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Review

Diet and Metabolic Syndrome

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Recent change in lifestyle, including physical inactivity and unhealthy diets, are likely to have played an important role in global epidemic of obesity, type2 diabetes mellitus (T2DM), and the metabolic syndrome (MetS). Implementation of a healthy lifestyle, with an increase in physical activity and reduction of body weight, based on the regulation of calories and fat intake, are the basis for the prevention and treatment of lifestyle related disease. This review highlights some recent advances in the understanding of metabolic and molecular mechanisms concerning the effect of diet and focuses on the prevention and/or improvement of dyslipidemia, insulin resistance, impaired glucose homeostasis, obesity, T2DM and MetS in experimental rodent models, with some extension to humans.

Keywords: metabolic syndrome, obesity, nutrition , diet

Introduction

Diet is cornerstone of lifestyle related disease prevention. Calorie-enriched diet and lack of exercise are causing a worldwide surge of obesity [1, 2]. The metabolic syndrome (MetS) is a cluster of metabolic disorders, namely dyslipidemia, hypertension, obesity and glucose intolerance. MetS is highly prevalent conditions, affecting between one in six and one in three adults in most developed countries, and a similar proportion in the urban areas of many developing countries. This condition has a big public health importance because they are associated with a markedly increased risk of diabetes and cardiovascular disease (CVD), thus contributing to the epidemic proportions of these diseases.

Obesity is a key aetiological factor in development of MetS. Insulin resistance is the core phenomenon. Co-occurrence is associated with a high risk of subsequent development of type 2 diabetes mellitus (T2DM), CVD and premature death [3]. It is obvious that appropriate animals models are crucial for studies on the pathogenesis and therapy of this complex metabolic disorder, but it is less clear how exactly to define the term “appropriate”.

From a scientific and an ethical point of view, it is reasonable to require that not only the phenotype but also the pathogenesis of the animal’s condition resembles the human disease examined. Looking at the polygenic nature of the human MetS, it seems that studies examining monogenic [such as the ob/ob mouse or Zucker-(*fa/fa*) fatty rat] or pharmacologically induced (such as the gold-thioglucose mouse model) obesity models must be interpreted with care. The question of whether the results obtained arise from the obese phenotype or the model’s genetic/ pharmacological background is difficult to answer completely.

In this review, we describe some recent advances in the understanding of metabolic and molecular mechanisms concerning the effect of diet.

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Macronutrient and MetS

Fat - high fat

Approximately 60 years ago, Samuels described that rats fed with a diet containing 70% energy as fat developed obesity and elevated basal and postprandial blood sugar values [4, 5]. Such high fat (HF) diet effects, noticed when the fat content is well above 30% energy [6-9], have been subsequently specified for different animal strains, fat types, and diet lengths.

Table shows the range of metabolic changes described under different HF diets in studies from the last 10 years, in which fat type, diet length, and animal strain were stated. Diet with extreme fat contents (>60% energy) and diets using chow-based HF diets were not included because the physiological significance of these results must be questioned. Due to the scarcity of studies using semi-purified, low-fat control diets, it chose not to use this point as an inclusion criterion for the table.

Fat - fatty acid

A important action of n-3 fatty acids is that they could play a key role in the prevention and management of several diseases such as coronary heart disease, dyslipidemia, T2DM, insulin resistance, hypertension and so on [10-12]. When added to the diet, the EPA and DHA (poly unsaturated fatty acids: PUFAs) present in fish or fish oil can alter the membrane phospholipid composition of the cells, impact eicosanoid synthesis and action, and regulate transcription factor activity and abundance. Recent studies suggest that n-3 fatty acids serve as important mediators of gene expression, working via the peroxisome proliferator-activated receptors (PPARs) controlling the expression of genes involved in lipid and glucose metabolism and adipogenesis [13].

