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Homeostasis Model Assessment (HOMA) and M Value in Daily Profile of Glucose

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Abstract

Background: Low Carbohydrate Diet (LCD) and Calorie Restriction (CR) have been on discussion for years. Authors have continued diabetic research about LCD, CR, Morbus (M) value and insulin secretion. In this study, homeostasis model assessment (HOMA) was investigated.

Subjects and Methods: Subjects enrolled were 52 patients with type 2 diabetes mellitus (T2DM) (average 62.3 years). Methods included the measurement of fasting glucose and immunoreactive insulin (IRI), daily profile of blood glucose and M value.

Results: The obtained data were as follows: average HbA1c 8.0%, average glucose of daily profile 222mg/dL. Median data were M value 151, HOMA-R 1.07, HOMA-β 11.1. Divided into 4 groups due to M value, the levels of HOMA-R and HOMA-β in each group were 0.68, 1.08, 1.64, 1.38 and 16.9, 16.3, 10.2, 5.3, respectively. Significant correlation were observed between M value and HOMA-R ($p<0.01$), and between M value and HOMA-β ($p<0.01$).

Discussion and Conclusion: As M value increases, HOMA-R increases and HOMA-β decreases. These findings suggested that diabetic patients would have insulin resistance and decreased β cell function correlated to the severity of diabetes, and that obtained results would become the basal data in this field, expecting the further development in the future research.

Keywords: Type 2 diabetes mellitus (T2DM), Morbus value (M value), Homeostasis model assessment of insulin resistance (HOMA-R), Homeostasis model assessment of β cell function (HOMA-β), Daily profile of blood glucose, immunoreactive insulin (IRI)

Abbreviations: T2DM: Type 2 diabetes mellitus, M value: Morbus value, IRI: Immunoreactive insulin, HOMA-R: Homeostasis model assessment of insulin resistance, HOMA-β: Homeostasis model assessment of β cell function

Introduction

Diabetes mellitus has been increasing and becoming medical and social problems in many countries. There are various developments for diagnosis and treatment of diabetes. Recently, managements of diabetes have been proposed by International Diabetes Federation (IDF), American Diabetes Association (ADA) and American College of Physicians (ACP) [1-3]. One of the controversies was the point concerning the recommended HbA1c in some situations.

The problem of diabetes has been known for its complications. They include microangiopathic complication with neuropathy, retinopathy and nephropathy, and macroangiopathic complication with arteriosclerosis of brain, heart and lower

extremities [4]. On the basis of these complications, there are crucial pathophysiological problems, including insulin resistance and impaired insulin secretion. These diabetic function could be studied as useful biomarker as the homeostasis model assessment (HOMA) such as HOMA-R and HOMA-β [5].

Regarding nutritional therapy for diabetes, recent focus has been the problem of carbohydrate intake. In clinical setting, the discussion has continued about the comparison with Low Carbohydrate Diet (LCD) and Calorie restriction (CR) [6-8]. LCD means the decreased intake of carbohydrate as meals, and CR means the decreased intake of fat leading to less calorie restriction.

LCD was started by Atkins and others in North American and European countries [9]. After that in Japan, authors and colleague researchers initiated LCD project and developed through Japan Low Carbohydrate Diet Promotion Association [10]. We have continued clinical practice for diabetes with three useful LCD methods, which are petit LCD, standard LCD, super LCD [11]. Moreover, we already presented various research reports concerning LCD, M value, ketone bodies and related investigation [12-14].

In this study, we combined two research methods together. One is the research axis from HOMA including HOMA-R and HOMA-β, and another is the axis of daily profile of glucose, average blood glucose a day and Morbus (M) value. M value has been one of the import biomarkers, which indicates average blood glucose level and mean amplitude of glycemic excursions (MAGE). In clinical research M value has been useful for its numerical value, because the degree of glucose variability can be indicated and compared in various situations.

Subjects and Methods

Subjects in this study were 52 patients with type 2 diabetes mellitus (T2DM). For further evaluation and treatment of T2DM, they were admitted to the hospital. The subjects were admitted to the hospital for 14 days. They were not given any medications that may have altered the glucose metabolism.

