Glycative Stress Research

Online edition : ISSN 2188-3610
Print edition : ISSN 2188-3602
Received : November 29, 2017
Accepted : January 10, 2018
Published online : March 31, 2018

Review article

Consideration of adequate carbohydrate intake

Satoru Yamada

Kitasato Institute Hospital Diabetes Center, Tokyo, Japan.

Abstract

The conventional wisdom of nutritional science for the last 40 years has radically reversed. In the past, it was considered that fat intake was suspected to be the cause of cardiovascular diseases, and the intake of protein to be the cause of the deterioration of renal function, so it was recommended to minimize their intake and make up the lack of energy with the intake of carbohydrates. However, today, there is no such concept in present nutritional science.

Meanwhile, the results of research in low carbohydrate diets were accumulated worldwide and it was shown that a diet with 120 g, or less than 150 g, of carbohydrates a day is effective in all components of metabolic syndrome such as blood glucose, body weight, blood pressure and lipid profile. Randomized control trials of low carbohydrate diets have been reported in Japan, which show the effectiveness of moderate low carbohydrate diets.

A low carbohydrate diet is assumed to have a great effect not only on metabolic syndromes, but also various diseases and clinical conditions such as dementia, locomotive syndrome (sarcopenia and frailty) and the appearance of aging. A low carbohydrate diet is also presumed to maintain and improve the functions of internal organs by inhibiting the glycation of proteins in each organ associated with the intake of carbohydrates.

In terms of the quality of carbohydrates, papers supporting diets consuming food with low Glycemic Index (GI) have been reported. Furthermore, papers supporting the style of eating called “eating order diet taking carbohydrates last” have also been reported.

It is desirable that many people recognize and practice appropriate methods of carbohydrate intake from the viewpoints of quantity, quality and order, and the concept of “enjoying tasteful meals and good health” will become a reality.

***KEY WORDS*:** obesity, diabetes mellitus, metabolic syndrome, nutrition therapy and low-carbohydrate diet (Locabo)

1 Introduction

Monnier *et al*. revealed more than 10 years ago that blood glucose fluctuation positively correlates with oxidative stress [1)]. Since then, it has become known that the amount of fluctuation in blood glucose level correlates with reduced cognitive performance [2)]. Transient postprandial hyperglycemia, called a “glucose spike,” is associated with organ disorder at the same level or more as stable hyperglycemia. At one time, it was considered that it takes more than certain hours to produce advanced glycation end products (AGEs) caused by being exposed to high blood glucose levels. However, recently it has become known that the production of AGEs occurs in a short time [3)]. In other words, the problems of glycative stress caused by this transient hyperglycemia became known. In this review, we will give an outline of the great changes in nutritional science at present, as well as discuss appropriate methods of carbohydrate intake as a diet preventing transient postprandial hyperglycemia and glycative stress following meals, as well as express our opinions on this topic.

2 Great Change in Nutritional Science

In order to discuss the appropriate intake of carbohydrates, it is important to know that nutritional science is in a period of great change at present. In 2015, the Dietary Guidelines Advisory Committee in the USA released a report stating that “Reducing total fat does not lower cardiovascular disease (CVD) risk” and “Limiting total fat was also not recommended for obesity prevention.” The committee also reversed nearly 4 decades of nutrition policy and raised the upper limit on the recommended amount of fat intake [4)].

Correspondence to: Satoru Yamada MD, PhD
Kitasato Institute Hospital Diabetes Center
5-9-1 Shirokane, Minato-ku, Tokyo 108-0072, Japan
Tel: +81-3-3444-6161
eMail: Yamada-s@insti.kitasato-u.ac.jp

(c) Society for Glycative Stress Research

These changes in nutritional policies were not something the Dietary Guidelines Advisory Committee in the USA suddenly came up with. For example, "Eat Butter" was headlined on the cover of the Time magazine June 23, 2014 issue. Compared with the article "Hold eggs and butter" posted in the magazine's March 26, 1984 issue, the way of thinking about fat intake (the lipid in this case is saturated fatty acid, which is often considered to be animal fat) was clearly reversed in 2014 (***Fig. 1***).

The thinking regarding carbohydrate intake also was clearly reversed. In 2006, the American Diabetes Association (ADA) declared "Low-carbohydrate diets are not recommended (which means the Association cannot recommend it)" [5]. However, it changed their description to "For weight loss, either low-carbohydrate or low-fat calorie-restricted diets may be effective" [6], and finally in 2013, it recommended low carbohydrate diets, saying "prescribed diabetic eating patterns have been shown to be moderately effective in managing diabetes, including Mediterranean-style diets and lower-carbohydrate patterns" [7]. It is clear from the changes in these descriptions that their thinking had been gradually changed. In short, they said that they could not recommend low carbohydrate diet but they recommended it only seven years later (from 2006 to 2013).

Furthermore, their way of thinking about protein has also been reversed. The American Diabetes Association had insisted that a reduction of protein intake may improve measures of renal function" until 2008 [6]. However, in 2013, it said "Reducing the amount of dietary protein is not recommended because it does not alter the course of GFR decline" [7].

Although, even now in Japan, a low-energy diet is accepted as the only dietary method for the treatment of diabetes, and it is handled differently in the USA. Since the time when it prepared its first Nutritional Guidelines in 1971, the American Diabetes Association had said "The single most important objective in dietary treatment of diabetic patients is the control of total caloric intake to attain an ideal body weight" [8]. However, in 1994, the Association excluded it from the most important tasks, saying "Traditional dietary strategies, and even very-low-calorie diets, have usually not been effective in achieving long-term weight loss" [9].

In other words, all of the following items that had been recommended until several years ago were no longer thought to be effective; (1) low-energy diet (moderate eating) is good for health (← denied because it cannot be maintained in the long term), (2) low-fat diet is effective in the prevention of CVD (← denied because it is not effective) and (3) low-protein diet is effective in the protection of renal function (← denied because it is not effective). Furthermore, (4) low-carbohydrate diet, an item that had been denied until several years ago, became recommended as the first choice.

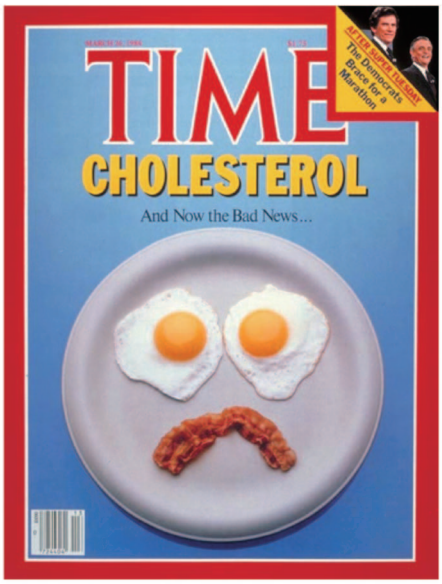
In order to consider the method of appropriate carbohydrate intake, it is extremely important to understand why a low-energy diet, low-fat diet and low-protein diet that had been regarded as effective were denied, so these diets are explained in detail as follows.

