Review

The Optimal Dietary Fat to Carbohydrate Ratio to Prevent Obesity in the Japanese Population: A Review of the Epidemiological, Physiological and Molecular Evidence

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(Received July 13, 2011)

Summary The prevention of obesity, which leads to diabetes and other diseases, is a major concern for public health. There might be an optimal dietary fat to carbohydrate ratio for prevention and treatment of obesity. According to the Japanese Dietary Reference Intakes (RDA) for 2010, the optimal fat intake is 20–30% of energy for ages 1–29 y and 20–25% for ages 30 y and over. Upper boundary values of this recommendation were the median of the percentage of energy from dietary fat in Japanese. In a systematic review to estimate the optimal dietary fat to carbohydrate ratio, it was found that obese subjects with hyperinsulinemia (or insulin resistance) lost more weight on a mild low-carbohydrate (LC) (or low-glycemic load diet; 40% carbohydrate, 30–35% fat) than on a low-fat (LF) diet (55–60% carbohydrate, 20% fat), whereas those without hyperinsulinemia showed the opposite. In non-obese primarily insulin-sensitive subjects, decreasing fat rather than carbohydrate intake is generally more effective to prevent obesity. Physiological and molecular evidence supports this conclusion. Increased carbohydrate intake, especially in high-glycemic food, leads to postprandial hyperglycemia and hyperinsulinemia, which are exaggerated in obese insulin-resistant subjects. Even in an insulin-resistant state, insulin is able to stimulate fatty acid synthesis in liver, activate lipoprotein lipase, and prevent lipolysis in adipose tissues, which all facilitate adipose tissue enlargement. Optimal dietary fat to carbohydrate ratio may differ in populations depending on their prevalence for obesity. Because the prevalence of overweight/obesity in Japanese is low, a LF diet is recommended in the general population.

Key Words low-carbohydrate diet, low-fat diet, RDA, insulin resistance, obesity

Obesity in the United States and in much of the westernized world has increased dramatically over the past several decades: 64.5% of adults in the United States are overweight (body mass index [BMI] ≥ 25 kg/m² and < 30 kg/m²) or obese (BMI ≥ 30 kg/m²) (1). Overweight/obesity (BMI ≥ 25 kg/m²) was the most important predictor of diabetes. In the Nurses' Health Study, during 16 y of follow-up, 3,300 new cases of type 2 diabetes were observed in the baseline population of 84,941 female nurses. The relative risk of diabetes was 38.8 for women with a BMI of 35.0 kg/m² or higher, 20.1 for women with BMI of 30.0 to 34.5 kg/m², and 7.59 for women with BMI of 25.0 to 29.9 kg/m², as compared with women who had a BMI of less than 23.0 kg/m² (2).

In Japan, the prevalence of overweight/obesity (BMI ≥ 25 kg/m²) in adults is very low compared with the United States: 30.4% in men and 20.2% in women in 2007, according to Japanese cross-sectional nationwide surveys (3). However, a strong positive association between baseline BMI and the incidence of diabetes in

the follow-up period was observed similar to that in the United States. In a Japanese cohort of healthy men ($n=16,829$) and women ($n=8,370$) followed for 7.4 y, new cases of diabetes were documented in 869 men and 224 women (4). The relative risk of diabetes was 5.55 for men with a BMI of 25.2 to 26.3, compared with men who had a BMI of 15.0 to 19.7, and the relative risk of diabetes was 5.70 for women with a BMI of 24.4 to 25.9, compared with women who had a BMI of 14.9 to 19.1. Therefore, in Japan also, the prevention of overweight/obese subjects is a major public issue.

The role of dietary fat and carbohydrate in the obesity epidemic has been a hotly debated topic for decades and remains unresolved. To reduce the incidence of obesity in general populations, public statements on optimal ratios of dietary fat to carbohydrate have been issued. Health organizations have recommended diets that are low in total and saturated fat and high in carbohydrates obtained from vegetables, fruits, and whole grains or fiber-rich foods (5–7). Dietary guidelines for Americans published in 2005 emphasized the importance of the amount of energy consumed rather than the proportions of protein, fat, and carbohydrate in the diet, pro-

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vided that the macronutrients are within the AMDR, the acceptable macronutrient distribution range: 10–35% of energy from protein, 45–65% from carbohydrate, and 20–35% from fat (8). Dietary reference intakes for Japanese issued by the Ministry of Health, Labour, and Welfare in 2010 indicated that optimal fat intake is 20–30% for ages 1–29 y and 20–25% for ages 30 y and over. Upper boundary values of this recommendation were a median of the percentage of energy from dietary fat in Japanese, a recommendation that most Japanese are able to follow.