Moreover, experimental studies have shown that fish oil could down-regulate the hepatic mRNA level of the sterol regulatory element-binding protein-1 (SREBP-1), which also controls several lipogenic genes [14-16].

Several studies have shown a consistent relationship between plasma fatty acid composition and insulin resistance. A prospective cohort study has investigated the interaction between serum fatty acid composition and the development of impaired fasting glycemia or T2DM in cohort of middle-aged normoglycemic men [17]. It was found that at baseline the proportions of serum esterified and non-esterified saturated fatty acids (SFA) were increased and PUFA were decreased in men who after 4 years developed impaired fasting glycemia or T2DM.

This finding is also in line with recent epidemiological evidence from the Nurses' Health Study, which shows that a higher intake of saturated fat and a low polyunsaturated fat: saturated fat are related to increased CVD risk among women with T2DM [18].

This study also estimates that replacement of 5% energy from saturated fat with equivalent energy from carbohydrates or mono unsaturated fatty acids (MUFA) is associated with 22 and 37% lower risk of CVD respectively. These findings suggest that replacement of SFA by MUFA may be more effective at reducing CVD risk than low-fat high-carbohydrate diets. Thus, several studies suggest a casual relationship between dietary fatty acid composition and insulin resistance. In comparison with the number of studies that have determined the relationship between dietary fatty acid composition and CVD risk factors, in particular lipoprotein metabolism, there are relatively few that have used insulin sensitivity as the primary metabolic end point.

Dietary fatty acids play an integral role in the pathogenesis and prevention of the MetS. Given the increasing prevalence of obesity a key objective should be to reduce the impact of modifiable risk factors, within the context of the obese phenotype. Whilst there is evidence to suggest that high-saturated-fat diets have deleterious effects on the MetS, there is a paucity of information in relation to the most effective fatty acid intervention therapy. In addition, future research will have to take account of an individual's.

Table. Effects of HF diets in rodent.

	Rodent type	Strain	Fat type	Energy percentage from fat	Length (days)	Effect (%)
Weight	rats	Wistar	Lard	60	120	+15
	rats	Wistar	Lard	58	42	+10
	rats	Wistar	Safflower oil	59	21	NC
	rats	Wistar	Safflower oil	60	300	+28
	rats	Wistar	Fish oil	48*	28	NC
	rats	Lewis	Coconut fat	40	70	+16
	rats	Lewis	Olive oil	40	70	+8
	rats	Lewis	Safflower oil	40	70	+19
	rats	Lewis	Fish oil	40	70	+21
	rats	Fischer	Fish oil	45	28	-8
	rats	Long Evans	Butter	43	75	+10
	mice	Balb/c J	Milk fat	42	136	+11
	mice	C57BL/6	Coconut fat	42	105	+8
	mice	C57BL/6	Corn oil	42	105	+11
Serum glucose	rats	Wistar	Lard	58	42	+14
	rats	Wistar	Safflower oil	59	21	+11
	rats	Wistar	Safflower oil	45	14	+15
	rats	Wistar	Safflower oil	60	300	NC
	rats	Wistar	Safflower oil	58	28	+26
	rats	Wistar	Fish oil	58	28	+24
	rats	Wistar	Fish oil	48*	28	NC
	rats	Fischer	Fish oil	45	28	-5
	mice	C57BL/6	Milk fat	42	50	+11
Seru insulin	rats	Wistar	Lard	25	21	+81
	rats	Wistar	Lard	60	120	-18
	rats	Wistar	Lard	58	42	NC
	rats	Wistar	Safflower oil	59	21	+20
	rats	Wistar	Safflower oil	60	300	+170
	rats	Wistar	Safflower oil	45	14	+85
	rats	Wistar	Safflower oil	58	28	+95
	rats	Wistar	Fish oil	58	28	+80
	rats	Wistar	Fish oil	48*	28	-45
	rats	Fischer	Fish oil	45	28	-50
	rats	Long Evans	Butter	43	75	+35
	mice	129S1	Lard	45	98	+100
	mice	C57BL/6	Milk fat	42	50	+510
Serum triglycerides	rats	Wistar	Lard	58	42	+90
	rats	Wistar	Safflower oil	60	300	-25
	rats	Lewis	Coconut fat	40	70	+175
	rats	Lewis	Olive oil	40	70	+190
	rats	Lewis	Safflower oil	40	70	NC
	rats	Lewis	Fish oil	40	70	-35
Serum fatty acids	rats	Wistar	Lard	58	42	+100
	rats	Wistar	Lard	60	120	-41
	rats	Wistar	Safflower oil	60	300	-30
	rats	Lewis	Coconut fat	40	70	+87
	rats	Lewis	Olive oil	40	70	+112
	rats	Lewis	Safflower oil	40	70	+19
	rats	Lewis	Fish oil	40	70	+9
	mice	129S1	Lard	45	98	NC
Leptin	rats	Long Evans	Butter	43	75	+66
	mice	C57BL/6	Milk fat	42	50	+1560
Adiponectin	mice	129S1	Lard	45	98	-11
	mice	129/Sv-C57BL6	Lard	40	105	-5
Resistin	mice	C57BL/6	Milk fat	42	136	+50