(1) Low-energy diet

A low-energy diet has played a central role for a long time as diet therapy for anti-aging therapy and the treatment of diabetes.

Actually, a low-energy diet has shown life-extending effects in experiments with various animal species. An experiment with rhesus monkeys conducted by the University of Wisconsin showed not only that a low-energy diet significantly reduced age-related deaths, but also that it prevented the onset of diabetes, CVD, cancer and dementia [10]. Therefore, the same effects in humans were expected. In

a. 1984



b. 2014

Fig. 1. **Front page of the journal "TIME".**

The difference between blue color "Hold the eggs and butter" in 1984 and block color "Eat butter" in 2014 shows a paradigm shift in nutrition. **a.** "Cholesterol", Mar 26, 1984; Vol. 123, No. 13. **b.** "Ending the War on Fat", June 23, 2014; Vol. 183, No. 24.

other words, a low-energy diet had played the most important role in the prevention and treatment of metabolic syndrome (clinical conditions where CVDs are easily caused by the integration of blood glucose abnormality, blood pressure abnormality and lipid profile abnormality based on the accumulation of visceral fat) for a long time. However, in the Look AHEAD trial where diabetic patients were administered a low-energy diet, a reduction in total mortality and a decrease of CV events were not recognized, and the bone mineral density (BMD) of male's femoral neck were significantly reduced compared with that of the control group [11]. The deterioration of bone metabolism like this also was recognized in the rhesus monkeys mentioned previously [12]. Furthermore, the life-extending effects of a low-energy diet were not recognized in the experiment with monkeys conducted by the National Institute of Aging (NIA) in the USA [13]. In addition, according to a recently reported CALERIE trial, problems in reduction of BMD, decrease in muscle mass, and treatment-resistant anemia occurred in healthy subjects who were guided to restrict their energy intake to 75% of their previous intake [14-16]. In other words, we have had to recognize that a low-energy diet possibly accelerates locomotive syndrome (clinical conditions tending to become bed-ridden caused by osteoporosis, joint degeneration and muscle atrophy), far from a solution for metabolic syndrome.

It is known that if the actual energy intake is presumed to be 100, the energy recorded personally as consumed is around 15-25% less than 100 [17, 18]. The more overweight the person is, the smaller this figure becomes. For example, in the case of an obese person with a body mass index (BMI) greater than 30, this figure decreases to around 70 [19]. Therefore, energy restriction has a problem from a realistic standpoint.

Even in Europe and the United States where almost 100% of the cases of type2 diabetes develop through obesity as previously mentioned, since the end of the 20th century, the optimization of energy intake has no longer remained an important task because of the difficulty in maintaining the effect [9]. Even in Japan, where the development of type2 diabetes is not always related to obesity [20], a low-energy diet only is not enough as an effective diabetes countermeasure, so it must be reviewed.

(2) Low-fat diet

The Seven Countries Study that was reported in 1953 investigating the relationship between fat intake ratio and cardiovascular motility in the USA, Canada, Australia, England, Wales, Italy and Japan clarified that cardiovascular mortality is higher in countries where the fat intake ratio is high [21]. Epidemiological data (observational study) like this hold bias and confounding factors, so that it is clear that correlation does not imply causation. The concept, whether there is causation or not in observational studies, had not sufficiently prevailed prior to 1991, when it was finally advocated for evidence-based medicine. Therefore, the concept that a reduction of fat intake leads to the prevention of cardiovascular death blindly prevailed.

However, after the turn of this century, as the results of a systematic review of a randomized controlled trial (RCT), in research designed to approach the causation, it was not confirmed that a low-fat diet supported the improvement of blood glucose [22], and it was confirmed though meta-analysis of RCT that a low-fat diet did not support the reduction of cardiovascular mortality or all-cause mortality [23, 24].

On the contrary, the results of the research that fish oil supplements (ω-3 polyunsaturated fatty acids) can prevent cardiovascular death and all-cause mortality was reported in the beginning of this century [25], and, furthermore, that it can also prevent cardiovascular events by adding plant oil (nuts 30 g/day or extra virgin olive oil 1 L/week) was reported [26]. As a result, the concept that the restriction of fat is not needed took root. There are several research results from Australia [27] and the USA [28] that show cardiovascular events and mortality increase by changing animal fat (saturated fatty acid) to plant oil. There are several reports that in the case of the Japanese, in particular, the larger the intake of saturated fatty acid, the more they are protected from the onset of stroke [29-31]. Therefore, it seems not to be necessary to also avoid saturated fatty acids.

According to the PURE Study [32] which was reported recently, in an observation study of 18 countries on five continents, the more fat a group consumes, the lower its all-cause mortality is. Therefore, no one could express the medical significance of low-fat diet in the level of a randomized control trial or observational study level any longer.

Therefore, at present, the lipids that should be avoided are old and damaged ones (lipid peroxide) and artificial lipids (trans-fatty acids) only.

(3) Low-protein diet

It has been reported that protein load has renal toxicity since 1919 [33] and the load from a high protein diet had shown renal toxicity in various experiments with animals until the 1980s, so that the concept of the treatment of renal failure by low protein diet was established [34]. Furthermore, in humans, according to Nurses' Health Study, no relationship between the amount of protein intake and the worsening of renal function (lowering of estimated glomerular filtration rate: eGFR) after intake was observed in the group without renal failure (eGFR > 80 mL/min). However, the speed of the worsening of renal function (lowering of eGFR) was faster in the group with the largest protein intake among the group with renal function damaged to a certain extent (80mL/min > eGFR > 50 mL/min); as a result, the hypothesis that protein intake worsens renal function and low protein diet protects renal function prevailed [35].

However, no significant protective effect of the low-protein diet on renal function was recognized, not only in the persons with normal renal function, but also in those with impaired renal function in the MDRD Study trying to confirm the effectiveness of a low protein diet by randomized control trial that can exclude bias and confounding factors [36]. Following up after that, it was reported that mortality significantly rose with a strict low-protein diet [37].

After this follow-up of the MDRD Study was reported, the American Diabetes Association came to deny the effectiveness of a low protein diet for the protection of renal function in their nutrition recommendations [7].

