

## Editorial

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# Issues Related With Calorie Restriction for Prevention and Treatment of Obesity

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The prevalence of obesity has dramatically increased in the US and worldwide over the last 2 to 3 decades.<sup>1</sup> Obesity is developed when lipids in the form of triacylglycerol are accumulated in the adipose tissue. However, obesity is not only a problem of energy imbalance since it is associated with changes of concentrations of circulating nutrients, metabolites, and adipokines. These adipokines, a type of cytokines secreted from adipocytes, are involved in regulation of satiety, inflammation, and other physiological functions.<sup>2</sup> The increased levels of certain metabolites and decreased levels of essential nutrients in obesity are related with its complications as well. Therefore, obesity is a risk factor of type 2 diabetes, coronary heart disease (CHD), stroke, hypertension, and cancer, despite the fact as one of the major chronic diseases worldwide. Recently, obesity has been defined as a medical condition by the American Medical Association (AMA).

The most useful methods to prevent and to treat obesity are still focused on energy balance at present. The combination of calorie restriction and physical exercise has been proved to be the most effective way to maintain a healthy weight status. However, the trials with short periods of time for prevention and treatment of obesity might have not demonstrated the importance of micronutrients.

Calorie restriction is an old concept for body weight control. This concept was based on the theory that the calories stored in the fat tissue were equal to the total calorie intake minus the calorie expenditure. Therefore, as a strategy to control body weight by reducing calorie intake, a portion of the fat components in food products were replaced by refined carbohydrates in 1970's since fats contain more calories than carbohydrates.<sup>3</sup> This change was well correlated with the first peak of dramatic increase of obesity in early 1980's. Recent studies indicated that high fat intake was associated with high energy expenditure and refined carbohydrates were associated with high prevalence of obesity/type 2 diabetes.<sup>4</sup> Therefore, the new emerging weight control strategy is focused on using high quality foods with reduced amount of simple carbohydrates than paying attention on quantity of total calorie intake, of course, while still limiting total calorie intake. Therefore, this old concept has a new meaning now. In 2016, the Dietary Approaches to Stop Hypertension (DASH) diet was ranked as the number 1 for the "Best Diets Overall" and for "Best Diets for Healthy Eating", number 2 for "Best Diabetes Diets", and number 3 for "Best Heart-Healthy Diets" out of 38 diets tested in the US News & World Report's annual Best Diets rankings. The DASH diet is rich in vegetables, fruits, whole grains, low-fat dairy products, includes fish, poultry, nuts, beans, and is limited in foods with simple sugar. As the diet is rich in fat, Atkins Diet was ranked as the number 3 for "Best Fast Weight-Loss Diets" in the same rankings. These ranking results are a good reflection of the new understanding of calorie restriction in obesity management.

The question why low calorie intake of diets containing high refined carbohydrates is associated with obesity is not totally clear at this moment.<sup>5</sup> It is suspected that refined carbohydrates can change the metabolism to the fat storage mode. It is likely that increased blood insulin levels associated with high blood glucose levels induced by refined carbohydrate might be involved in storing extra energy as lipids in the adipocytes.<sup>5</sup> The detailed mechanisms need to be addressed by studies at the molecular level using nutritional genomics, epigenetics, and cell signaling approaches. These studies might be able to identify target molecules that can

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switch our metabolism between the fat storage mode and the fat consuming mode. Therefore, it will be possible to design new drugs that target the molecules for the purpose to reduce body fat at a controlled speed.

During calorie restriction, artificial sweeteners are often used in place of simple sugars such as table sugar (sucrose), glucose, and fructose to reduce calorie intake, although current available scientific data in the literature do not provide proof that artificial sugar substitutes are beneficial in terms of weight management, blood glucose control, and the incidence of type 2 diabetes.<sup>6</sup> In addition, the possibilities of inducing cancer and other negative effects such as oxidative stress by certain sweeteners are not totally excluded.<sup>6,7</sup> More importantly, there is no evidence indicating that artificial sweeteners do not affect levels of hormones that are related with carbohydrate metabolism.<sup>8</sup> Therefore, it is ideal at this time that artificial sweeteners are only used during the transient time of weight loss. At the same time, it is necessary to carry out studies using animal models to address whether the artificial sweeteners affect hormones involved in energy homeostasis or not.

Most obesity treatment strategies involve lifestyle management including to increase physical exercise. Physical exercise is not only helpful to increase energy expenditure but also, more importantly, is able to activate enzymes involved in metabolism pathways, able to improve vascular mitochondrial function, and able to modulate oxidative stress and inflammation.<sup>9</sup> It has been demonstrated that certain enzymes can only be activated by physical exercise. Some hormones such as adiponectin can be increased by physical exercise, good life-style, and certain drugs such as statins while obesity decreases circulating adiponectin concentration.<sup>10</sup> Adiponectin is secreted from adipocytes is the hormone with almost all positive effects. It increases glucose uptake, decreases gluconeogenesis, stimulates fatty acid oxidation, increases insulin sensitivity, upregulate uncoupling protein levels, decrease tumor necrosis factor alpha (TNF $\alpha$ ) levels.<sup>2</sup> Glucose is a preferred energy source for high intensity exercise and also used during moderate-intensity exercise.<sup>11</sup> It has been proved that exercise increases blood glucose regulation by increase cell membrane glucose transporter GLUT4 localization in muscle and adipose tissue.<sup>11</sup> The mechanism is not yet clear at this time.

In conclusion, community based prevention strategies based on the new understanding of calorie restriction should be used to battle the high and increasing prevalence of obesity while mechanism studies should be used to search for drug targets for treatment.

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