendation of the patient for his or her family and acquaintances and 5) social information and recognition of short and long term effects of LCD.

2) Weight reduction of LCD

Our results could be compared with recent reports for LCD. Randomized controlled trials (RCTs) have consistently shown that LCD reduces body weight, with mean reductions ranging from 2.1 to 14.3 kg over at least six months of intervention [14].

Weight reduction between CR and LCD showed that 7.4% versus 9.0% in 227 cases [15], and 1.5 kg versus 5.3 kg in 148 cases one year later [16]. From 53 reports with 68,128 cases, the long-term effects depend on the intensity of the intervention [17]. On the contrary, meta-analysis of 19 papers of 3,209 cases revealed no significant difference of weight reduction in LCD and other diets [18].

Compared with these reports, our result would be successful particularly because weight reduction for LCD was remarkable in the cases, reducing more than 10% in 25.6%, and more than 5% in 57.6%.

3) International comparison of LCD

In Japan, our methods for LCD have been utilized and prevalent in clinical practice for years because of simple and easy to understand the content. Three types and ratios of carbohydrates were super-LCD without three staple foods (12%), standard-LCD without two staple foods (22% - 25%) and petit - LCD without one staple food (35% - 40%).

The content of LCD can be compared with the international situation of LCD. Recently, Bernstein and Feinman *et al* [19] suggested definitions and related comments of LCD as follows: 1) Very low-carbohydrate ketogenic diet (VLCKD): Carbohydrate, 20 to 50 g/day or <10% of the 2,000 kcal/day diet. 2) Low-carbohydrate diet: <130 g/day or <26% total energy. The ADA definition of 130 g/day is its recommended minimum. 3) Moderate-Carbohydrate Diet: 26% to 45%. Upper limit, approximate carbohydrate intake before the obesity epidemic (43%).

4) High-Carbohydrate Diet: >45%

Despite the differences in weight change on diets, LCD resulted in similar or greater improvement in inflammation, adipocyte dysfunction, and endothelial dysfunction than a standard low-fat diet among obese persons.

In the light of appellation, LCD and CR have been used for a long time, but recently, new and different terms have been used. They are high fat, low carbohydrate (HFLC) diet; low fat, high carbohydrate (LFHC) diet [20]; very low-carbohydrate ketogenic diet (VLCKD); low fat diet (LFD) [21-23]; higher-protein (HP) diet (38% carbohydrate, 30% protein, 29% fat);higher-carbohydrate diet [24]; and low carbohydrate (120 g carbohydrates/day) and low fat diets (30% energy from fat/day) [25].

Consequently, our three types of LCDs seem to be equivalent as follows: Super-LCD is equivalent to 1) VLCKD, standard-LCD to 2) LCD and petit-LCD to 3) Moderate-Carbohydrate Diet. In actual medical practices of diabetes, we have adapted three types of LCDs to each patient with adequate situations.

5) Short-term effects of glucose and TG

TG levels showed rapid and significant decreases through super-LCD for ten days from 143.4 ± 91.4 mg/dL to 93.9 ± 34.8 mg/dL. It is well known that LCD makes TG decrease in former studies. RCT of 23 reports until 36 months with 29.7 mg/dL decrease [26], RCT of 227 cases at 12 months with 37 mg/dL decrease [15], meal of carbohydrate less than 40 g/day for 12 months with a 14.1 mg/dL decrease [27], lack of supple meals (rice) one to two times per day for six months with 16 mg/dL decrease [28], LCD including 43% of carbohydrate with 14.9 mg/dL decrease for five weeks [29] and Atkin's method for 14 days with TG decrease from 154 mg/dL to 89.9 mg/dL [30, 31] which is similar to our result.

As for human research of LCD for six to 12 months, there is a limitation in research design because subjects have meals at home. In contrast, our design was performed that the patients were admitted and examined with super-LCD including carbohydrates of 12%, suggesting higher reliability and significance of LCD research.

6) Trial for IGI-carbo70

To speculate the function of pancreatic beta cells, insulinogenic index (IGI) analysis in 75g OGTT has been used until now [32-34]. However, IGI is not so applied to diabetic patients already diagnosed, because of rapid hyperglycemia.

Current study includes blood glucose and insulin values on 0 and 30 minutes after breakfast including carbohydrate 70 g. From these data, we calculated and showed "insulinogenic index-carbo70 (IGI-carbo70)" in ***Figs. 5*** and ***6***, because of almost same weight of glucose.

As a reference, there is a report of hyperglycemia due to a bowl of rice topped with beef (gyudon) [35]. Twelve healthy subjects were given three test foods, which were steamed rice (230 g), "gyudon" with or without ginger (15 g), including 78 g, 82.9 g, and 83.5 g of carbohydrates each. Blood glucose was elevated by 65 to 75 mg/dL after 30 min, and details were investigated in light of the area under the curve (AUC) of glucose increments.

From these data, it is noteworthy that even normal subjects have hyperglycemia against 80 g of carbohydrate in food, and that postprandial research of glucose and insulin would be useful and important. In ***Fig. 6***, 3/4 of cases of IGI-carbo70 were less than 0.5, suggesting a possible useful marker in the future.