3 Appropriate Amount of Carbohydrate of Nutritional Science in the Past

It has been generally considered that the three macronutrients consisting of the ratios of carbohydrate 50-65%, protein 13-20% and fat 20-30% (or 25%) to total

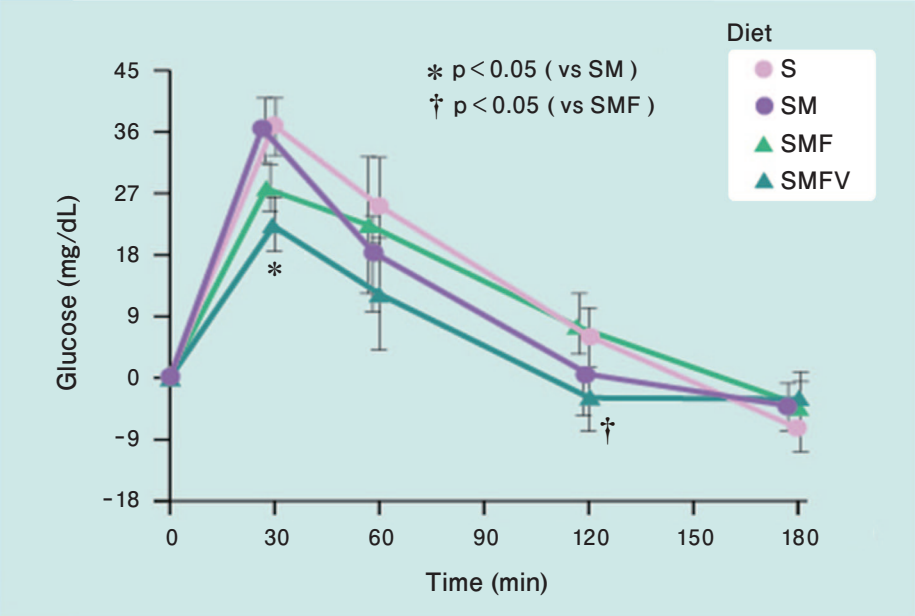
energy are good for health[38]. There are many pieces of literature stating that this amount (ratio) of carbohydrates is appropriate, even now. However, these ratios are only hypothetically calculated as follows; calculate energy requirement by multiplying basal metabolic rate by physical activity coefficient, set a minimum (or a little more) required protein from essential amino acids, set a minimum (or a little more) required fat amount from essential fatty acids, and fill the rest with carbohydrates. As stated above, a paradigm shift occurred in nutritional science. In the present situation regarding nutritional science, it is not necessary to set an upper limit on fat intake, and it is not considered that renal dysfunction is caused by protein intake, so we have to say that the above three macronutrient ratios are meaningless. Ideal ratios for the three macronutrients are unknown at present, so that should be established from now on[7].

4. Appropriate Carbohydrate Intake to be Considered in terms of Volume

The method to calculate the amount of carbohydrate intake by setting total energy amount, reducing minimum required amounts (or a little more) of protein and fat, and obtaining carbohydrates is meaningless when the negative effect of protein intake on renal function and the promoting effect of fat intake on arterial sclerosis are denied. In this situation, a low-carbohydrate diet is being reconsidered from the viewpoint of its intake volume. The low-carbohydrate diet that prevailed as a treatment method for lifestyle-related diseases in the 20th century, similar to folk medicine, was completely discredited[39]. The reasons for the criticism are insufficient scientific grounds and the increase in cardiovascular risk caused by excess fat intake. It has become clearly verified that a low-fat diet does not decrease cardiovascular risk and the scientific grounds for low-carbohydrate diets have accumulated, and as a result, these criticisms disappeared.

In the first place, only carbohydrates cause postprandial hyperglycemia except in the case of type1 diabetes, and it is known that the intake of protein, fat and dietary fiber reduce postprandial hyperglycemia (*Fig. 2*)[40-42]. In other words, diets restricting carbohydrate intake and increasing the intakes of protein, fat and dietary fiber can more effectively adjust postprandial hyperglycemia and prevent glycative stress.

A low-carbohydrate diet is expected to reduce the occurrence of glycative stress[43], reduce oxidative stress[44] and acquire an anti-aging effect (extending longevity and healthspan)[45]. The medical merits that can be gained from it are anti-aging effects on the changes associated with aging including cardiovascular events, cognitive impairment, the loss of skin suppleness (formation of wrinkles) and bone degeneration. Actually, it is shown that the appearances of aging in twins are greatly defined by wrinkles of the skin,



S diet	S	Steamed rice 200 g	338 kcal
SM diet	S + M	Steamed rice 200 g + Tofu + Boiled egg	486 kcal
SMF diet	S + M + F	Steamed rice 200 g + Tofu + Boiled egg + Mayonnaise	573 kcal
SMFV diet	S + M + F + V	Steamed rice 200 g + Tofu + Boiled egg + Mayonnaise + Spinach & Broccoli	604 kcal

Fig. 2. **Plasma glucose change after 4 types of foods.**

S, staple food; M, main dish; F, fat; V, vegetable; Tofu, soy bean curd. * $p < 0.05$ vs. SM diet, † < 0.05 vs. SMF diet. The figure is quoted from Reference[41].

and the appearance of aging has strong correlations with mortality and cognitive function afterwards [46, 47]. In other words, the inhibition of glycative stress and oxidative stress of the whole body due to a low-carbohydrate diet has merits not only for the prevention and treatment of metabolic syndrome, but also for the prevention of locomotive syndrome.

The A to Z Study [48] and the DIRECT Study [49] boosted the position of the low-carbohydrate diet to be the first choice of treatment for obesity or diabetes worldwide. The low-carbohydrate diet employed in these studies was the Atkins diet. It is a diet that restricts carbohydrates to 20 g/day in the early period and later changes to a moderate restriction of up to 120 g/day.

The A to Z Study [48] is a randomized control trial targeting American patients with obesity. Four types of diets (1) Atkins diet, (2) traditional diet (low fat and low energy diet), (3) Ornish diet (a substyle of vegetarianism) and Zone diet (proportions of carbohydrate, fat and protein are 40:30:30) were compared. The low-carbohydrate diet group (Atkins diet group) achieved the best effects in the change of body weight and the improvements of lipid profile and blood pressure (***Fig. 3***).

The DIRECT Study is a randomized control trial targeting 322 patients with abnormal body weight (BMI 27 or more) working in one facility in Israel. The following three diets were compared; (1) Low-carbohydrate diet (Atkins diet), (2) Mediterranean diet (energy intake of 1,800 kcal for males and 1,500 kcal for females, with less meat and a high volume of fish, vegetables, and lipids, mainly by olive oil, up to an energy ratio of 35%) and (3) a low fat diet (energy is 1,800 kcal for male and 1,500 kcal for female with a lipid ratio of less than 30%). Although all groups successfully lost weigh over two years, the low-carbohydrate diet group resulted in the best effect (***Fig. 4***) [49]. Low-carbohydrate diet resulted in the best improvement in lipid profile, high sensitivity C-reactive protein (hsCRP), adiponectin and HbAlc [49]. In the sub-analysis that followed, the low-carbohydrate diet improved eGFR [50] and carotid intima-media thickness [51] and its effects on weight loss and lipid profile improvements were maintained for 6 years [52].

While the reports of the randomized control trials for the low-carbohydrate diet shown above were accumulated, the reports in which Santos *et al*. meta-analyzed 17 pieces of data showed that a low-carbohydrate diet significantly improved the control of blood glucose, lipid profile, body weight, blood pressure and hsCRP. It was also shown that the low-carbohydrate diet is very appropriate as a therapeutic diet for metabolic syndrome and diabetes (***Table 1***) [53].

