Diet Composition for the Management of Obesity and Obesity-related Disorders

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Review Article

ABSTRACT

Healthy nutrition is essential for prevention of disease and for maintenance or promotion of health; although healthy nutrition remains to be precisely defined. Over the past several decades, various types of nutrients have been functionally validated and considered as critical components of healthy nutrition, which commonly include fiber-enriched carbohydrates, mono- or poly-unsaturated fatty acids, essential amino acids, and certain micronutrients. When managing obesity and obesity-associated metabolic diseases, much attention has been paid to the content of nutrients that is considered as healthy nutrition. Accumulating evidence also suggests that nutrient composition could be more important than the content of individual nutrients in the context of reducing body weight and obesity-associated risk for metabolic diseases. Consistently, it would be more important to focus on diet with differences in nutrient ratios rather than individual type(s) of nutrients in terms of managing obesity and metabolic diseases. In this review, recent advances in dietary management of obesity and obesity-related metabolic diseases have been discussed. This review also has highlighted several specific diet compositions and their differences in managing hypertension, type 2 diabetes, and non-alcoholic fatty liver disease.

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INTRODUCTION

Prevalence rates of overweight and obesity have dramatically increased within the United States over the past several decades. The most recent data from the CDC and nutritional health and examination surveys (NHANES) estimate that 70% of American adults are overweight or obese [1]. The prevalence rate of obesity specifically, from 2011-2014, was roughly 36.5% of adults aged 20 and older [1]. Given the significant association between obesity and chronic metabolic disorders, the increased prevalence of concomitant comorbidities is no surprise. In fact, the rate of type 2 diabetes mellitus (T2DM) within North America and the Caribbean has increased from 7.6% to approximately 10% from 2003-2013 [2]. Rates of hypertension and chronic liver diseases, such as non-alcoholic fatty liver disease (NAFLD), have also increased over recent years [3].

Given the epidemic nature of obesity, much research has focused on lifestyle and pharmaceutical interventions [4, 5]. Weight loss remains the most effective approach for obesity and reducing the risk of related diseases; however, weight loss can be difficult to achieve and maintain [6, 7]. Multiple pharmaceuticals have thus attempted to reverse obesity and offer “fast weight loss”; however, virtually all have been unsuccessful for various reasons. More effective are the pharmaceuticals to manage obesity-related diseases. For example, angiotensin-converting enzyme (ACE) inhibitors are useful for managing hypertension, while biguanides, thiazolidinediones and sulfonylureas are successful treatments for managing insulin signaling and systemic glucose utilization and thus, hyperglycemia/T2DM [8-10]; Blood Pressure Lowering Treatment Trialists’ Collaboration, 2015 #3368. The interventions for T2DM can subsequently aid in the management of NAFLD given their actions on stimulating adipogenesis and uptake of free fatty acids, thereby reducing fat accumulation in the liver. Although great progress has been made in the pharmaceutical industry, many of these interventions may be undesirable due to cost or risk of side effects. Therefore, continued education on the benefits of diet as a lifestyle intervention is important now more than ever. Several diets have proven very successful in maintaining obesity and obesity-related diseases [11]. The purpose of this review is to highlight such diets, particularly the specific diet compositions proven to be effective in managing hypertension, T2DM and NAFLD including details on the underlying mechanism(s).

DIET COMPOSITION FOR OBESITY AND PREVENTING EXCESS WEIGHT GAIN

The biggest factor leading to excess weight gain and the development of obesity is overnutrition. Energy consumption that exceeds metabolic requirements leads to lipogenesis and fat storage within white adipose tissue (WAT), the primary storage site of fat within the body. Overconsumption of dietary fat can lead to weight gain relatively quickly since dietary fat is metabolized to free fatty acids, the primary substrate for triglycerides (TG) and subsequently, lipid synthesis. However, overconsumption of any macronutrient can ultimately lead to fat synthesis and accumulation. Therefore, the key dietary habit to reducing obesity is twofold: manage total caloric intake and fat content within the diet.