The present review was conducted to determine the optimal dietary fat to carbohydrate ratio to prevent obesity in the Japanese population. As a result, it was suggested that a mild low-carbohydrate (LC) diet was effective in reducing body weight in obese subjects with hyperinsulinemia (or insulin resistance), whereas a low-fat (LF) diet favored prevention of obesity in non-obese subjects or treatment of obese subjects without hyperinsulinemia. In addition, to elucidate the molecular mechanisms of obesity in response to a carbohydrate-rich diet, several aspects of insulin actions, namely lipogenesis in the liver, activation of lipoprotein lipase (LPL), and lipolysis under insulin-resistance state were also reviewed.

Methods of Review and Definitions

Selection of publications of epidemiological studies. For epidemiological studies, key words “(Diet, Fat-Restricted [MESH]) AND (dietary OR intake OR consumption) AND ((randomized controlled trial [PTYP] OR random [WORD]) OR (cohort studies [MESH] OR risk [MESH] OR (odds [WORD] AND ratio [WORD]) OR (relative [WORD] AND risk [WORD]) OR case control [WORD] OR case-control studies [MESH]))” with a limitation of “humans” were used in PubMed to select all publications through June 1, 2011 ($n=1,004$), initially to review the effects of dietary fat on mortality and mobility reported therein. From these publications, those related to changes in body weight were selected and reviewed. Other important topics, such as the effects of dietary fat subtypes, i.e., saturated, mono-unsaturated, $n-6$, and $n-3$ fatty acids, on obesity, are not discussed in this review. Because several reviews and meta-analyses have been published since the original search date, publications that appeared after this date are presented in this study with comments relating their findings to those of the previous reviews and meta-analyses. To show a visual representation of the results of the review, findings from representative publications are presented here in figures.

Current body weight is the result of the accumulated daily balance of energy intake and expenditure over previous days. Therefore, the causes of obesity are multifactorial, including such factors as physical activity level, energy intake, and food availability. It is difficult to assess these factors, and there are strong limitations to examining the effects of dietary macronutrients on obesity in cross-sectional and prospective studies (confounding factors may not be measured adequately). For

this reason, carefully conducted intervention studies in which dietary fat to carbohydrate ratios were changed were mostly selected for this review.

Selection of publications of physiological and molecular studies. In a review of the mechanism of lipogenic action of insulin (covered later in this review), key words “insulin AND obesity AND ((lipogenesis AND liver) OR LPL OR (lipolysis and adipose tissues))” were used initially in PubMed to select appropriate publications, including reviews. Additional publications, which were necessary to describe the effects of insulin in an insulin-resistance state, were included from citations obtained from review articles and personal reference lists.

Definitions of LF and LC diets. The term LF diet is used relative to that of a high-fat diet in the literature; therefore, the absolute amounts of fat were diverse. In general, a high-fat diet means fat intake provides more than 30% of energy and a LF diet means less than 30%. The LC diet has been used in two different types of diet: a very LC diet (ketogenic diet) and a mild LC diet (low-glycemic load diet). Glycemic load is the mathematical product of glycemic index and carbohydrate amount. In the ketogenic diet, carbohydrate intake is less than 40 g/d (9), whereas in the low-glycemic load diet, the total amount of carbohydrate is decreased by 10–20% of energy, and foods containing carbohydrate with lower glycemic index were used. In Japanese, median intake of energy in adults was 1,856 kcal/d, and median intakes of carbohydrate, fat, and protein were 258 g/d (56% of energy), 51 g/d (24.8%), and 68 g/d (15%), respectively, according to The National Health and Nutrition Survey in Japan, 2007 (3). In this review, these two types of LC diets are reviewed separately.

Results and Discussion

A LF diet prevents obesity in general populations

In a meta-analysis of general populations under free-living conditions, weight loss was positively and independently associated with a reduction in the percentage of energy as fat (0.37 kg/%, $p<0.005$) (10). Another meta-analysis of intervention studies also supports this conclusion (11). For every 1% decrease in energy from fat, there was a 0.28-kg decrease in body weight.