We released a report on a randomized control trial targeting the Japanese for the first time [54]. Type 2 diabetic patients were randomly assigned to (1) a moderately low-carbohydrate diet or (2) low-energy diet. In this research, diet was restricted to more than 20 g and less than 40 g per meal, and not less than 120 g a day. It inhibited blood glucose spikes after meals. They were encouraged to take snacks with carbohydrates of up to 10 g a day (This resulted in encouraging the intake of carbohydrate 70-130 g/day). This was for the purpose of ensuring the pleasure of eating. This moderately low-carbohydrate diet called Locabo resulted in an improvement in the control of blood glucose and triglyceride (***Fig. 5***) [54]. In this research, changes in body weight were not observed. However, as a result of the analysis of the changes in body weight of 200 subjects who were instructed with Locabo in another case, the more obese they were, the more substantially they could achieve weight loss, there was no change in those with a normal BMI, and those who had been thin gained body weight (due to increase of muscles) (***Fig. 6***) [55].

Another group drew on our research and released a report that the instruction of a low-carbohydrate diet of 130 g/day was superior in the control of blood glucose level and body weight than a low-energy diet [56].

As described above, there are some differences in the contents of the low-carbohydrate diets employed in each clinical trial. However, there is a report that there was no difference in body weight-loss effect between very low- and moderately low-carbohydrate diets, and the moderately low-carbohydrate diet maintained a weight loss effect for a longer period (***Fig. 7***) [57]. We are employing a moderately low-carbohydrate diet. Although there is also a report that a very low-carbohydrate diet is superior in the improvement of HbAlc than a moderate one [58], if several outliers are excluded, there appears to be no difference (***Fig. 8***).

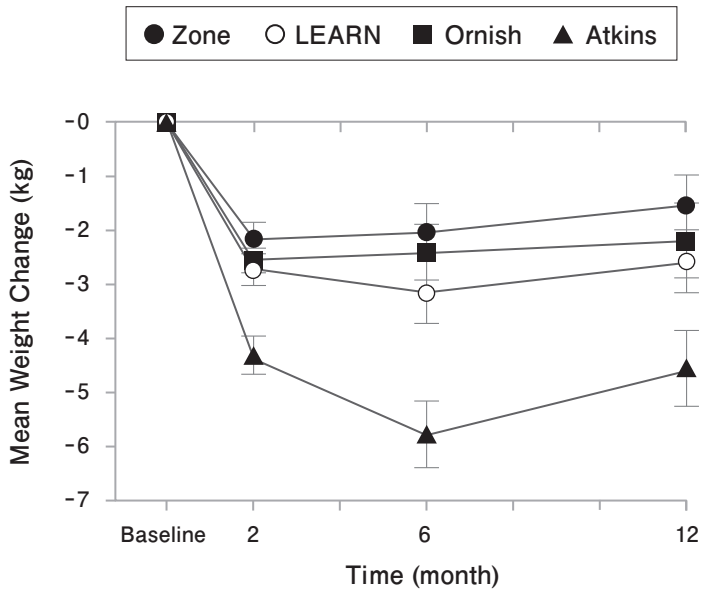


Fig. 3. **Body weight change in 4 types of dietary intervention in A to Z study.**

LEARN, Lifestyle, Exercise, Attitudes, Relationships and Nutrition; The LEARN diet is low in fat, is high in carbohydrates. The figure is quoted from Reference [48].

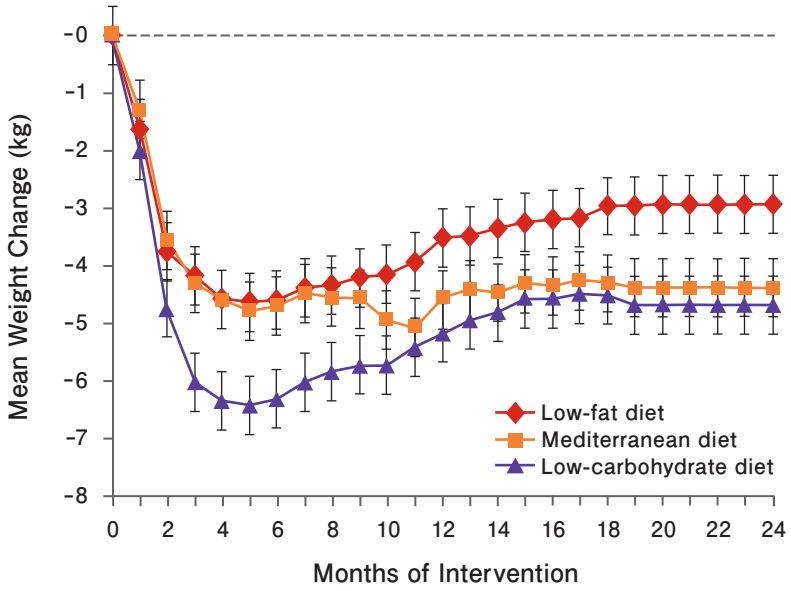


Fig. 4. **Body weight change in 4 types of dietary intervention in DIRECT trial.**

* $p < 0.001$ for both comparisons with the low-fat diet. The figure is quoted from Reference [49].

Table 1. Results of meta-analysis of RCT in 1,141 obese patients of 17 institutes.

Risk factor	Effect of low-carbohydrate diet	
Weight	−7.04 kg	(−7.20 to −6.88)
BMI	−2.09kg/m^2	(−2.15 to −2.04)
Abdominal girth	−5.74 cm	(−6.07 to −5.41)
BP (systolic)	−4.81 mmHg	(−5.33 to −4.29)
BP (diastolic)	−3.10 mmHg	(−3.45 to −2.74)
TG	−29.71 mg/dL	(−31.99 to −27.44)
FPG	−1.05 mg/dL	(−1.60 to −0.44)
Glycohemoglobin	−0.21%	(−0.24 to −0.18)
Serum IRI	−2.24 μIU/mL	(−2.65 to −1.82)
HDL-C	1.73 mg/dL	(1.44 to 2.01)

Parentheses indicate 95% CI. RCT, randomized controlled trial; BMI, body mass index: BP, blood pressure; TG, triglyceride; FPG, fasting plasma glucose; IRI, immune-reactive insulin; HDL-C, high-density lipoprotein-cholesterol; CI, confidence interval. The data are based on Reference [53].