*** Seven percent fish oil.**

Carbohydrate

Fructose (a simple sugar found in honey, fruit and table sugar (sucrose)) may cause obesity via several different mechanisms.

First, Havel *et al.* [19] conducted a clinical study that found that fructose may not cause the level of satiety equivalent to that of a glucose-based meal. Specifically, the differences in the effect of fructose and glucose consumption (consumed beverages with 3 meals) on ad libitum food intake and hunger rating were observed on the day after the exposure to the sweetened beverages. The mechanism was related to the inability of fructose to acutely stimulate insulin and leptin, and to inhibit ghrelin, all factors that are known to affect the satiety center in the central nervous system.

Yudkin [20] also argued that sweetness of fructose (or sucrose) often makes food more platable, and, indeed, the food industry has capitalized on this by frequently adding high-fructose corn syrup or sugar to normally non-sweetened foods (such as crackers) to enhance the taste. This may stimulate more food intake. Furthermore, mice fed fructose-sweetened water gain more weight than do mice given the same calories as starch, which suggests that fructose may also slow the basal metabolic rate [21]. One unique aspect of fructose is that it is the only sugar that raises uric acid concentrations, and this can be shown in both human [22] and rodents [23]. Fructose enters hepatocytes and other cells (including tubular cells, adipocytes, and intestinal epithelial cells), where it is completely metabolized by fructokinase with the consumption of ATP; unlike in glucose metabolism, there no negative regulatory mechanism to prevent the depletion of ATP.

As consequence, lactic acid and uric acid are generated in the process, and uric acid concentrations may rise by 1-4 mg/dL after the ingestion of large fructose-based meal [24]. Although the rise in uric acid concentrations has historically been viewed as simply a potential risk factor for inducing gout, recent studies suggest that this may be a key mechanism to explain how fructose causes cardiovascular disease. In addition, it also provides a mechanism to explain why rodents are relatively resistant to effects of fructose.

Rodents are resistant to fructose because they synthesize vitamin C, have low uric acid concentrations, and have good endothelial function [25]. If uric acid concentrations are raised [26] or if low doses are prolonged [27], then insulin resistance is readily induced.

Micronutrient and MetS

Magnesium

Micronutrient plays a central role in metabolism and in maintaining tissue function. Recently, biochemical function and effects of trace elements in preventing or treating diseases were extensively studied. Magnesium plays an essential role in wide range of fundamental cellular reactions and it not surprising that an increasing number of clinical disorders have been found to be associated with magnesium deficiency [28, 29].