A large randomized intervention trial including 48,835 post-menopausal women in the United States (The Women's Health Initiative Dietary Modification Trial) also supports a LF diet for the prevention of obesity (12). This intervention included group and individual sessions to promote a decrease in fat intake and did not include weight loss or energy restriction goals. Energy from fat was decreased from 38.8% to 29.8% in the intervention group, whereas there was no alteration of fat intake in the control group (from 38.8% to 38.1%). Concomitantly, energy from carbohydrate was increased from 44.5% to 52.7% in the intervention group, whereas there was no alteration of carbohydrate intake in the control group (from 44.5% to 44.7%). Women in the intervention group lost weight in the first year and maintained a lower weight than the control

Fig. 1. Differences in body weight by body mass index (BMI) at screening in response to a low-fat (LF) diet. A large randomized intervention trial including 48,835 post-menopausal women during an average 7.5 y of follow-up supports a LF diet (energy from fat decreased from 38.8% to 29.8%) but not energy intake for the prevention of obesity. Women in the intervention groups lost weight in the first year and maintained lower weight than did women in the control groups. No tendency toward weight gain was observed in the intervention groups, whereas body weights in the control groups gradually increased. Error bars indicate 95% confidence intervals. Patient numbers at baseline for the intervention and control groups by BMI: BMI <25 kg/m², 5,072 and 7,585; BMI 25–29.9 kg/m², 6,940 and 10,446; and BMI ≥30 kg/m², 7,442 and 11,126, respectively. Reproduced with permission (12).

women over an average 7.5 y of follow-up (Fig. 1). No tendency toward weight gain was observed in the intervention group, whereas body weights in the control group gradually increased. In both groups, weight loss was greatest among women who decreased their percentage of energy from fat. Weight loss in response to fat reduction was also slightly greater in subjects with a baseline BMI of <25 kg/m².

Several mechanisms for body fat increase in response to a high-fat intake have been proposed (13, 14). Fat is the most energy-dense of the macronutrients and is palatable. Fat produces less of a thermogenic effect than does carbohydrate (15, 16), and fat intake is not regulated, whereas carbohydrate intake is regulated for combustion of carbohydrate substrates (17). A prompt increase in glucose oxidation occurs after ingestion of carbohydrate-containing meals, whereas fat oxidation is reduced after food consumption, even when meals provide substantial amounts of fat (18). These findings indicate that when energy intake is not intentionally restricted, a LF diet prevents body weight increase in the general population.

A very LC diet (ketogenic diet) decreases body weight in obese subjects

Intervention studies to compare the efficacy of LF and very LC diets to reduce body weight in obese subjects have been conducted and summarized in several meta-analyses (19–22). All analyses revealed that a very LC diet is more effective than a LF diet in reducing body weight in obese subjects. In a recent meta-analysis performed by Hession et al., studies comparing the weight loss effects of a very LC diet (less than 60 g/d carbohydrate without intentional energy restriction) against a LF diet with energy restriction (less than 30% fat with 600 kcal/d energy restriction) of more than 6 mo were included (21). Among 9 studies analyzed ($n=690$ in total), 6 studies (23–28) showed greater reduction in body weight by LC diet than by LF diet, whereas 3 studies (29–31) reported no differences between LC and LF diets in the decrease of body weight when measured at 6 mo of intervention.

However, several adverse effects were observed in a very LC diet. A meta-analysis showed an increase in LDL cholesterol (22). Increased blood ketone productions showed unfavorable effects, such as hyperuricemia and orthostatic hypotension (32). Recently, even under energy restricted conditions, it was reported that a very LC diet (60% fat/5% carbohydrate) for 6 wk (33) or a very LC diet (60% fat/4% carbohydrate) for 1 y (34) reduced endothelium-dependent flow-mediated dilation of brachial arteries. A relatively very LC diet (60% fat/20% carbohydrate) worsened the aortic augmentation index (35). These adverse effects might be mediated by a large amount of dietary fat. Therefore, a very LC diet was not recommended in the general population.

Mixed evidence that a mild LC diet (low-glycemic diet) decreases body weight in obese subjects

In a Cochrane review, a low-glycemic-index or low-glycemic load diet was compared with a high-glycemic-index or high-glycemic-load diet on different indices of body fat in 6 studies (36). Pooled data from 4 studies (37–40) showed that weight loss was significantly greater in participants ($n=163$ in total) receiving the low-glycemic diet (-1.1 kg of difference, $p<0.05$). Other studies reported a favorable percent change in body mass (41) or a favorable change in BMI on a low-glycemic diet (39, 42).