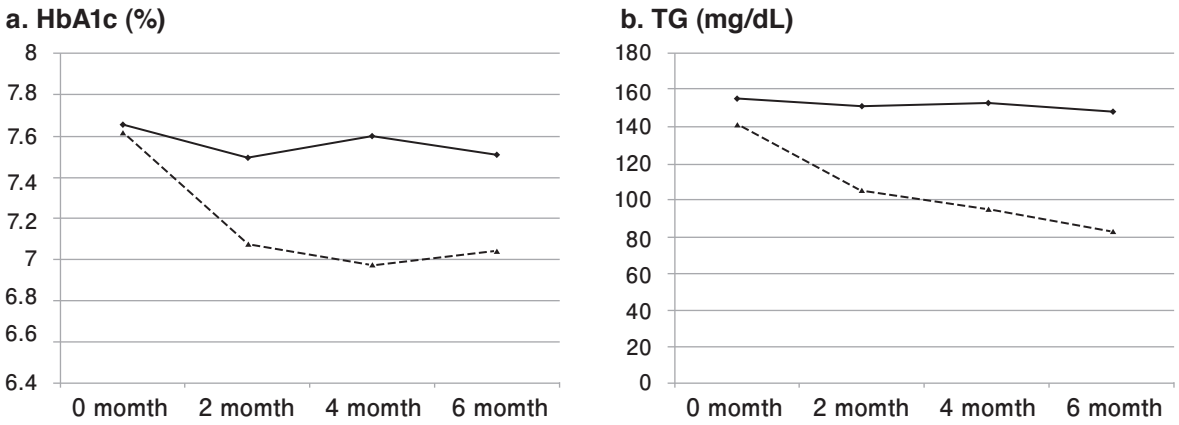
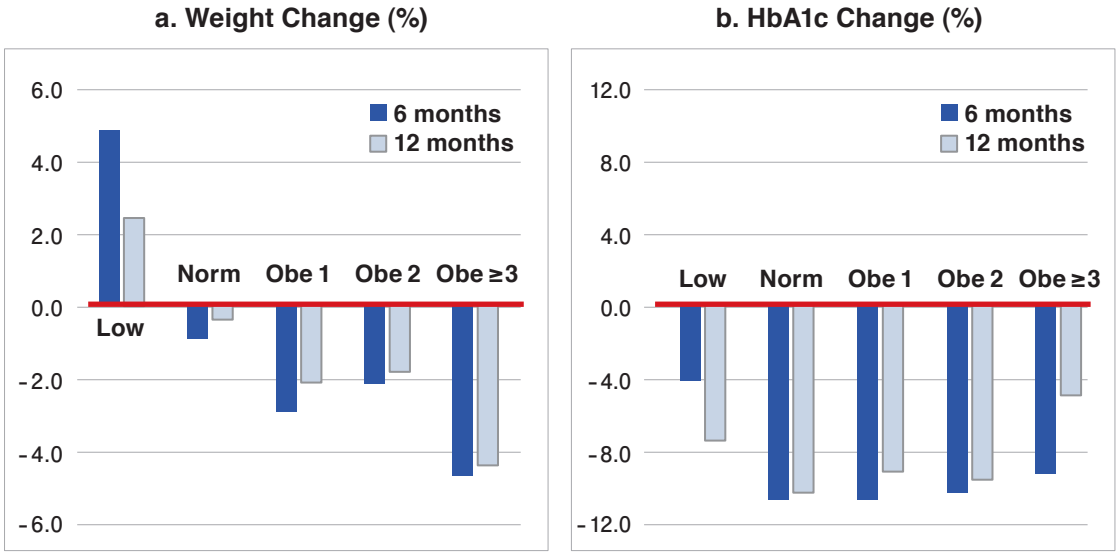


Fig. 5. **The changes in HbA1c and TG in Kitasato Institute Hospital Study.**

a. HbA1c, **b.** TG. TG, triglyceride. The figures are quoted from Reference [54].



	Classification	BMI	N
Low	Low weight (Thin)	<18.5	9
Norm	Normal weight	≧18.5, <25	73
Obe 1	Obesity (Level 1)	≧25, <30	74
Obe 2	Obesity (Level 2)	≧30, <35	29
Obe ≧3	Obesity (Level≧3)	≧35	9

Fig. 6. **Changes in body weight and HbA1c after Locabo induction.**
a. Weight change, **b.** HbA1c change. Locabo, low-carbohydrate diet; BMI, body mass index. The figures are quoted from Reference [55].

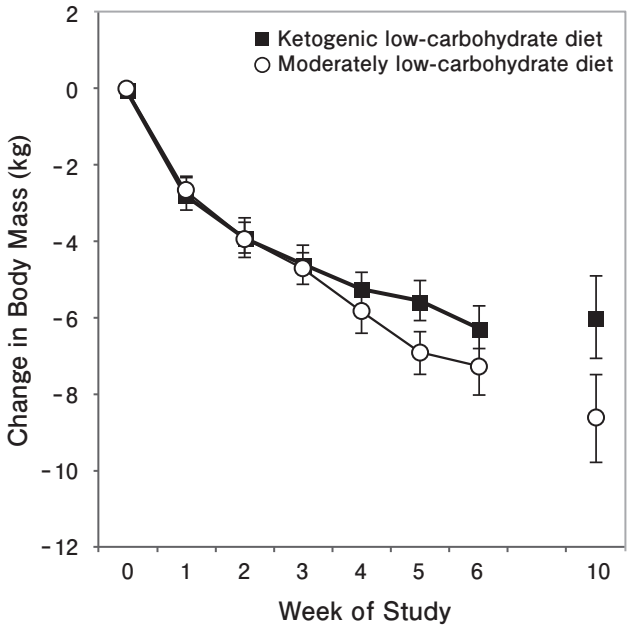


Fig. 7. **Body weight changes in ketogenic low-carbohydrate diet and non-ketogenic moderately low-carbohydrate diet.**
○ Non-ketogenic moderately low-carbohydrate diet;
■ Ketogenic low-carbohydrate diet. The figure is quoted from Reference [57].

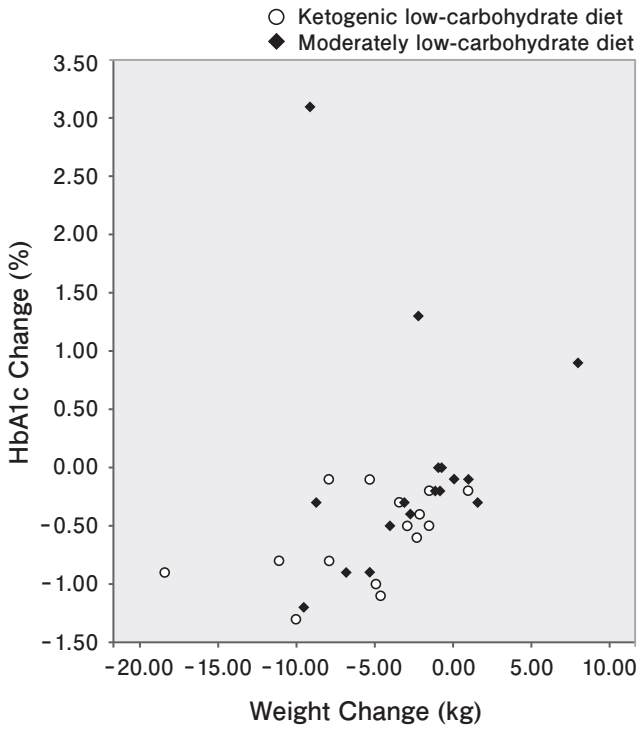


Fig. 8. **Body weight and HbA1c changes in ketogenic low-carbohydrate diet and non-ketogenic moderately low-carbohydrate diet.**
◆ Non-ketogenic moderately low-carbohydrate diet;
○ Ketogenic low-carbohydrate diet. The figure is quoted from Reference [57].