7) HOMA-R and HOMA-β

As for mutual correlations, higher HbA1c suggests lower HOMA-β, indicating decreased secretion ability (***Figs. 7a, b***). Glucose profile seems to be influenced with factors such as obesity, insulin resistance, secretion ability, and mean amplitude of glycemic excursions (MAGE) (***Figs. 7c, d***). Increased IRI value indicating of insulin secretion ability showed no significant correlation with HOMA-R, suggesting less of a relationship with insulin resistance (***Figs. 7e, f***).

It is known that IRI values in 120 min for 75g OGTT correlates with the level of HOMA-β, which is compatible with the significant correlation with $p<0.001$ (***Fig. 7h***). HOMA-R showed a significant correlation with IRI values in 120 min without a significant correlation with IRI increase (***Figs. 7e, g***), suggesting elevated fundamental IRI values, due to insulin resistance.

HOMA-R and HOMA-β were applied to the evaluation for insulin resistance and secretion, in which reliability would be increased when fasting glucose is less than 140 mg/dL and 130 mg/dL, respectively. Consequently, there are possible fluctuations of reliability that the former has rather decreased, and the latter has rather increased. As for the limitation of the research design, further investigation would be necessary.

HOMA-R and HOMA-β were originally proposed by Matthews *et al*[36], and have been used widely and highly estimated. Recent development includes using C-peptide values alternatively[37], and newly trials for iHOMA2[38], expecting further useful analysis methods.

8) Ketone bodies and LCD

Hyperketonemia has usually been classified as 1) diabetic ketoacidosis (DKA) and 2) physiological ketosis. The former shows that blood sugar is more than 300 mg/dL with acidosis, and ketone bodies are 20 to 25 mmol/L[21, 39]. As for the report of DKA 19 cases, average values are as follows: glucose 650 mg/dL, pH 7.13, T-ketone 10.2 ± 1.8 mmol/L, and acetoacetic acid (AcAc) 2.7 ± 0.5 mmol/L, 3-OHBA 7.5 ± 1.3 mmol/L, the ratio of 3-OHBA 74%[40].

On the contrary, the latter shows that blood glucose is in a normal range and plasma ketone body levels increase six to eight mM during a prolonged fast without giving rise to clinically hazardous acidosis[21]. The cause is usually from starvation and a ketogenic diet, and was proposed by the famous biochemist Crebs, who was given the Nobel Prize[41].

In our study (***Figs. 8, 9***), we started diet therapy as super-LCD that has 1,400 kcal/day, 12% carbohydrates and 42 g of carbohydrates per day. Blood values of ketone bodies were 160 to 4,000 μmol/L (0.16 to 4 mmol/L) in ***Fig. 8***, and that of 3-OHBA was 136 to 3,577 μmol/L (0.14 to 3.58 mmol/L) in ***Fig. 9***. Our data would be compared with similar situations of previous reports.

The blood values of a healthy person are 72 to 90 mg/dL of glucose and less than 0.2 mmol/L of ketone bodies. Fasting increases blood ketone bodies, and 3-OHBA levels after fasting are 0.3 to 0.5 mmol/L in 24 hours, one to two mmol/L in two to three days, three mmol/L in three to four days[42] and four to five mmol/L in seven to ten days.

When patients with obesity continue fasting for 40 days, they would not show acidosis and their 3-OHBA values are six to eight mmol/L with the ratio of 3-OHBA at about 78%[43].

During fasting, giving 150 g of glucose per day for seven days would make 3-OHBA less than 0.5 mmol/L. In contrast, discontinuing glucose administration would result in elevated 3-OHBA, with 4.3 mM in ten days and 4.8 mM in 12 days[42]. Glucose intake of 20 to 40 g is associated with 3-OHBA of approximately one mM, but wide variations exist between people[42].

From several comparisons of previous reports, we can compare 3-OHBA value in three to four days, where three mmol/L in fasting[42] versus 0.36 mmol/L in 42 g of carbohydrate for super-LCD (***Fig. 8***). Furthermore, we can compare the ratio of 3-OHBA in ketone bodies, where approximately 78% in six to eight mmol/L of ketone bodies due to continuous fasting[43] versus about 60% to 90% in 0.1 to three mmol/L due to LCD (***Fig. 9***). These data would be the fundamental data in the research concerning ketone bodies.

Conclusion

We have continued clinical studies and research of LCD for many years. These studies revealed that for 1) long–term effects; weight reduction more than 10% was 25.6%, more than 2.5% was 78.8% in 2,699 cases, 2) short-term effects; blood glucose and triglyceride values decreased significantly in 10 days, 3) ketone bodies and 3-OHBA were elevated due to super-LCD meals from four to five days. These findings are fundamental data in the LCD area and contribute the research of glycative changes.

Acknowledgements

A summary version of this article was presented at the 89th Scientific Meeting of Japan Endocrine Society Annual Congress, Kyoto, 2016.

Statement of conflict of interest

Non contributory.

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