However, two recent intervention studies suggested that reduced-calorie diets resulted in meaningful weight loss, regardless of macronutrient balance. In one study, a total of 34 healthy overweight adults ate a high-glycemic load diet (20% fat, 20% protein, and 60% carbohydrate) or a low-glycemic load diet (30% fat, 30% protein, and 40% carbohydrate) under 30% energy-restricted conditions (43). There was no significant change in body weight between the two groups: percentage weight change at 12 mo was $-8.04 \pm 4.1\%$ in the high-glycemic load diet group and $-7.81 \pm 5.0\%$ in the low-glycemic load diet group. In the other study, a total of 811 overweight adults (BMI >25 kg/m²) ate one of four diets for 2 y (44). The targeted percentages of energy derived from fat, protein, and carbohydrate in

Fig. 2. Changes in body weight in insulin-sensitive and -resistant obese subjects. Obese nondiabetic insulin-sensitive (insulin concentration $\leq 57.5 \mu\text{U/mL}$ at 30 min after 75-g dose of oral glucose, $n=28$) and obese nondiabetic insulin-resistant (insulin concentration $> 57.5 \mu\text{U/mL}$ at 30 min after 75-g dose of oral glucose, $n=28$) young adults were randomized to either a low-fat diet (55% carbohydrate of energy, 20% fat, and 25% protein) or a low-glycemic load diet (or a low-carbohydrate diet; 40% carbohydrate, 35% fat, and 25% protein) for a 6-mo intervention and a 12-mo follow-up period. In the insulin-resistant groups, a low-glycemic load diet produced a greater decrease in weight than did the low-fat diet at 18 mo. Reproduced with permission (47).

the four diets were 20%, 15%, and 65% (LF/low protein [LP] diet); 20%, 25%, and 55% (LF/high protein [HP] diet); 40%, 15%, and 45% (LC/LP diet); and 40%, 25%, and 35% (LC/HP diet). At 2 y, weight loss remained similar in those who were assigned to a diet with 15% or 25% protein (3.0 and 3.6 kg, respectively), in those assigned to a diet with 20% fat or 40% fat (3.3 kg for both groups), and in those assigned to a diet with 65% carbohydrate or 35% carbohydrate (2.9 and 3.4 kg, respectively). There were no differences in reduction of body weights between groups when measured at 6, 12, and 18 mo. When considering the results of recent intervention studies, it is not conclusive that a mild LC diet is preferable for obese subjects.

A mild LC diet preferentially reduces body weights in obese subjects with hyperinsulinemia (insulin resistance)

The studies described above comprised mixed populations of insulin-sensitive and insulin-resistant obese subjects. However, when only the publications that separately examine the effects of LF and mild LC diets on body weight decrease in insulin-sensitive and insulin-resistant subjects were selected, a clear picture appeared. In obese subjects with hyperinsulinemia and insulin resistance, a mild LC diet was more likely than was a LF diet to reduce body weight under energy-restricted conditions (45–47).

In the first intervention study, obese nondiabetic insulin-sensitive (fasting insulin $< 10 \mu\text{U/mL}$, $n=12$) and obese nondiabetic insulin-resistant (fasting insulin $> 15 \mu\text{U/mL}$, $n=9$) women were randomized to either a LF diet (60% carbohydrate, 20% fat, and 20% protein) or a mild LC diet (40% carbohydrate, 40% fat, and 20% protein) for 16 wk under a 400-kcal energy deficit/d (45). A marked difference was observed in body weight reduction. Insulin-sensitive women on the LF diet lost $13.5 \pm 1.2\%$ ($n=6$) of their initial body weight, whereas those on the mild LC diet lost $6.8 \pm 1.2\%$ ($n=6$). In contrast, among the insulin-resistant women, those on the mild LC diet lost $13.4 \pm 1.3\%$ ($n=5$) of their initial body

weight as compared with $8.5 \pm 1.4\%$ ($n=4$) lost by those on the LF diet. Differences in resting metabolic rate, physical activity, or energy intake between the two dietary groups were not observed (45).

In the second intervention study, obese (BMI $25\text{--}29.9 \text{ kg/m}^2$) insulin-sensitive (insulin concentration $\leq 66 \mu\text{U/mL}$ at 30 min after 75-g dose of oral glucose, $n=16$) and obese nondiabetic insulin-resistant (insulin concentration $> 66 \mu\text{U/mL}$ at 30 min after 75-g dose of oral glucose, $n=16$) adults were randomized to either a LF diet (or high-glycemic diet; 60% carbohydrate, 20% fat, and 20% protein) or a mild LC diet (or low-glycemic diet; 40% carbohydrate, 30% fat, and 30% protein) for 6 mo at 30% calorie restriction compared to baseline individual energy needs (46). In the insulin-resistant groups, the mild LC diet produced a greater decrease in weight (-10.2 vs -6.2 kg) than did the LF diet at 6 mo. There were no significant differences in weight decrease between the mild LC and LF diets in the insulin-sensitive groups.