5. Appropriate Carbohydrate Intake to be Considered in terms of Quality

Along with the accumulation of medical evidence of low-carbohydrate diets controlling the quantity of carbohydrates, low glycemic index (GI) controlling the quality of carbohydrate has drawn attention. This was advocated by Jenkins *et al*. of Canada in 1981 [59] for the purpose of controlling blood glucose based upon the fact that when different carbohydrates of the same amount were consumed, the area under the blood glucose rising curve is different based on the food consumed.

However, because GI is an absolutely average value of multiple people, the blood glucose levels of all subjects are not always inhibited according GI [42]. The consumption of large amounts of food, even if it is of low GI, raises blood glucose level by that much.

The Omni Carb Trial is a clinical trial to verify whether quantity or quality of carbohydrates is more useful for the control of cardiovascular risk, and the results show that the quantity of carbohydrate was found to be more useful [60].

According to the research on the comparison between a low-carbohydrate diet and a low-energy diet with low GI food by Westman *et al*., the low-carbohydrate diet was more useful than the low energy diet for blood glucose control (improvement of HbA1c), even though it could not be statistically significant [61].

Furthermore, the direct effect of fructose in raising blood glucose level is small and its GI is around 20 (it is 100 for glucose). However, the comparison between the fructose only group and the glucose only group showed that the impaired glucose intolerance of the fructose consuming group was worse after three months. The reason for this is considered to be that the fatty liver of the fructose consuming group was more severe, and more visceral fat also was also accumulated. As a result, their insulin resistance became strong [62]. It is considered to be that because fructose works in the reward system of the brain, dependence tends to occur [63].

From the above, the way of thinking to depend upon GI only cannot inhibit postprandial hyperglycemia, so oxidative stress and glycation reactions cannot be stopped.

Nevertheless, owing to the aggressive study by Brand-Miller *et al*., it is known that a low GI diet is effective for blood glucose control [64]. When it is difficult to control the intake of carbohydrates by quantity, it will be effective to consider the quality.

6. Appropriate Carbohydrate Intake to be Considered in terms of Eating Order

There is an eating order for the diet to make the best use of the actions by proteins, fat and dietary fibers in the inhibition of postprandial hyperglycemia. Although in the earliest years, the importance of eating vegetables first was advocated [65], and after that it was verified that meat and fish also have the same effect as vegetables [65], so that it has come to be recognized that it is important to eat carbohydrates last. Although enough data have not been collected from a global standpoint, it may be theoretically correct.

7. Appropriate Carbohydrate Intake to be Considered in terms of Consistency

So far it has been shown that postprandial hyperglycemia can be corrected by focusing on the fact that (1) it is a time of a great paradigm shift in nutritional science (2) in which low-carbohydrate diet has been verified to be medically effective and (3) low GI diet and eating order diet in addition to a low carbohydrate diet are also focused on.

However, we consider that a moderately low-carbohydrate diet (Locabo) is the best way to consume carbohydrates from the perspective of the consistency of the Japanese diet.

The definition of Locobo is described here again. Consume 20-40 g of carbohydrates per meal, and additionally consume up to 10 g/day as a snack. As a result, the carbohydrate intake amount per day is from 70 to 130 g/day. When advocating Locabo, its slogan is “Enjoy delicious meals and good health.” More specifically considered, the intake of carbohydrates by the Japanese at present, 260-300 g/day, should be reduced by more than half. According to the experience in the Kitasato Institute Hospital, the ratios of carbohydrates and fat and protein of the Locabo diet are 30%, 40-45% and 25-30%, respectively. According to Dietary Reference Intakes, an appropriate ratio of carbohydrate, fat and protein is 50-65%, 20-30% and 13-20%, respectively. As previously mentioned, although there is no medical reason for these nutrition ratios, due to the Locabo diet, the present carbohydrate intake of Japanese is halved.

Furthermore, studies on how to decide the ratios of fat and protein for this low-carbohydrate diet is insufficient. Prof. Westman of Duke University and other research groups of Nordic countries prefer a low-carbohydrate and high-fat diet, and Prof. Ebbeling *et al*. consider a low-carbohydrate and high-protein diet to be preferable. We personally consider that you have to only consume meat, fish and soybean products regardless of likes or dislikes as to the sources of protein intake and to use olive oil, sesame oil and butter as seasoning when necessary without being biased by either a low-carbohydrate and high-fat diet or low-carbohydrate and high-protein diet.

I think that the diet called Locabo presumably has merit to men and women of all ages and it has no demerit. It is not that the merit cannot be obtained at all if your diet doesn’t perfectly fall under the definition of Locabo. Because the carbohydrate restriction and its effect on the improvement of blood glucose are in linear correlation [67, 68], if the intake of 100 g of carbohydrates per meal is reduced to 60 g, the effect for that amount can be expected (2/3 of the effect at the time when it is 40g).

Meanwhile, even if a strict low-carbohydrate diet of less than 20 g per meal is practiced, there is no guarantee that the merit will increase but it may possibly cause medical demerits [57]. In addition to these medical demerits, a strict low-carbohydrate diet of less than 20 g per meal limits the kinds of vegetables that can be eaten and it will possibly reduce the quality of life. We should enjoy happy eating habits, not being stoic. This is the condition of Locabo which we consider to be an appropriate method of intake for carbohydrates.

8. Conclusion

Japanese people consumed large amount of rice (carbohydrate) in the past but they did not suffer lifestyle-related diseases as they do today. Therefore, a prevalent way of thinking is that it is not necessary to decrease carbohydrates. It sounds persuasive to some people. However, we should remember that Japan had been importing rice until around 1950 and it was around 1965 when Japan was able to achieve self-sufficiency in rice [69]. Even though Japanese eating habits were healthy during the 10 years around 1960, it should not be forgotten that it was under the condition at the time "when the physical activities of Japanese during 10 years around 1960 could be regained".

There is a report that the amount of physical activity is correlated not only with insulin sensitivity (ability to process glucose in response to a certain amount of insulin) but also the insulin secretion ability of the pancreas (ability to secrete insulin in response to certain blood glucose levels) [70].

Locabo is an appropriate carbohydrate intake method for most Japanese people at present. However, those who want to consume more carbohydrates will be able to enhance the ability to process carbohydrates and appropriately consume more carbohydrate by increasing their physical activities and building their muscle mass.

