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Forum Minireview

Pharmacology in Health Foods: Merits and Demerits of Food With Health Claims for the Prevention of Metabolic Syndrome

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Abstract. The merits and demerits of food with health claims for the prevention of metabolic syndrome (MS) are reviewed. One major underlying cause of MS is obesity. Diet and lifestyle changes remain the cornerstones of therapy for obesity, but resulting weight loss is often small and long-term success is extremely uncommon and disappointing. Many anti-obesity drugs have been associated with unintended therapeutic outcomes. Currently, only one drug (mazindol) is approved in Japan for short-term treatment of individuals with a BMI over 35 kg/m^2. Treatment with orlistat with dietary modification, caffeine, or protein supplementation; consuming a low-fat diet; adherence to physical activity routines; prolonged contact with participants; problem-solving therapy; and the alternative treatment of acupressure are efficacious in reducing weight regain after weight loss treatment. Because obesity is highly stigmatized, any effective treatment should be made available to improve quality of life and self-image. Therefore, it is necessary to provide information to consumers through the media concerning 1) basic knowledge about health foods and laws concerning them, 2) scientifically based information on safety/effectiveness of health foods and food elements, and 3) reports on health disturbances associated with health foods around the world.

Keywords: metabolic syndrome, obesity, mazindol, orlistat, health food

1. Introduction

Both the metabolic syndrome (MS) and type 2 diabetes mellitus (T2DM) confer an increased risk of coronary heart disease and cardiovascular disease (CVD). Strategies for the effective management of cardiovascular risk factors in patients with MS or T2DM are essential to help reduce cardiovascular morbidity and mortality. One major underlying cause of MS or T2DM is obesity. Obesity has emerged as one of the principal health concerns throughout the world in the modern era. According to the World Health Organization, there were about 1.6 billion overweight adults aged 15 years and above and at least 400 million adults are obese worldwide in 2005 (1). The clinical requirement of safe and effective therapies to combat this global pandemic is unmet. Because of the increasing prevalence of obesity and comorbidities associated with obesity, including cardiovascular and metabolic diseases, scientists are working on drug discovery and development to generate effective modalities for obesity treatment and prevention. Although the prevalence of obesity (BMI ≥25 kg/m^2) in Japanese men and elderly women has increased in the last 20 years, the mean BMI in younger women, especially those in metropolitan areas, has decreased (2). Obesity results from a prolonged imbalance of small positive energy, and treatment is required to reverse this imbalance. Diet and lifestyle changes remain the cornerstones of therapy for obesity, but the resulting weight loss is often small and long-term success is extremely uncommon and disappointing. Therefore, the merits and demerits of food with health claims for the prevention of MS are reviewed.

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2. Metabolic syndrome and public awareness

Patients with metabolic syndrome have a 1.5- to 3-fold increase in the risk of coronary heart disease and stroke. Metabolic syndrome generally precedes and is often associated with type 2 diabetes (3). The importance of prevention of diabetes in high-risk individuals (such as people with metabolic syndrome) is highlighted by the recent substantial and worldwide increase in the prevalence of type 2 diabetes. Special health checkups and healthcare guidance focusing on metabolic syndrome were started for all Japanese citizens aged 40 – 74 years in 2008, with the goal of reducing the rate of patients with and those at high risk of developing metabolic syndrome to 25% by 2015 (4). The original metabolic syndrome diagnosis criteria in Japan were presented by the Examination Committee of Criteria for Metabolic Syndrome in April 2005. This guideline defines waist circumference measurement as an essential component, accompanied by at least 2 of the following 3 risk factors: dyslipidemia, raised blood pressure, and glucose intolerance. These risk factors were based on multiple representative Japanese cohort studies.

Cardiovascular risk reduction in individuals with metabolic syndrome should include at least 3 levels of interventions: 1) control of obesity, unhealthy diet, and lack of physical activity; 2) control of the individual components of metabolic syndrome, particularly atherogenic dyslipidemia, hypertension, dysglycemia, and prothrombotic state; and 3) control of insulin resistance, a defect closely linked to metabolic syndrome (5).

Cardiovascular risk factors such as hypertension are only the tip of the iceberg (Fig. 1) (6). A comprehensive cardiovascular diseases (CVD) risk factor approach is imperative for effectively controlling the global CVD epidemic.