In the third intervention study, obese nondiabetic insulin-sensitive (insulin concentration $\leq 57.5 \mu\text{U/mL}$ at 30 min after 75-g dose of oral glucose, $n=28$) and obese nondiabetic insulin-resistant (insulin concentration $> 57.5 \mu\text{U/mL}$ at 30 min after 75-g dose of oral glucose, $n=28$) young adults were randomized to either a LF diet (or high-glycemic diet; 55% carbohydrate, 20% fat, and 25% protein) or a mild LC diet (or low-glycemic diet; 40% carbohydrate, 35% fat, and 25% protein) for a 6-mo intervention and 12-mo follow-up period (47). Although both the mild LF- and LC-diet groups decreased energy intake similarly by 400 kcal/d, effects of LF and LC diets on body weight reduction were markedly different between the insulin-sensitive and -resistant groups. In the insulin-resistant groups, the mild LC diet produced a greater decrease in weight (-5.8 vs -1.2 kg) and body fat percentage (-2.6 vs -0.9%) than did the LF diet at 18 mo (Fig. 2). There were no significant differences in decreases in weight and body

Fig. 3. Prevalence rates of insulin resistance, hyperinsulinemia, and insulin hypersecretion (all defined as the top decile of the respective distributions in lean subjects) as a function of the body mass index (BMI). Black bars, hyperinsulinemia; light gray bars, insulin resistance; dark gray bars, hypersecretion. Reproduced with permission (51).

fat between the mild LC and LF diets for any subjects or in the insulin-sensitive group.

Metabolic syndrome is closely associated with hyperinsulinemia (48). A recent study examining the effects of LF and mild LC diets in subjects with and without metabolic syndrome under 500-kcal/d energy deficit conditions indicated that a LF diet is preferable in insulin-sensitive obese subjects (49). In this study, 202 obese subjects were randomized to either a LF diet (55–60% carbohydrate, less than 30% fat, and 15% protein) or a mild LC diet (or low-glycemic diet; 30–35% carbohydrate, 35–40% fat, and 25–30% protein) for a 12-mo follow-up period. In the subjects with metabolic syndrome, both the mild LC and LF diets were equally effective in reducing waist circumference, whereas in subjects without metabolic syndrome, the LF diet was preferable to that of the mild LC diet: the change in waist circumference was -7.8 ± 7.1 cm in the LF diet group versus -3.8 ± 5.0 cm in the mild LC diet group.

Thus, these four studies suggest that a mild LC diet preferentially reduces body weight in obese subjects with hyperinsulinemia (insulin resistance), whereas a LF diet preferentially reduces body weight in obese subjects without hyperinsulinemia.

Physiological aspects of a mild LC diet making it preferable in obese, insulin-resistant subjects to reduce body fat

It is known that not all obese subjects show insulin resistance (50, 51). In a European study of insulin resistance in the obese, hyperinsulinemia, insulin resistance, and insulin hypersecretion were found to increase linearly with an increase in BMI (Fig. 3) (51). In this study, hyperinsulinemia was defined as the upper 10% of fasting plasma insulin concentrations in the lean groups. Insulin resistance was defined as the bottom 10% of glucose disposal estimated by euglycemic insulin clamp technique in the lean groups, and insulin hypersecretion was defined as the upper 10% of the distribution of posthepatic insulin delivery rate.

According to these criteria, roughly one-half of the obese subjects ($\text{BMI} > 30 \text{ kg/m}^2$) were insulin resistant. The frequency of insulin resistance was 20% in subjects with a BMI of 25–30 kg/m^2 , 34% in subjects with a BMI of 30–35 kg/m^2 , and 60% in subjects with a BMI of $> 35 \text{ kg/m}^2$, relative to 10% in subjects with a BMI of 25 kg/m^2 (51). Similar trends were observed in regard to hyperinsulinemia and insulin hypersecretion.