There was a necessary condition when we enrolled the subjects. The level of immunoreactive insulin (IRI) should be 5 μU/mL and less than 5 IU/ml in the morning after overnight fast. The subjects with more than 5 μU/mL of IRI were excluded.

As to the methods, there have been standard protocols of evaluation and treatment for T2DM in our clinical study. It includes nutritional therapy of standard meal with CR in day 1 and 2, and LCD in after day 3. According to current study, the procedures were described in the following:

a) On the morning of day 2 after overnight fast, blood samples were drawn for basal blood tests. They included complete blood count, liver and renal function, lipids, HbA1c, glucose, IRI, C-peptide and so on. From these data, HOMA-R and HOMA-β and other biomarkers were calculated.

b) In our protocol, subjects are to take CR on day 1 and 2, with 1400 kcal/day. The content of CR has 15% of protein, 25% of fat and 60% of carbohydrate. It is along the standard ratio of the macronutrients due to Japan Diabetes Association [15].

c) Regarding to daily profile of blood glucose in the subjects, blood samples were taken seven times a day on Day 2.

d) This report has concentrated in the investigation of 1) fundamental data related to diabetes such as HbA1c, glucose, insulin, C-peptide, lipid and so on, 2) daily profile of blood glucose in day 2, with the calculation of M value, 3) HOMA-R and HOMA-β with the calculation of glucose and IRI on Day 2. This study is focused these aspects, and is not studied after clinical situation after Day 3.

Daily Profile of Blood Glucose

As to glucose variability in a day, we checked the daily profile of blood glucose on day 2 for 7 times a day. The clock time was 0800, 1000, 1200, 1400, 1700, 1900, 2200h. According to these data, the results of average blood glucose and M value were obtained [16,17].

Morbus Value

One of the biomarker indicating the glucose variability is Morbus (M) value. It means the average blood glucose level and also the mean amplitude of glycemic excursions (MAGE) [16-18]. In clinical studies, M value has been useful, because it shows numerical values that can be compared and evaluated in various diabetic situations with glucose variability. Thus, M value indicates the degree of high blood glucose and the degree of swinging blood glucose. In the light of mathematics, M value is obtained by the logarithmic transformation. Its clinical significance would be the glucose deviation from the ideal glucose variability [17-19].

The formula of M value is described as follows:

$$\text{M-value} = \frac{\Sigma}{N}\left|\text{M}\frac{BS}{BS}\right| + \text{W}/20 \quad \text{where} \quad \text{M}\frac{BS}{BS} = \left|10\log\frac{PG}{120}\right|^3$$

Firstly, $M = M^{BS} + M^{W}$: M value means the total of M^{BS} and M^{W}. Secondly, M^{W} means maximum blood glucose − minimum glucose)/20. Lastly, M^{BS} is the mean of MBSBS. When summarized the content above, MBSBS has been the individual M-value for each blood glucose, calculated as (absolute value of [10 × log (blood glucose level/120)])^3 [17-19]. In the formula of M value, there is one part of 10xlog plasma glucose / 120. It means that when the blood glucose value is 120 mg/dL, the level of M value becomes minimum. Moreover, there is a part to calculate by the cube of the absolute value. Therefore, as the average blood glucose increases, the degree of increase in M value increases to large extent.

Generally, the obtained data of the M value is clinically judged as follows: less than 180 is normal range, from 180 to 320 is

borderline, more than 320 is abnormal.

By the level of M value, 52 subjects were divided into 4 groups with 13 cases each. M values shows both of mean blood glucose and mean amplitude of glycemic excursions (MAGE), then the purpose of the classification was to compare the variability of 4 groups in several biomarkers.

Statistical Analysis

Regarding this study, data were shown by mean and standard deviation. In addition, data was described as the median and quartile of 25% / 75% according to the necessity of the biomarkers. Boxplot was used for the comparison among some groups, which expresses the median and the quartile of 25% / 75%, maximum and minimum. As to investigation for the correlation with biomarkers, we used Spearman test to obtain the correlation coefficients. We used the standard statistical tool for analytical evaluation [20].