3. Medication of obesity for preventing of MS

Recent discoveries regarding metabolic and genetic control systems governing the regulation of body weight and energy expenditure have led to the development of pharmacological agents that can be used as adjunctive treatments for patients with obesity. However, the scarcity of medications available or those that have made it to Phase III trials reflects the difficult challenge of manipulating the biology of appetite regulation. Potential anti-obesity targets can be classified into 5 broad categories: 1) decreasing appetite through central action; 2) increasing metabolic rate or affecting metabolism through peripheral action; 3) modulating gut peptide receptors; 4) modulating targets to affect overall cardiometabolic parameters; and 5) combination therapies directed against several targets (7, 8). Effective treatments for people with BMI >30 include intensive counseling and behavioral interventions for lifestyle change and pharmacotherapy in the United States (US). Primary care practice counseling plus pharmacotherapy may help obese pa-

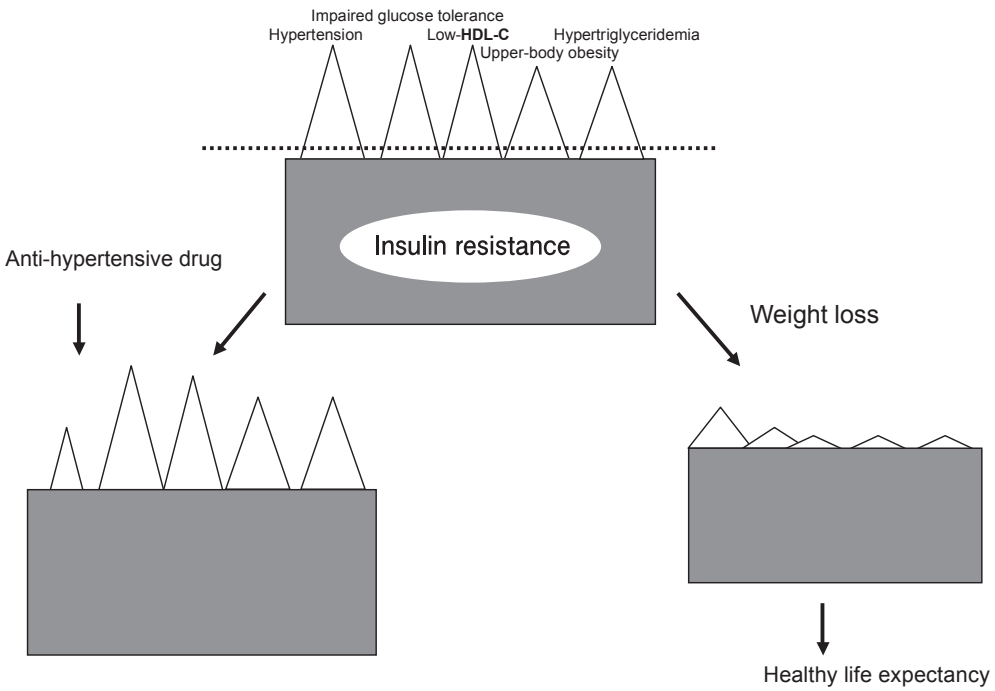

Fig. 1. The tip of the iceberg: multiple risk factor syndrome.

tients achieve the goal of weight loss in the US (9).

Many anti-obesity drug treatments have been associated with unintended therapeutic outcomes (Table 1). Thyroid hormone administration produced hyperthyroidism. Dinitrophenol produced neuropathies and cataracts. Amphetamine was addictive. Fenfluramine produced a form of valvular heart disease. Currently, only one drug is approved in Japan for long-term use in the treatment of obesity and 4 others for short-term use (10). Since the discovery of rimonabant, significant effort has been directed toward discovery of new, potent, and selective cannabinoid receptor CB1 antagonists that serve as anti-obesity drugs. A number of compounds have reached various stages of clinical trials by late 2008. However, the announcement by Sanofi-Aventis to discontinue all ongoing rimonabant trials after finding that risks associated with depression and anxiety outweighed benefits had a major impact on this area of research. Taranabnt was also withdrawn from the market. Dr. Bray stated "To treat or not to treat: that is the question." (11). One combination of 2 standardized dietary herbal supplements that result in clinically significant weight loss was found. Obesity is poised to enter the era of combined therapy, as is now routine in the treatment of other clinic diseases such as hypertension and diabetes. The advent of combination drug or supplement therapy for obesity treatment offers hope of increasing metabolic treatment efficacy (12, 13).

4. Drug therapy for obesity in Japan

Only one drug has been approved in Japan for short-term use in the treatment of individuals with a BMI 35 kg/m^2. The combination of mazindol and diet therapy is effective in treating severe obesity (14). Mazindol possesses both an anti-obesity action, due to inhibition of appetite as well as brown adipose tissue (BAT) thermogenesis activation and an anti-diabetic action (15). Clinical trials of orlistat have been performed for more than 2 years in adults, which showed safety and efficacy, but long-term studies with mazindol for obesity treatment have not been performed. However, orlistat is not approved in Japan.