Insulin resistance in liver and skeletal muscles elevates glucose concentrations, by which insulin secretion is increased. Moreover, pancreatic beta cells can acutely assess the body's sensitivity to insulin and translate this information into an insulin response that is precisely balanced to offset the severity of insulin resistance (52). In patients with insulin resistance, the increment of insulin secretion from β -cells in response to a fixed amount of glucose is greater than that in normal subjects (53). Therefore, the sensitivity of glucose to an increased blood insulin level is augmented in obese subjects. Diets with higher glycemic load resulted in higher postprandial insulin concentration in a dose-dependent manner in lean young adults (54). It is well known that obese subjects show hyperinsulinemia after oral glucose tolerance testing (glucose is a substance of high glycemic load) (55, 56). Postprandial hyperglycemia and hyperinsulinemia augmented by an increase in dietary carbohydrate intake in obese subjects may further promote fat cell enlargement (57).

Increased blood insulin stimulates the synthesis of fatty acid in liver and the preferential uptake of fatty acids in adipose tissues to store fat and prevents lipolysis in adipose tissues, all of which facilitate adipose tissue enlargement. Furthermore, these lipogenic effects of insulin are not impaired in obese subjects, whereas the glucose-lowering effects of insulin (inhibition of gluconeogenesis/glycolysis in the liver and stimulation of glucose uptake in skeletal muscles) is severely impaired. Recently, it was shown that hyperinsulinemia is associated with increased production of intestinal apolipoprotein B-48, which is one of the causes of postprandial hypertriglyceridemia (58). This effect of insulin also indirectly promotes obesity. In the following sections, the mechanisms of insulin-mediated increases in lipid synthesis and fat accumulation in the insulin-resistant state are reviewed.

Insulin-induced lipogenesis in liver is not impaired in insulin-resistant animals or humans

The insulin signaling pathway is thought to proceed through receptor-mediated tyrosine phosphorylation of insulin receptor substrate (IRS)-1 and/or IRS-2. This leads to activation of phosphoinositide 3-kinase (PI3K) and activated Akt (also known as protein kinase B). In activating hepatic lipogenesis, insulin increases transcription of genes encoding acetyl-CoA carboxylase, fatty acid synthase, and others. These actions are caused by an insulin-induced increase in sterol regulatory element-binding protein-1c (SREBP-1c) mRNA (59).

To examine the insulin signaling pathway and lipogenesis in the insulin-resistant state, two different ani-

mal models of insulin resistance and hyperinsulinemia, those of lipodystrophy induced by overexpression of the aP2-SREBP1c transgene in adipocytes and obesity induced by mutational disruption of the leptin gene (ob/ob mice) were investigated (60). Both animal models showed a reduction of IRS-2 mRNA and protein and increased gluconeogenesis in livers, whereas they showed an increase in SREBP-1c mRNA and lipogenesis. IRS-1 mRNA in the liver was not altered in these animal models. In addition, prolonged insulin treatment in isolated rat hepatocytes led to a fall in IRS-2 mRNA and protein and an increase in SREBP-1c transcript, suggesting that chronic hyperinsulinemia promotes gluconeogenesis in the liver and hyperglycemia, whereas it stimulates fatty acid synthesis in the liver and hypertriglyceridemia (60). It was shown with IRS-1 and IRS-2 liver knockout mice that IRS-1 could convey signals to increase SREBP-1c mRNA and lipogenesis (61, 62). The complete blockage of insulin signaling observed in liver insulin receptor knockout mice showed a decrease in the expression of SREBP-1c (63), suggesting that selective insulin resistance may occur in animal models of insulin resistance (64). Recently, a branch point in the insulin signaling pathway that may account for selective insulin resistance (in which insulin loses its ability to block glucose production but retains its ability to stimulate lipogenesis) was identified (65). In rat hepatocytes, subnanomolar concentrations of rapamycin, an inhibitor of the mammalian target of rapamycin complex 1 (mTORC1), blocked insulin induction of SREBP-1c but had no effect on insulin suppression of phosphoenolpyruvate carboxylase (PEPCK), suggesting that the kinase complex designated mTORC1 was a branch point in the insulin signaling pathway. Therefore, the IRS-1/Akt/mTORC1 pathways are thought to mediate the increase of lipogenesis in the insulin-resistant state.

The finding that insulin-induced lipogenesis in the liver was not impaired in the insulin-resistant state in animal studies could apply to humans. The pattern of stored energy distribution derived from a high-carbohydrate meal is different in young, lean, insulin-resistant individuals (fasting insulin concentration of 12.1 ± 1.2 $\mu\text{U/mL}$) compared with young, lean, insulin-sensitive individuals (fasting insulin concentration of 7.6 ± 0.6 $\mu\text{U/mL}$) (66). In contrast to the insulin-sensitive subjects, who stored most of their ingested energy in the liver as glycogen, the insulin-resistant subjects had a marked defect in muscle glycogen synthesis and diverted much more of their ingested energy into hepatic de novo lipogenesis, as assessed by incorporation of deuterated water into plasma triglyceride, resulting in increased liver and plasma triglycerides (TGs). Increasing very-low-density lipoprotein-TG secretion from the liver may lead to increased fat accumulation in adipose tissue (67). Therefore, insulin activation of the liver IRS-1/Akt/mTORC1 pathway in the insulin-resistant state may lead to obesity.