Ethical Standards

Current research was conducted in compliance with the ethical principles which were based upon the Declaration of Helsinki. Moreover, additional commentary was performed in 2004 General Assembly Tokyo, Japan. It was conducted with Personal Information Protection Law and in reference to "Standards for the Implementation of Clinical Trials (GCP), an ordinance of the Ministry of Health, Labor and Welfare No. 28 of March 27, 1997. In addition, there was the "Ethical Guidelines for Epidemiology Research" by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare.

Authors and colleagues had an ethical committee including physician, nurse, pharmacist and other experts in the legal specialty. We have discussed and confirmed that current study is valid and agreed with all members. Furthermore, informed consents and written paper agreements have been taken from the subjects. This study has been registered by National University Hospital Council of Japan (ID: #R000031211).

Results

1) Fundamental data

Basal data of 52 subjects were shown in (Table-1). Average age was 62.3 years old, and the HbA1c and average blood glucose was 8.0% and 222 mg/dL, respectively. The median value of Morbus value, HOMA-R, HOMA-β was 151, 1.07, 11.1, respectively. Lipid profile and renal function tests revealed within normal range.

Table 1 : Subjects and basal data

	Mean ± SD	**median [25%-75%]**
Subjects		
numbers (M/F)	52 (33/19)	52 (33/19)
age(years old)	62.3 ± 10.2	65 [58-69]
Glucose profile		
HbA1c (%)	8.0 ± 1.8	8.0 [6.4-9.2]
average glucose (mg/dL)	222 ±85	210 [148-281]
Morbus value	271 ± 310	151 [40-412]
Insulin resistance		
HOMA - R	1.21 ± 0.60	1.07 [0.77-1.61]
HOMA - β	131± 8.6	11.1 [7.3-9.3]
Lipid profile		
Triglyceride (mg/dL)	113 ± 92.7	79 [60.3-142]
HDL-C (mg/dL)	71.9 ± 20.8	66.5 [57.5-82.0]
LDL-C (mg/dL)	134 ± 38.3	136 [110-158]
Renal function		
Creatinine(mg/dL)	0.72 ± 0.15	0.73 [0.62- 0.79]
Ccr (ml/min)	95.9 ± 24.3	94.0 [79.7-109]
Uric Acid (mg/dL)	5.0 ± 1.2	4.9 [4.3-5.9]

Morbus value was calculated from daily profile of glucose.
HOMA - R : Homeostatic model assessment of insulin resistance
HOMA - β : Homeostasis model assessment for β cell function

2) Categorization by M value

Subjects were divided into 4 groups due to the level of M value. Each group has 13 cases. The median of M value in group 1,2,3,4 was 14.9, 77.3, 222, 701, respectively (Figure-1). From group 1 to group 4, the level of M value has increased remarkably.

3) Comparison of biomarkers

As to average blood glucose, group 1 to 4 revealed 132 mg/dL, 175 mg/dL, 232 mg/dL, 333 mg/dL in median value, respectively (Figure-2a). In four groups, median HbA1c value revealed 6.1%, 7.0%, 8.1%, 9.8%, respectively (Figure-2b).

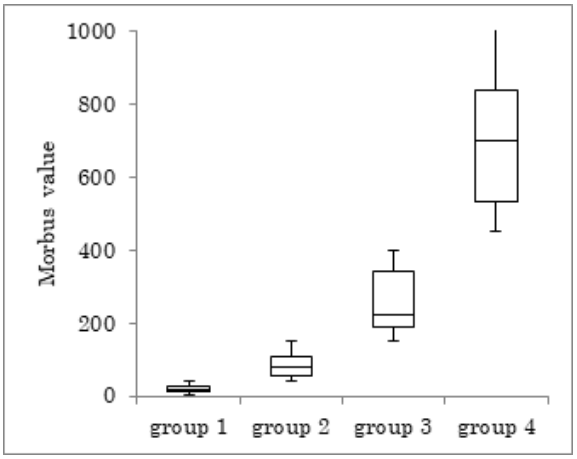
Similarly, median value of HOMA-R revealed 0.68, 1.08, 1.64, 1.38, respectively (Figure-3a). The distributions of group 3 and group4 were rather overlapped. In addition, median value of HOMA-β revealed 16.9, 16.3, 10.2, 5.3, respectively (Figure-3b). The distribution of group 1 and 2 showed rather wide, while that

of group 3 and 4 showed less.