Bofu-tsusho-san (BF) is an oriental herbal medicine (24 mg/day ephedrine in Ephedrae Herba with an efficacy equivalent to 280 mg caffeine and has the phosphodiesterase-inhibitory effect of *Glycyrrhizae radix*, *Forsythiae fructus*, *Schizonepetae spica*, and an additional 14 crude drugs). BF works via BAT thermogenesis activation and phosphodiesterase activity inhibition in mice (16). Eighty-one Japanese women (BMI 36.5 ± 4.8 kg/m^2) with impaired glucose tolerance and insulin resistance who had been treated with a low-calorie diet (5016 KJ/day: 1200 kcal) and an exercise regimen (1254 KJ/day: 300 kcal) were randomized to receive either placebo (n = 40) or BF treatment (n = 41) 3 times a day. After 24 weeks of treatment, the BF group lost significantly more abdominal visceral fat without a decrease in adjusted resting metabolic rate, whereas the placebo group lost bodyweight and had no significant change in abdominal visceral fat. The BF group had a lower fasting serum insulin level, a lower insulin area under the curve, and a lower level of the homeostasis model assessment of insulin resistance than the values before treatment (17). However, physicians should be aware that BF can cause liver injury and this drug is commonly used as an over-the-counter (OTC) medicine.

5. An OTC drug and weight control

Few prescription drugs exist for obesity treatment, although many drugs exist for the treatment of hyperten-

Table 1. Unintended consequences of anti-obesity drugs

Year	Drug	Consequence
1892	Thyroid extract	Hyperthyroidism
1932	Dinitorophenol	Cataracts, neuropathy
1937	Amphetamine	Addiction
1967	Rainbow pills (digitallis, diuretics)	Arthymias, death
1971	Aminorex	Pulmonary hypertension
1997	Phen/Fen (phentermine+fenfluramine)	Valvulopathy
1998	PPA (phenylpropanolamine)	Strokes
2004	Ephedra (Ma huang)	Heart attacks, stroke
2008	Rimonabant	Depression, suicide
2010	Sibutramine	Heart attacks, stroke

sion, dysglycemia, and dyslipidemia. Due to the complex pathophysiology and phenotypic expression of metabolic syndrome, lifestyle changes are crucial as they are able to positively and simultaneously influence nearly all components of the syndrome. If such measures are not sufficient or not adequately followed, pharmacological intervention may be considered. However, no official guidelines are available concerning the pharmacological management of metabolic syndrome patients.

Pharmacists in a community pharmacy may recommend an OTC drug to patients with obesity. Orlistat first became available (as 120 mg capsules [Xenical]) around 10 years ago as a prescription-only obesity treatment. Earlier this year, 60 mg orlistat capsules (alli; Glaxo-SmithKline Consumer Healthcare, UK) became available for sale without a prescription to the European Union public. Orlistat (60 mg) is available in UK pharmacies and so can be purchased OTC from pharmacies. OTC orlistat is promoted as a new weight loss aid, "boosting weight loss by 50%" when added to a reduced calorie, lower-fat diet (18, 19).

"Nontraditional" or "alternative" treatments are extremely popular, particularly with respect to obesity and body composition (20, 21). Herbal weight-loss supplements are marketed with claims of effectiveness. For herbal ephedra and ephedrine-containing food supplements, an increased risk of psychiatric, autonomic, or gastrointestinal adverse events and heart palpitations have been reported. Adverse events are reported for a number of herbal food supplements used for reducing body weight (22).

6. Role of food with nutrient function claims

In the early 1980s, the Japan Scientific Academy defined a functional food as a food having a tertiary or physiologically active function. The current Japanese "Food with Nutrient Function Claims" includes 2 categories. For the first category "Food with Nutrient Function Claims", this label may be freely used if a product satisfies the standard minimum and maximum levels per daily portion typically consumed. The second category is defined as "Food for Specified Health Uses" (FOSHU) (23). FOSHU foods contain dietary ingredients with beneficial effects on the human physiological functions, maintain and promote health, and improve health-related conditions. Manufacturers can emphasize the characteristics of their products and promote sales through Health Claims. Many "health foods" unknown even to specialists in the area are marketed at shops, mail-ordered, sold door-to-door, and imported privately over the Japanese internet. Some of these can carry illegal health claims and others can contain medical or chemical components with adverse effects. A warning should be issued to result in removal of these foods from the market by the central or local government.

7. Conclusion

Approximately, one-third of lost weight is often regained in the first year after treatment and, at times, the weight gain continues. Turk et al. reviewed that treatment with orlistat combined with dietary modification, caffeine, or protein supplementation; consuming a low-fat diet; adherence to physical activity routines; prolonged contact with participants; problem-solving therapy; and the alternative treatment of acupressure were efficacious in reducing weight regain after weight loss treatment (24). Because obesity is highly stigmatized, effective treatment is required to improve quality of life and self-image. Thus, both prescription and non-prescription anti-obesity drugs must have very high safety profiles. Reliable knowledge and information about health foods must be provided to consumers so that health foods can be used safely and with confidence (25). Therefore, it is necessary to provide information to consumers through the media concerning 1) basic knowledge about health foods and laws concerning them, 2) scientifically based information on the safety/effectiveness of health foods and food elements, and 3) reports of health disturbances associated with health foods around the world.

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