Large epidemiological studies indicate that lower dietary magnesium and lower serum magnesium are associated with insulin resistance [30, 31]. Low-magnesium serum levels are strongly related to elevated serum concentrations of both TNF-α and C-reactive protein (CRP) suggesting that magnesium deficiency may also be involved in the development of low-grade chronic inflammatory syndrome including metabolic disorders.

Other studies show the association of low-serum magnesium and TNF-α in obese [32] and nonalcoholic steatohepatitis (NASH) subjects [33].

A way to investigate the pathogenesis of metabolic syndrome is the use of appropriate animal model. Of particular interest is the fact that high-fructose diet induces a metabolic syndrome including insulin resistance, hypertension and dyslipidemia in the rat [34, 35].

Recent findings also indicate the implication of inflammation and oxidative stress in this model and show the aggravating effect of magnesium deficiency on the development of insulin resistance [36, 37]. The pro-inflammatory effect of magnesium deficiency may contribute to other aspects of metabolic syndrome such as hyperlipidemia, blood pressure elevation, endothelial dysfunctions and thrombotic tendency.

Calcium

One hypothesis postulates that dietary calcium plays a critical role in the regulation of energy metabolism.

Studies in cell culture and in rodent models like the agouti mouse demonstrated a key role for intracellular Ca^{2+} in the regulation of adipocyte metabolism. Increased dietary calcium reduces vitamin D activity and intracellular Ca^{2+} influx, decreasing fatty acid synthesis and increasing lipolysis, leading to decreased triglyceride stores.

Furthermore, decreased vitamin D activity may up-regulate the expression of uncoupling protein 2 (UCP2) and this may contribute to the increased thermogenesis observed with high-calcium diets [38]. Calcium increases also faecal fat excretion, presumably by formation of insoluble calcium-fatty acid soaps or by binding of bile acids that impair the formation of micelles [39].

In addition to dietary calcium other dairy-derived bioactive compounds may contribute to the augmented effect of whole dairy food intake vs. calcium supplementation alone [40]. Preliminary data suggest that this additional activity lies in the whey fraction [41].

Vitamin D

It is now known that insufficient serum vitamin D alters metabolite function causing perturbation of many cellular functions, including that of the endocrine pancreas [42].

Recently, there has been a resurgence of hypovitaminosis D in many populations [43]. In parallel, there has been a world-wide increase in obesity [44]. Links between hypovitaminosis D and obesity have been reported when obesity is defined using body mass index [45, 46] and waist circumference [47]. Large waist, a surrogate for abdominal obesity, is the key marker required for metabolic syndrome as defined by International Diabetes Federation (IDF) [48].

Evidence indicates that patients with diabetes have hypovitaminosis D and persons at risk for diabetes or metabolic syndrome have inadequate serum concentrations of vitamin D [49].

Food factors and MetS

Dietary fiber

Several foods or food factors may contribute to the beneficial effects, by affecting insulin sensitivity, body weight, blood pressure and lipid levels, and possibly others.

A high dietary fiber intake is emphasized in the recommendations of most MetS and nutritional associations.

Consumption of soluble dietary fiber reduces postprandial glucose responses after carbohydrate-rich meals, as well as lowering total and LDL cholesterol levels [50]. These effects are likely explained the viscous and/or gel-forming properties of soluble dietary fiber, which thereby slow gastric emptying and macronutrient absorption from the gut.

Colonic fermentation of naturally available high fiber foods can also be mainly attributed to soluble dietary fiber, whereas no difference between soluble and insoluble dietary fiber consumption on the regulation of body weight has been observed. However, it is not soluble dietary fiber, but mainly the consumption of insoluble cereal dietary fiber and whole grains, that is consistently associated with reduced risk of T2DM in large prospective cohort studies [51, 52].

Recent research indicates that dietary fiber consumption contributes to a number of unexpected metabolic effects independent from changes in body weight, which include improvement of insulin sensitivity, modulation of secretion of certain gut hormones, and effects on various MetS.