Total Caloric Intake

The estimated daily caloric need for the average American male and female is approximately 2500 and 2000 calories, respectively (2015 - 2020 Dietary Guidelines for Americans, 8th Edition, December 2015; http://health.gov/dietaryguidelines/2015/guidelines/). This estimate pertains to moderately active adults and has remained relatively stable over the past several decades despite arguments as to the appropriate dietary composition. Interestingly, much research has demonstrated that caloric restriction (CR) is highly beneficial in managing obesity and stimulating weight loss. The majority of research focuses on three methods of CR: alternate day fasting (ADF), which consists of a fasting day (0% - 25% of caloric need) alternating with a fed day (ad libitum consumption), daily acute restriction (DAR) of ~ 25% of total calories, and intermittent fasting (IF). All three are
shown to successfully induce weight loss in multiple obese populations\textsuperscript{[12, 13]}; however, no one intervention seems to be more beneficial than another\textsuperscript{[14]}. Further, compliance rates are similar between the three approaches. It seems that the success of each method is attributable to the slower rate of weight loss which stimulates lipolysis while preserving lean body mass. Perhaps, ADF, DAR or IF may be more easily incorporated and maintained by obese populations vs other methods of weight loss (“no-carb” diets, increased physical activity, etc). In addition to weight loss, all three methods improve HBA1c, insulin levels, HOMA-IR score and several aspects of lipid metabolism\textsuperscript{[15]}, all of which can be significantly impaired in obesity.

The overall mechanism tying CR to weight loss is obvious: less calories in equates to less calories stored. However, the underlying mechanisms of CR and an improved metabolic profile are less understood. The majority of studies conclude that CR, even periodically, leads to reduced inflammatory responses and production of oxidative stress. For example, diet-induced obese rats subjected to CR of 40% of ad libitum showed reduced hepatic triglycerides, hepatic levels of inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2) and thus, levels of lipid peroxidation and reduced impairment of fasting glucose\textsuperscript{[16]}. Additional studies have demonstrated similar results in other obese rodent models\textsuperscript{[17, 18]}. Mechanistic studies in humans are limited, but few have demonstrated these same findings in obese individuals\textsuperscript{[19-21]}. It seems these mechanisms of CR also contribute to increased life span, although this aspect is outside the scope of this review.

**Fat Content**

Dietary fat can have a significant impact on overall health and metabolism. Inadequate fat intake impairs absorption of fat-soluble vitamins and leads to reduced production of hormones and lipoprotein particles, whereas excess fat can contribute to inflammation, obesity and steatosis in distal organs, for example, the liver. There is no specific recommended daily intake (RDI) for total fat, but the current acceptable macronutrient distribution range (AMDR) is 20-35% of total daily calories. Diets that exceed this range are labeled as high-fat diets (HFD) and contribute to weight gain and a worsened metabolic profile. In rodents, this equates to weight gain relatively quickly and increased inflammation and oxidative damage throughout the body\textsuperscript{[22-24]}. HFD can result in similar effects in humans, especially following chronic HFD, including weight gain/obesity, systemic inflammation, and impaired glucose homeostasis. The primary mechanism underlying the metabolic effects of HFD is adipocyte hypertrophy, which in turn contributes to increased expression of proinflammatory cytokines, impaired lipid metabolism and ultimately, increased free fatty acids in the circulation which have damaging effects to many tissues and cell types\textsuperscript{[5]}. To prevent excess weight gain and/or promote weight loss and thus, limit this mechanism, obese individuals are recommended to ingest a lower amount of total fat, all the while staying within the AMDR to prevent metabolic problems caused by malnutrition.

Arguably more important than total fat for the management of obesity is monitoring the type of fat ingested. Certain types of fat are known to be more detrimental than others and thus, can further exacerbate obesity-related metabolic impairments. Saturated fat in particular is significantly more inflammatory compared to unsaturated fat\textsuperscript{[25, 26]} primarily through its potent ability to activate multiple inflammatory mechanisms including macrophage infiltration and/or proinflammatory activation, and the c-Jun-N terminal kinase and TLR4 signaling pathways\textsuperscript{[22, 23, 27, 28]}. Saturated fat is also known to directly interfere with the insulin signaling cascade at multiple steps\textsuperscript{[22, 23, 29, 30]}. For these reasons numerous agencies, including the American Heart Association, American Diabetes Association and USDA, recommend low saturated fat intake.