4) Correlation between M value and HOMA

Correlation between Morbus value and HOMA was investigated (Figure-4). There was significant correlation ($p<0.05$) between M value and HOMA-R (Figure-4a). There was also significant correlation ($p<0.01$) between M value and HOMA-β (Figure-4b). The significant degree was larger in HOMA-β than HOMA-R.

Figure 1: Categorization to 4 groups due to Morbus value



Subjects were categorized into 4 groups due to the level of M value.
The level of M value ranges wide, which is one of the characteristic point.

Figure 2: Average Glucose and HbA1c in four groups

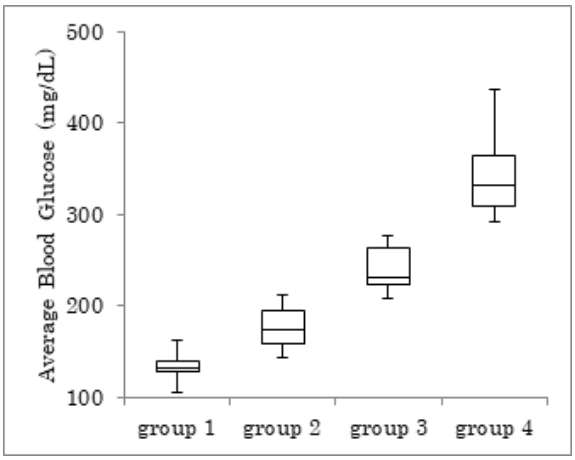


Figure 2a: The level of average blood glucose increased from group 1 to group 4.

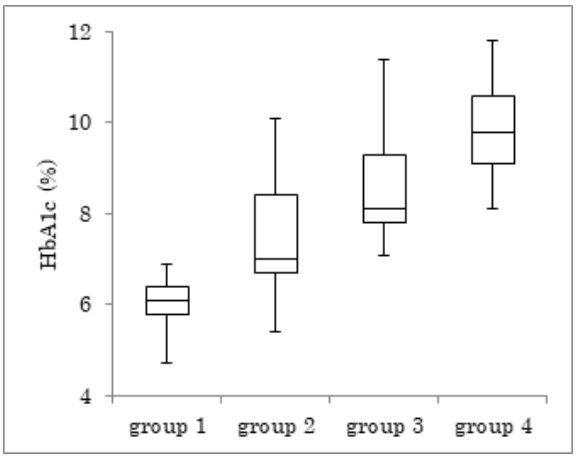


Figure 2b: The median HbA1c increased from group1 and 4.

Figure 3: HOMA-R and HOMA-β in four groups

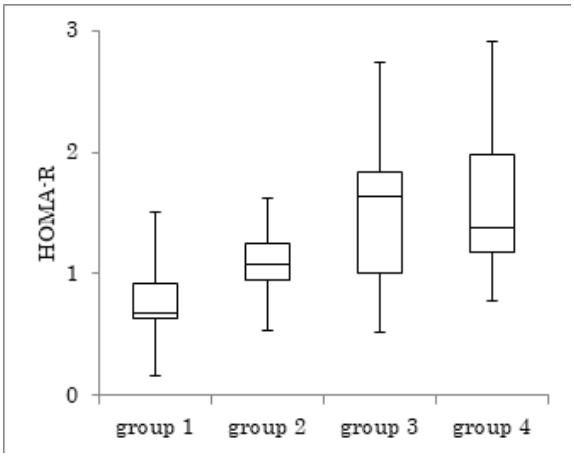


Figure 3a: The value of HOMA-R seems to be higher in group 3 and 4 compared with group 1 and 2.

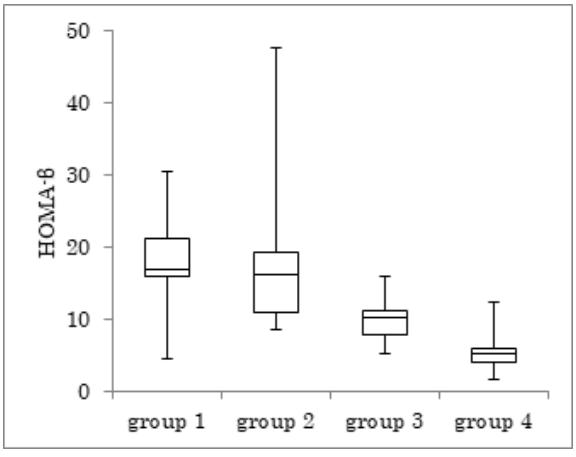


Figure 3b: The value of HOMA-β decreased from group 1 to group 4.