Meanwhile, there is a report that the amount of glycogen in the muscles and its performance in marathon runners and triathletes who were practicing carbohydrate restriction were not different from those of the people who were consuming a high carbohydrate diet (carbohydrate loading so to speak), so it does not mean carbohydrate intake should be increased just because the person is doing exercise [71, 72].

It is desirable that many Japanese promote their health while enjoying happy eating habits thanks to the prevalence of the thinking way of Locabo. We would be happy if the readers of this paper will participate in this approach.

Conflict of interest

The authors declare no conflict of interest in this study.

Acknowledgement

The outline of this study was presented at the 12th meeting of Society for Glycative Stress Research (May 26, 2017, Tokyo),

Reference

1) Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006; 295: 1681-1687.
2) Rizzo MR, Marfella R, Barbieri M, et al. Relationships between daily acute glucose fluctuations and cognitive performance among aged type 2 diabetic patients. Diabetes Care. 2010; 33: 2169-2174.
3) Delbridge LM, Benson VL2, Ritchie RH, et al. Diabetic cardiomyopathy: The case for a role of fructose in disease etiology. Diabetes. 2016; 65: 3521-3528.
4) Mozaffarian D,Ludwig DS. The 2015 US Dietary Guidelines: Lifting the ban on total dietary fat. JAMA. 2015; 313: 2421-2422.
5) Bantle JP, Wylie-Rosett J, Albright AL, et al. Nutrition recommendations and interventions for diabetes-2006: A position statement of the American Diabetes Association. Diabetes Care. 2006; 29: 2140-2157.
6) American Diabetes Association, Bantle JP, Wylie-Rosett J, Albright AL, et al. Nutrition recommendations and interventions for diabetes: A position statement of the American Diabetes Association. Diabetes Care. 2008; 31(suppl 1): S61-S78.
7) Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care. 2013; 36: 3821-3842.
8) American Diabetes Association. Principles of nutrition and dietary recommendations for patients with diabetes mellitus: 1971. Diabetes. 1971; 20: 633-634.
9) American Diabetes Association. Nutrition recommendations and principles for people with diabetes mellitus. Diabetes Care. 1994; 17: 519-522.
10) Colman RJ, Anderson RM, Johnson SC, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science. 2009; 325: 201-204.
11) Lipkin EW, Schwartz AV, Anderson AM, et al. The LookAHEAD Trial: Bone loss at 4-year follow-up in type 2 diabetes. Diabetes Care. 2014; 37: 2822-2829.
12) Colman RJ, Beasley TM, Allison DB, et al. Skeletal effects of long-term caloric restriction in rhesus monkeys. Age (Dordr). 2012; 34: 1133-1143.
13) Mattison JA, Roth GS, Beasley TM, et al. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. Nature. 2012; 489: 318-321.
14) Ravussin E, Redman LM, Rochon J, et al. A 2-year randomized controlled trial of human caloric restriction: Feasibility and effects on predictors of health span and longevity. J Gerontol A Biol Sci Med Sci. 2015; 70: 1097-1104.
15) Villareal DT, Fontana L, Das SK, et al. Effect of two-year caloric restriction on bone metabolism and bone mineral density in non-obese younger adults: A randomized clinical trial. J Bone Miner Res. 2016; 31: 40-51.
16) DAS SK, Roberts SB, Bhapkar MV, et al. Body-composition changes in the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE)-2 study: A 2-y randomized controlled trial of calorie restriction in nonobese humans. Am J Clin Nutr. 2017; 105: 913-927.
17) Rannie KL, Coward A, Jebb SA. Estimating under-reporting of energy intake in dietary surveys using an individualised method. Br J Nutr. 2007; 97: 1169-1176.

18) Redman LM, Kraus WE, Bhapkar M, et al. Energy requirements in nonobese men and women: Results from CALERIE. Am J Clin Nutr. 2014; 99: 71-78.
19) Ministry of Health, Labour and Welfare. Energy. Overview of Dietary Reference Intakes for Japanese (2015), pp45-87, 2014. (in Japanese)
20) Heianza Y, Arase Y, Kodama S, et al. Trajectory of body mass index before the development of type 2 diabetes in Japanese men: Toranomon Hospital Health Management Center Study 15. J Diabetes Investig. 2015; 6: 289-294.
21) Keys A. Atherosclerosis: A problem in newer public health. J Mt Sinai Hosp N Y. 1953; 20: 118-139.
22) Wheeler ML, Dunbar SA, Jaacks LM, et al. Macronutrients, food groups, and eating patterns in the management of diabetes: A systematic review of the literature, 2010. Diabetes Care. 2012; 35: 434-445.
23) Harcombe Z, Baker JS, Cooper SM, et al. Evidence from randomised controlled trials did not support the introduction of dietary fat guidelines in 1977 and 1983: A systematic review and meta-analysis. Open Heart. 2015; 2: e000196.
24) Harcombe Z, Baker JS, DiNicolantonio JJ, et al. Evidence from randomised controlled trials does not support current dietary fat guidelines: A systematic review and meta-analysis. Open Heart. 2016; 3: e000409.
25) Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: Time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation. 2002; 105: 1897-1903.
26) Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013; 368: 1279-1290.
27) Ramsden CE, Zamora D, Leelarthaepin B, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: Evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. BMJ. 2013; 346: e8707.
28) Ramsden CE, Zamora D, Majchrzak-Hong S, et al. Re-evaluation of the traditional diet-heart hypothesis: Analysis of recovered data from Minnesota Coronary Experiment (1968-73). BMJ. 2016; 353: i1246.
29) Sauvaget C, Nagano J, Hayashi M, et al. Animal protein, animal fat, and cholesterol intakes and risk of cerebral infarction mortality in the adult health study. Stroke. 2004; 35, 1531-1537.
30) Yamagishi K, Iso H, Yatsuya H, et al. Dietary intake of saturated fatty acids and mortality from cardiovascular disease in Japanese: The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC) Study. Am J Clin Nutr. 2010; 92: 759-765.
31) Yamagishi K, Iso H, Kokubo Y, et al. Dietary intake of saturated fatty acids and incident stroke and coronary heart disease in Japanese communities: The JPHC Study. Eur Heart J. 2013; 34: 1225-1232.
32) Dehghan M, Mente A, Zhang X, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): A prospective cohort study. Lancet. 2017; 390: 2050-2062.
33) Newburgh LH. The production of Bright's disease by feeding high protein diets. Arch Intern Med. 1919; 24: 359-377.
34) Klahr S, Buerkert J, Purkerson ML. Role of dietary factors in the progression of chronic renal disease. Kidney Int. 1983; 24: 579-587.
35) Knight EL, Stampfer MJ, Hankinson SE, et al. The impact of protein intake on renal function decline in women with normal renal function or mild renal insufficiency. Ann Intern Med. 2003; 138: 460-467.
36) Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med. 1994; 330: 877-884.
37) Menon V, Kopple JD, Wang X, et al. Effect of a very low-protein diet on outcomes: Long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. Am J Kidney Dis. 2009; 53: 208-217.
38) Ministry of Health, Labour and Welfare.Energy-providing Nutrient Balance. Overview of Dietary Reference Intakes for Japanese (2015). pp153-163, 2014. (in Japanese)
39) Council on Foods and Nutriton of American Medical Association. A critique of low-carbohydrate ketogenic weight reduction regimens: A review of Dr. Atkins' Diet Revolution. JAMA. 1973; 224: 1415-1419.
40) Bao J, Atkinson F, Petocz P, et al. Prediction of postprandial glycemia and insulinemia in lean, young, healthy adults: Glycemic load compared with carbohydrate content alone. Am J Clin Nutr. 2011; 93: 984-996.
41) Kameyama N, Maruyama C, Matsui S, et al. Effects of consumption of main and side dishes with white rice on postprandial glucose, insulin, glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 responses in healthy Japanese men. Br J Nutr. 2014; 111: 1632-1640.
42) Zeevi D, Korem T, Zmora N, et al. Personalized nutrition by prediction of glycemic responses. Cell. 2015; 163: 1079-1094.
43) Gao Y, Bielohuby M, Fleming T, et al. Dietary sugars, not lipids, drive hypothalamic inflammation. Mol Metab. 2017; 6: 897-908.
44) Kitabchi AE, McDaniel KA, Wan JY, et al. Effects of high-protein versus high-carbohydrate diets on markers of β-cell function, oxidative stress, lipid peroxidation, proinflammatory cytokines, and adipokines in obese, premenopausal women without diabetes: A randomized controlled trial. Diabetes Care. 2013; 36: 1919-1925.
45) Roberts MN, Wallace MA, Tomilov AA, et al. A ketogenic diet extends longevity and healthspan in adult mice. Cell Metab. 2017; 26: 539-546.
46) Gunn DA, Rexbye H, Griffiths CE, et al. Why some women look young for their age. PLoS One. 2009; 4: e8021.
47) Christensen K, Thinggaard M, McGue M, et al. Perceived age as clinically useful biomarker of ageing: Cohort study. BMJ. 2009; 339: b5262.
48) Gardner CD, Kiazand A, Alhassan S, et al. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: The A TO Z weight loss study: A randomized trial. JAMA. 2007; 297: 969-977.
49) Shai I, Schwarzfuchs D, Henkin Y, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med. 2008; 359: 229-241.