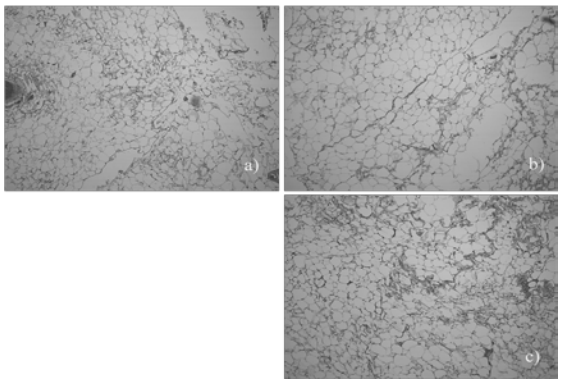

Figure 1. Histological images of white adipocytes at 8-weeks treatment. a) Basal diet, b) High fat diet, c) High fat diet + astaxanthin.

Tea catechin

Tea catechins reduce serum cholesterol concentrations and suppress postprandial hypertriacylglycerolemia in experimental rodents and humans. These effects are mainly ascribed to the gallate esters of catechins, (-)-epicatechin gallate, and (-)-epigallocatechin gallate.

During pasteurization of tea drinks, tea catechins are epimerized to so-called heat-treated tea catechins such as (-)-catechin gallate, and (-)-gallocatechin gallate. Both tea catechins and heat-treated tea catechins with the galloyl moiety lowerd intestinal absorption of cholesterol by inhibiting micellar solubility of cholesterol.

Since they inhibited pancreatic lipase in vitro and slowed down lymphatic absorption of triacylglycerols after the feeding of catechin preparations causes suppression of postprandial hypertriacylglycerolemia. It has been reported that tea catechins and heat-treated tea catechins with galloly moiety suppress deposition of visceral fat in rodents and humans [53-61].

Astaxanthin

Astaxanthin is a carotenoid in red pigment in nature and contained in salmon, shrimp, crab, krill, Phaffia yeast, and *Haematococcus* algae [62, 63]. It is a powerful antioxidant and has various actions such as anti-inflammation [64], anti-hypertension [65], anti-diabetic nephropathy [66], anti-muscle damage [67], and anti-cancer [68]. Several reports investigated the effects of astaxanthin supplementation in obese mice fed a HF diet. Astaxanthin inhibited the increases in body weight and weight of adipose tissue that result feeding a HF diet. In addition, astaxanthin reduced liver weight, triglyceride, and plasma triglyceride, total cholesterol [69-71].

We found that size of adipocytes in white adipose tissue was increased by >200% in HF diet mice compared with no treatment mice and found that astaxanthin inhibited the increase in size of adipocytes as shown in Figure 1 [71]. This result suggested that astaxanthin might be effective to prevention of obesity.

Astaxanthin is ingestible with marine products of the salmon etc. However, it is a very breakable carotenoid. Recently, the mass production of astaxanthin became possible by improving technique culturing and extraction of *Haematococcus* algae. The supplement can efficiently intake of astaxanthin.

Kampo (Oriental Herbal Medicine)

In management of MetS, kampo medicine (oriental herbal medicine) is an excellent representative in alternative and complementary medicines with a complete theory system and substantial herb remedies.

Obesity is prescribed Daisaikoto, Saikokaryukotuboreito, Tokakujiokito, Daionotanpito, Bofutsushosan, Tudosan, Kumibinroto, Boiogito, and so on [72].

Generally, obesity falls into two board categories depending on its cause. In western medicine, obesity is classified into two types characterized by either visceral or subcutaneous fat accumulation. On the other hand, in kampo medicine, obesity is classified into the “robust constitution” type and the “asthenic constitution” type.