**Micronutrients**

Micronutrients play an active role in virtually all aspects of metabolism including glucose homeostasis, fat deposition and protein metabolism. Thus, adequate intake is paramount in maintaining health and an appropriate
body weight, and staving off metabolic disorders. Obesity is associated with several micronutrient deficiencies including vitamins A, C and D, selenium, and thiamine \[31-33\]. In turn, these deficiencies can exacerbate the obese phenotype and significantly contribute to the development of comorbidities, namely T2DM \[31, 32\]. For example, insufficient status of vitamin A and C are associated with leptin concentrations, and increased adipogenesis and fat deposition \[32, 34\], while deficiency in vitamin D is linked to reduced pancreatic β-cell function \[35\]. Therefore, the most important dietary approach related to micronutrients for the maintenance of obesity, and any subsequent comorbidities, is adequate intake. This can be attained either through consumption of a wide variety of foods or supplementation. It is important to note that the exact relationship between obesity and micronutrient deficiencies remains unclear. Thus, additional research is needed to further explore the direction of causality.

**DIET COMPOSITION FOR MANAGING INSULIN RESISTANCE**

The relationship between obesity and insulin resistance is well established. Excess weight gain and maximum lipid storage ability of adipose tissue lead to abnormally enlarged adipocytes and subsequently, impaired lipid metabolism and secretion of inflammatory cytokines within adipose tissue. Chronic overnutrition and/or obesity and thus, inflammation within the adipose contribute to low-grade systemic inflammation, a major defining characteristic of obesity. In fact, the term “metainflammation” is commonly used to describe the idea that inflammation is the primary causal factor in many obesity-associated metabolic diseases, including insulin resistance \[36\]. Indeed, several inflammatory cytokines are known to impair the insulin signaling cascade at multiple sites in numerous tissues \[37, 38\]. Therefore, diet composition for managing obesity-related insulin resistance is primarily aimed at preventing additional weight gain, with diets low in fat and simple carbohydrates but high in fiber, and reducing the generation of inflammation and promoting insulin signaling via adequate intake of micronutrients.

**Carbohydrates and Fiber**

Overconsumption of carbohydrates, as with any macronutrient, can contribute to overnutrition and thus, exacerbate the obese phenotype. However, monitoring the type of carbohydrate consumed seems more vital in managing obesity-related insulin resistance. In both obese and non-obese patients, complex carbohydrates (such as amylose and fibers) are associated with a reduced-risk for T2DM and insulin resistance compared with consumption of primarily simple carbohydrates \[39-41\]. Animal studies using rodent models of diet-induced obesity demonstrate similar results \[42-44\] and attribute the insulin desensitizing effects of simple carbohydrates to elevated spikes in plasma glucose, stimulation of lipogenesis, and the promotion of proinflammatory mechanisms \[45-47\]. For this reason the current Dietary Guidelines for Americans (DGA) suggests limiting simple/refined grains such as ready-to-eat cereals and white breads, and increasing intake of whole grains such as whole-wheat breads and oatmeal (USDHHS). The underlying mechanisms and full effect(s) of simple versus complex carbohydrates on human metabolism, especially in the context of obesity, remain relatively controversial; however, several clinical trials are underway to further elucidate their role in insulin resistance and obesity \[48\].

Dietary fiber, which the DGA recommends 25g and 38g per day for women and men, respectively, promotes colonic health, regulates satiety and cholesterol levels, and slows the release of chyme into the small intestine, which culminates in slower nutrient absorption (including glucose) through intestinal epithelial cells and ultimately, reduced postprandial glucose responses. Indeed, multiple clinical trials and/or intervention studies in humans have demonstrated that increased dietary fiber reduces fasting plasma glucose and HOMA-IR scores and is associated with weight loss in obese and non-obese diabetic individuals \[49-52\]. Mechanistic studies in animal models demonstrate that dietary fiber exerts these effects by improving lipid metabolism, reducing adiposity, and increasing lean body mass \[53, 54\].
Fat Content