Figure 4: Correlation between Morbus value and HOMA

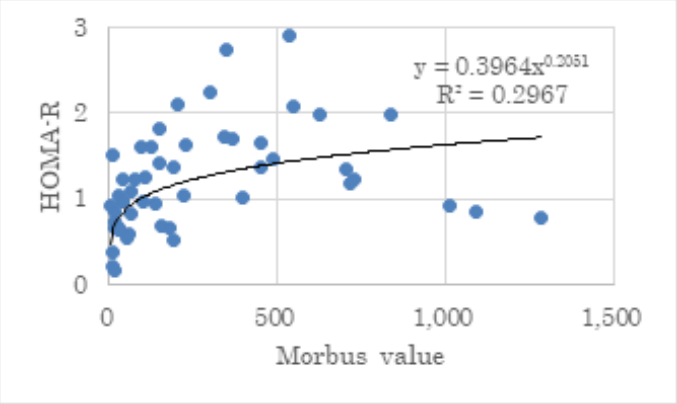


Figure 4a: There was significant correlation between Morbus value and HOMA-R ($p<0.01$).

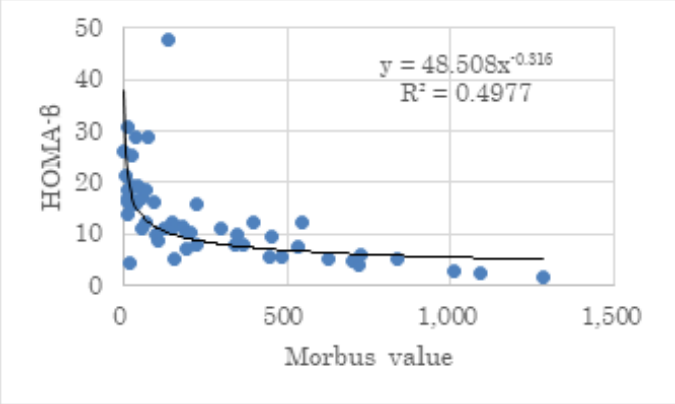


Figure 4b: There was significant correlation between Morbus value and HOMA-β ($p<0.01$).

Discussion

Regarding the effects on blood glucose, carbohydrates, lipids, and proteins were previously thought to be involved. However, nutritional therapy for diabetes has changed since the announcement of ADA in 2004 [21]. Among three macronutrients, it is only glucose that directly affects blood sugar after ingestion.

In succession, clinical risk of hypoglycemia due to intensive therapy for diabetes has been known by the results of ACCORD study and others [22,23]. Consequently, LCD has been rather developed in many countries and its beneficial aspects were reported [6,7,24]. According to the result of PURE study, high carbohydrate intake was associated with higher risk of total mortality, whereas total fat and individual types of fat were related to lower total mortality [25].

The authors have continued clinical practice and research for many patients with diabetes. Among them, the authors have firstly reported on LCD study in Japan, and developed investigation utilizing both CR and LCD as a diet therapy. There are three directions in the following.

Firstly, we reported the effect of LCD on many cases, and also developed three kinds of LCD, which are super-, standard- and petite-LCD meal [11]. Among them, there are investigations of elevated ketone bodies in subjects on LCD meal and in the axes of fetus, placenta, newborn and pregnant women [12].

Secondly, our research has focused on the comparison with CR and LCD. One of the protocols includes that subjects are provided CR on days 1 and 2, LCD on 3-14 days for diabetic patients. Thus, all related biomarkers have been investigated such as daily profile of blood glucose, mean blood glucose level, M value, insulin, blood and urine value of C peptide, lipid, renal function and so on [13].

Thirdly, 70 g of carbohydrate in standard CR breakfast has been used for research, which is similar to 75g OGTT. It can show enough responses of glucose, insulin and c-peptide, where there is clinically significant for simple and usual loading of carbohydrate [31]. Consequently, CR breakfast with carbohydrate 70g can be used and recommended for clinical research because of its practical convenient efficacy.