An increase in lipoprotein lipase (LPL) activity in adipose tissue in response to insulin is not impaired in obese subjects

LPL, located on the capillary endothelium of tissues, catalyses the rate-limiting step in the hydrolysis of TGs from circulating chylomicrons and very-low-density lipoproteins. Most LPL is found in adipose tissues and skeletal muscles, where some of the liberated free fatty acids are taken up and are either stored or oxidized, respectively (68). In healthy humans, a combination of stable isotope labeling and arteriovenous difference measurements in adipose tissues showed that in postprandial periods, there is preferential uptake of fatty acids released from chylomicrons by LPL in adipose tissues and also a release of LPL-derived fatty acids into plasma (69). Therefore, an increase in LPL activity in adipose tissues may promote fat cell enlargement via increased uptake of fatty acids into adipocytes, in addition to an increased supply of fatty acids to muscle and liver.

Regulation of LPL activity is complex and is controlled by several modulators, such as apoproteins and angiopoietin-like proteins ANGPTL3 and ANGPTL4 (70). LPL is active as a dimer, whereas its monomer is inactive. ANGPTL4 inhibits LPL activity by promoting the conversion of active LPL dimers into inactive LPL monomers. Insulin not only increases the level of LPL mRNA but may also regulate LPL activity through both posttranscriptional and posttranslational mechanisms (71). The fact that feeding increases active dimeric LPL from inactive monomeric LPL in adipose tissues suggests that insulin may stimulate dimer formation of LPL by an unknown mechanism (72). Glucose also increases adipose tissue LPL activity and enhances the stimulatory effects of insulin, possibly by the glycosylation of LPL (73).

In humans, feeding or insulin/glucose infusion stimulates LPL activity in adipose tissues, whereas its activity decreases in skeletal muscles (74). This divergent response would serve to direct lipoprotein TG-derived fatty acids away from muscle to adipose tissue for storage. A high-carbohydrate diet for 16 d in normal-weight subjects increased postprandial LPL activity in adipose tissue, with elevation of blood glucose and insulin concentrations after meals, relative to a high-fat diet (75). Therefore, increased insulin and glucose from a high-carbohydrate diet may promote obesity via activation of LPL in adipose tissues.

The LPL activity in adipose tissues in response to insulin during maintenance of euglycemia was examined in 22 obese and 8 normal-weight subjects (76). Basal levels of LPL activity per g of fat tissue in the obese and control groups were 18.7 ± 2.0 and 9.6 ± 2.7 nEq/g/min, respectively. When the responses of LPL in absolute change from basal values were compared between the obese and control groups, no significant differences were found. However, because of the higher baseline LPL activity in the obese subjects, the percent increase in LPL from the basal value was significantly blunted in obese subjects. Basal LPL activity expressed per 10^6 cells correlated positively with cell size, and both the

obese and normal-weight subjects were found to respond similarly to insulin. These data suggest that insulin activates LPL in adipose tissues in obese subjects, irrespective of insulin resistance.

Inhibition of lipolysis in adipocytes in response to insulin is not impaired in insulin-resistant subjects

The concentration of blood free fatty acids (FFA) is determined primarily by their rate of appearance from adipose tissues (lipolysis) and also by their rate of disappearance from plasma. Blood FFA concentrations are elevated during fasting and decreased after feeding. Lipolysis is stimulated by catecholamines during fasting and inhibited by insulin after feeding. If the antilipolytic effect of insulin in obese subjects were impaired due to insulin resistance, fat mass would be smaller in obese subjects. However, most of the studies suggested that insulin resistance is not observed at this step in obese subjects (see following paragraph), although the resistance of insulin to increased glucose oxidation in enlarged adipocytes was clearly shown and is due to a marked decrease in GLUT4 in adipocytes (77, 78).