In western medicine, the obesity causing MetS is of the visceral fat accumulation type, corresponding to the “robust constitution” type in kampo medicine. Of the above kampo prescriptions, Daisaikoto and Bofutsushosan are used for the high physical energy type obesity, *i.e.* obesity of the “robust constitution”

type, and several report suggesting that Daisaikoto and Bufutsushosan have effects on "visceral fat accumulation type" obesity and various metabolic disorders such as abnormal lipid metabolism, hyperinsulinemia, insulin resistant, hypertension and peripheral neuropathy [73, 74]. Studying the mechanisms by Bofutsushosan caused less body fat accumulation, we found increased white adipose tissue uncoupling protein 1 (UCP-1) mRNA levels (Figure 2) [75].

Recently, the Oriental Herbal medicine can be easily obtained. However, choosing what suitable for the constitution should consult a professional because it is difficult.

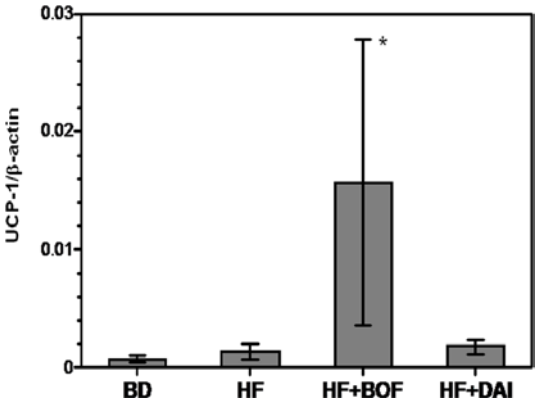

Figure 2. UCP-1 mRNA expression levels of the epididymis adipose tissue of mice fed basal diet (BD), high-fat diet (HF), HF + bofutsushosan (HF+BOF), or HF + daisaikoto (HF+DAI). The data are expressed as the means±SE of 5-6 mice.

Intestine and MetS

Generally, target organs in metabolic syndrome are liver, skeletal muscle, pancreatic beta-cell, and adipose tissue.

Emerging research has focused on the physiological processes associated with how the intestine may exacerbate dyslipidemia in obesity and insulin resistance.

The intestine is no longer considered a passive organ, but is involved in active regulation of lipid absorption, intracellular transport and metabolism, and has become inextricably linked to whole body lipoprotein metabolism. The significance of the intestine in lipid metabolism was highlighted with the discovery of specific mucosal brush border membrane transporters for cholesterol and long chain fatty acids [76-79].

Conclusion

Until not so long ago, nutrition research focused on single nutrient interventions. Recognizing that nutrients are not consumed individually but as combined constituents of a varied diet, efforts in this area have shifted to the role of the overall diet, or dietary patterns.

That eating habits play a role in development of MetS has also been concluded from the CARDIA study [80]. Fast-food frequency was directly associated with changes in body weight and insulin resistance. New food-based dietary recommendations by the American Heart Association, with the objective of reducing risk for CVD, promote an inclusionary approach. Obviously several risk factors for CVD can be reduced with diets that meet the current recommended dietary guidelines.

The dietary approaches to stop hypertension (DASH) dietary pattern, which is rich in fruits, vegetables and low-fat dairy products, has become famous as a successful approach to tackle several disorders of the MetS.

In several studies dairy consumption was inversely associated with occurrence of one or several phases of the MetS. Several foods or food factors may contribute to the beneficial effects, by affecting insulin sensitivity, body weight, blood pressure and lipid levels, and possibly others. The extent of the benefits is not clear yet. But even small effects are relevant if additive and if exerted during a lifetime.

The fact that dairy consumption may improve the bioavailability of folate and other secondary plant components makes it plausible that the DASH dietary patterns is more effective than the same diet without low-fat dairy products. Dairy intake may be associated with other prudent eating habits or healthy lifestyles. Medium-chain fatty acids may play a

role, as they affect spontaneous behavior such that food and thus energy intake is reduced [81].

In conclusion, most important word for prevent of the MetS is “balance”. Diet is cornerstone of lifestyle related disease prevention.

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