50) Tirosh A, Golan R, Harman-Boehm I, et al. Renal function following three distinct weight loss dietary strategies during 2 years of a randomized controlled trial. Diabetes Care. 2013; 36: 2225-2232.
51) Shai I, Spence JD, Schwarzfuchs D, et al. Dietary intervention to reverse carotid atherosclerosis. Circulation. 2010; 121: 1200-1208.
52) Schwarzfuchs D, Golan R, Shai I. Four-year follow-up after two–year dietary intervention. N Engl J Med. 2012; 367: 1373-1374.
53) Santos FL, Esteves SS, da Costa Pereira A, et al. Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. Obes Rev. 2012; 13: 1048-1066.
54) Yamada Y,Uchida J, Izumi H, et al. A non-calorie-restricted low-carbohydrate diet is effective as an alternative therapy for patients with type 2 diabetes. Intern Med. 2014; 53: 13-19.
55) Yamada S. Paradigm shifts in nutrition therapy for type 2 diabetes. Keio J Med. 2017; 66: 33-43.
56) Sato J, Kanazawa A, Makita S, et al. A randomized controlled trial of 130 g/day low-carbohydrate diet in type 2 diabetes with poor glycemic control. Clin Nutr. 2017; 36: 992-1000.
57) Johnston CS, Tjonn SL, Swan PD, et al. Ketogenic low-carbohydrate diets have no metabolic advantage over nonketogenic low-carbohydrate diets. Am J Clin Nutr. 2006; 83: 1055-1061.
58) Saslow LR, Kim S, Daubenmier JJ, et al. A randomized pilot trial of a moderate carbohydrate diet compared to a very low carbohydrate diet in overweight or obese individuals with type 2 diabetes mellitus or prediabetes. PLoS One. 2014; 9: e91027.
59) Jenkins DJ, Wolever TM, Taylor RH, et al. Glycemic index of foods: A physiological basis for carbohydrate exchange. Am J Clin Nutr. 1981; 34: 362-366.
60) Sacks FM, Carey VJ, Anderson CA, et al. Effects of high vs low glycemic index of dietary carbohydrate on cardiovascular disease risk factors and insulin sensitivity: The OmniCarb randomized clinical trial. JAMA. 2014; 312: 2531-2541.
61) Westman EC, Yancy WS Jr, Mavropoulos JC, et al. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. Nutr Metab (Lond). 2008; 5: 36.
62) Stanhope KL, Schwarz JM, Keim NL, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. J Clin Invest. 2009; 119: 1322-1334.
63) Page KA, Chan O, Arora J, et al. Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways. JAMA. 2013; 309: 63-70.
64) Brand-Miller J, Hayne S, Petocz P, et al. Low-glycemic index diets in the management of diabetes: A meta-analysis of randomized controlled trials. Diabetes Care. 2003; 26: 2261-2267.
65) Imai S, Matsuda M, Hasegawa G, et al. A simple meal plan of 'eating vegetables before carbohydrate' was more effective for achieving glycemic control than an exchange-based meal plan in Japanese patients with type 2 diabetes. Asia Pac J Clin Nutr. 2011; 20: 161-168.
66) Kuwata H, Iwasaki M, Shimizu S, et al. Meal sequence and glucose excursion, gastric emptying and incretin secretion in type 2 diabetes: A randomised, controlled crossover, exploratory trial. Diabetologia. 2016; 59: 453-461.
67) Kirk JK, Graves DE, Craven TE, et al. Restricted-carbohydrate diets in patients with type 2 diabetes: A meta-analysis. J Am Diet Assoc. 2008; 108: 91-100.
68) Snorgaard O, Poulsen GM, Andersen HK, et al. Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. BMJ Open Diabetes Res Care. 2017; 5: e000354.
69) Agriculture, Forestry and Fisheries Research Council. Changes in supply and demand of rice. Research and development of rice aimed at new applications. Agriculture Research and Development Report. 2006; 18: 1-2. (in Japanese)
70) Chen Z, Black MH, Watanabe RM, et al. Self-reported physical activity is associated with β-cell function in Mexican American adults. Diabetes Care. 2013; 36: 638-644.
71) Volek JS, Freidenreich DJ, Saenz C, et al. Metabolic characteristics of keto-adapted ultra-endurance runners. Metabolism. 2016; 65: 100-110.
72) McSwiney FT, Wardrop B, Hyde PN, et al. Keto-adaptation enhances exercise performance and body composition responses to training in endurance athletes. Metabolism. 2017; Nov 3.