Based on our research background as mentioned above, we have conducted current research. Concerning the results in this study, the levels of M value in 4 groups showed large difference. It has been useful biomarker because its numerical values indicate both of mean blood glucose and mean amplitude of glycemic excursions (MAGE) [16-19]. In addition, average glucose was calculated from blood sampling 7 times a day. There were previous clinical data concerning the result of comparison between sampling of 7 times and 20 times. Both showed similar results about average blood glucose. Consequently, both would have compatible data, as well as the results from continuous glucose monitoring (CGM) [27-29].

Regarding the average glucose and HbA1c in 4 groups, their distribution seemed to be rather divided in the former, and rather overlapped in the latter. The median values of HbA1c in 4 groups were increased from group 1 to 4.

As to HOMA-R, the median value was not so divided in 4 groups; especially the values in group 3 and 4 were overlapped, suggesting increased insulin resistance. In the case of HOMA-β, the distributions of group 1 and 2 were almost overlapped, while the value of group 3 and 4 were remarkably low. The median value of HOMA-β decreased clearly from group 1 to 4, suggesting the decreased ability of β cell function and low secretion of insulin.

There are significant correlation between M value and HOMA-R, and between M value and HOMA-β. The correlation coefficient is higher in HOMA-β than HOMA-R, suggesting higher relationship of secretion of insulin and clinical significance of M value.

In clinical studies, HOMA has been known as the useful biomarker for diabetes. In the case of calculation for HOMA, fasting blood glucose and fasting insulin value are utilized. Originally, HOMA was developed by Matthews [5]. By mathematical assessment, HOMA is calculated from the balance between hepatic glucose output and insulin secretion from fasting levels of glucose and insulin [30]. Regarding clinical significance and

implications of HOMA, we can infer the functions of both ability to secrete insulin and resistance of insulin. There have been used two formula of HOMA, which are HOMA-R and HOMA-β.

As the value of HOMA-R becomes higher, the insulin resistance shows higher. Regarding the standard value of HOMA-R, it has been 1.73 or more with the presence of insulin resistance [31]. In addition, people with higher HOMA-R tend to suffer from myocardial infarction and cerebral infarction, regardless of diabetes. In other words, HOMA-R is not only for the judgment of insulin resistance but also for an indicator of cerebral cardiovascular events.

Regarding HOMA-β, the standard value for people in western countries would be 100%. On the other hand, it is known that Japanese people have less ability to secrete insulin. Therefore, the standard value for Japanese people has been set at 70% [32]. From previous studies, the following tendency has been known.

Higher HOMA-R and lower HOMA-β were independently and consistently associated with an increased diabetes risk [31]. Compared the obtained data of HOMA-R and HOMA-β, most subjects in this study did not show normal ranges, suggesting the existence of insulin resistance and decreased β-function.

For the limits of the research, several matters would be considered. This report has focused in the investigation of the following 3 aspects, which are fundamental data related to diabetes, daily profile of blood glucose and M value in day 2, HOMA-R and HOMA-β on Day 2. Data obtained from Day 2 were utilized. Other factors would be explored in the light of the correlation with biomarkers related to diabetes. For example, urinary excretion of C-peptide, the response of glucose and IRI against 70g of carbohydrate as breakfast, basal data of renal and liver function tests and so on. As to fasting IRI level, subjects with 5 μU/mL and less than 5 μU/mL were included in this study. The reason was to reduce the larger error in calculating HOMA values. Consequently, subjects with more than 5 μU/mL of IRI would be investigated in the future study.

Conclusion

In summary, we investigated 52 patients with T2DM. Several related biomarkers such as HbA1c, the daily profile of glucose, average glucose, M value, HOMA-R, HOMA-β were measured and correlations were studied. Current results suggest that patients have insulin resistance and decreased β cell function correlated to the severity of diabetes. These findings would become the basal data in this field, and further development would be necessary in the future research.

Acknowledgement

As to this article, some part was presented at annual conference of Japan Diabetes Society (JDS) Conference, Tokyo, 2018. The authors express gratitude to all staff and patients for their cooperation.

Conflicts Of Interest

The authors state that they have no conflicts of interest.

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