The antilipolytic effects of insulin on fat cells of different sizes were examined in the 1970s by measuring glycerol release. Basal lipolysis was larger in larger cells (79). The antilipolytic effects of insulin on noradrenalin-stimulated lipolysis were more pronounced in the large cells at all tested concentrations (80, 81). Responsiveness and sensitivity to insulin was not altered in adipose tissues of either control or obese subjects (82). Rather, a marked resistance to the lipolytic effect of noradrenalin was observed in isolated adipocytes from obese subjects (83).

In vivo studies also show that the antilipolytic effect of insulin is not impaired in obese subjects. Both antilipolytic and antiketotic actions occurred at lower insulin concentrations ($<90 \mu\text{U/mL}$) than those required for hypoglycemic activity ($>1,000 \mu\text{U/mL}$) (84), suggesting that marked insulin resistance might be required to reduce antilipolytic action in adipose tissues. Decreases in blood FFA and glycerol observed during oral glucose tolerance tests were not impaired in obese subjects (85). Insulin and glucose infusion rapidly produced antilipolysis in obese and normal groups, as evidenced by large falls in FFA at 20 min after insulin infusion, where FFA was 47% of the basal level in the obese subjects and 31% of the basal level in the normal subjects (76).

Triglycerides in tissues are hydrolyzed in a sequential process involving different lipases. Adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) are necessary for proper hydrolysis of tri- and diglycerides, respectively. The last step in lipolysis is performed by monoglyceride lipase (MGL), which hydrolyzes monoglycerides to form glycerol and fatty acids (86). The activity of ATGL and HSL is tightly regulated by catecholamines and insulin. β -Adrenergic stimulation of the G-protein-coupled receptor activates adenylate cyclase to increase cellular cAMP levels. The antilipolytic action of insulin is mediated by lowering cAMP levels via activation of phosphodiesterase 3B (87). The IRS-1/PI3K/PDE3IK (an insulin-stimulated protein serine

Fig. 4. A proposed model of optimal dietary fat to carbohydrate ratio according to the degree of hyperinsulinemia (or obesity). A key to macronutrient balance in the reduction of body weight is the state of hyperinsulinemia (insulin resistance or obesity); thus, optimal dietary fat to carbohydrate ratios may differ between prevention and treatment of obesity. A mild low-carbohydrate diet (40% carbohydrate) is preferable for obese, hyperinsulinemic, insulin-resistant subjects, whereas a low-fat diet (20–25% fat) is preferable for normal-weight, normoinsulinemic, insulin-sensitive subjects.

kinase) signaling pathway is involved in PDE3B activation (88). cAMP binding to protein kinase A (PKA) induces phosphorylation of HSL and perilipin, a protein coating the lipid droplet. PKA phosphorylation of HSL causes HSL translocation from the cytosol to the lipid droplet, whereas phosphorylation of perilipin by PKA alleviates the barrier function of this protein and promotes lipolysis (89). ATGL is phosphorylated on two conserved serine residues (Ser 404 and 428), although PKA does not phosphorylate ATGL (90). However, insulin treatment downregulates ATGL mRNA levels in adipocytes (91, 92). To my knowledge, it has not been shown that decreases in cAMP concentration or ATGL mRNA in adipocytes in response to insulin are blunted in adipocytes from obese subjects.

Shift from a mild LC diet to a LF diet during obesity treatment (hypothesis)

When a mild LC diet is given to obese subjects, body weights might decrease with improvement in hyperinsulinemia and insulin resistance. Data from the National Weight Control Registry of people who were successful in losing weight and maintaining reduced body weight show that despite wide variation in the methods used to lose body weight, there was remarkable similarity in how they maintained the weight loss, including a diet that was, on average, 24% fat (93). Therefore, fat intake might be gradually decreased with a concomitant increase in carbohydrate intake with improvement in obesity (Fig. 4).

Conclusions

In terms of epidemiological, physiological, and molecular aspects, the optimal dietary fat to carbohydrate ratio varies due to the amount of body fat present and

to hyperinsulinemia (insulin resistance). No evidence was found that the lipogenic effects of insulin were impaired in subjects with insulin resistance. In general, in non-obese subjects, most of whom are insulin sensitive, decreasing fat intake is more effective than decreasing carbohydrates to prevent obesity. However, for obese subjects with insulin resistance, a mild LC diet favors a reduction in body weight. The optimal dietary fat to carbohydrate ratio may differ depending on whether the goal is prevention or treatment of obesity, and public guidelines on macronutrients should either be based on the prevalence of obesity in the target society or individualized.

Acknowledgments

This work was supported by research grants from the Japanese Ministry of Health, Labor and Welfare (Tokyo, Japan).

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