A low-fat diet can greatly aid in the management of T2DM since it can help prevent weight gain and/or promote weight loss. However, specific types of fats are more detrimental than others for managing insulin sensitivity. For instance, because of their proinflammatory abilities, saturated fats are associated with impaired insulin signaling throughout the body \[22, 23, 55\]. Multiple studies in both obese and non-obese diabetic adults have confirmed these effects. For this reason the DGA suggests higher intake of unsaturated compared with saturated fats. Specifically, adults should consume less than 10% of daily calories from saturated fat, and ingest a variety of unsaturated fats, including mono- and polyunsaturated fats. Indeed, intervention studies have confirmed the benefits of following such a diet. For example, a recent meta-analysis by Qian et al. concluded that diets higher in monounsaturated fatty acids improve metabolic risk factors, including fasting glucose and HOMA-IR in patients with T2DM \[56\]. Replacing carbohydrates with either mono- or polyunsaturated fats can also greatly improve these factors \[57\]. Similarly, replacing saturated with polyunsaturated fats not only improves these factors but also reduces C-peptide, which is known to have a significant negative correlation with insulin sensitivity \[57\]. It seems polyunsaturated fats can also indirectly improve insulin sensitivity through its anti-inflammatory properties. For example, increased intake of omega-3 polyunsaturated fatty acids lead to increased production of 3-series prostaglandins, which are generally less inflammatory and more beneficial in several disease states than the otherwise produced 2-series \[58\]. For this reason a Mediterranean-style diet, which recommends a variety of healthy oils (i.e. mono- and polyunsaturated fats), has been shown beneficial for maintaining T2DM \[59\].

Micronutrients

Several micronutrients are shown to promote insulin signaling in humans, even in the presence of obesity, including vitamins D and E, thiamine, and several minerals. Specifically, supplementation with vitamins D and E contributes to enhanced systemic insulin sensitivity, as evidenced by improved HOMA-IR scores \[60, 61\], while intake of thiamine and zinc regulate fasting blood glucose and/or post-prandial glucose levels \[62, 63\] in patients with T2DM. The latter dietary components and their subsequent effects are also likely to benefit patients with impaired fasting glucose as they may slow the progression of hyperglycemia to diabetes. In overweight, diabetic individuals co-supplementation with vitamin D, K and calcium similarly improves HOMA-IR scores, but also significantly increases high density lipoprotein (HDL) cholesterol and reduces fasting plasma glucose, insulin levels, and C-reactive protein \[64\], an inflammatory marker linked to an increased risk for diabetes. Interestingly, it seems that vitamin D supplementation is also beneficial in reducing the development of gestational diabetes \[65\], another condition closely linked to obesity, although continued clinical research is necessary to further confirm its full affects.

Meal Timing

Meal timing can also be a key tool in successfully managing obesity-associated insulin resistance/T2DM. Much research has previously established the relationship between circadian rhythm (i.e. sleep-wake cycles) and metabolic elements in mammals, including genes that regulate glycolysis and insulin signaling \[66-68\]. More recently, the association between disrupted sleep cycles and obesity and obesity-related diseases, including T2DM, has been defined \[69, 70\]. Research to date has primarily revealed the cellular mechanisms, but has yet to fully elucidate how such mechanisms may be influenced by or interact within complex systems. Although clinical trials and/or intervention studies specifically relating meal timing to circadian rhythm parameters are lacking, it is reasonable to assume that syncing meals to specific points within the sleep-wake cycle would be beneficial to manage T2DM. More research and clinical trials in this area are therefore warranted. Additionally, meal timing seems significant to achieve successful weight loss \[71\], which is among the prescribed methods for preventing and managing T2DM.
There are no current recommendations related to specific meal timing, but overall the DGA recommends multiple, smaller meals throughout the day rather than a few, large meals.

**DIET COMPOSITION FOR MANAGING CARDIOVASCULAR DISEASE**

Risk factors for cardiovascular disease (CVD) including hypertension and dyslipidemia are commonly found in overweight and obese individuals. In fact, NHANES data from 2007-2010 showed prevalence rates of these disorders at 35.7% and 49.7%, respectively in obese adults \[72\]. The link between obesity and CVD is a combination of dietary factors, metabolic imbalances, and endothelial and vascular dysfunction \[10\]. Much research also points to obesity-induced inflammation as a major contributing factor \[10, 73\]. Thus, interventions and dietary components, including those discussed in previous sections, aimed to reduce obesity are of utmost importance. Indeed, weight loss remains the key recommendation to manage all obesity-related conditions; however, additional dietary components can greatly support heart health. These components, collectively named the Dietary Approach for Stopping Hypertension (DASH), and their underlying mechanism(s) are discussed in this section. Increased physical activity is also a key intervention for managing excess weight gain and CVD; however, that topic is outside the scope of this review.

**Sodium Content**

Sodium is an essential micronutrient that plays a critical role in maintaining blood volume and promoting nerve cell transmission and muscle contraction. Because of the widespread use of sodium/table salt, sodium deficiencies are infrequent in the average American adult. Excess intake on the other hand is exceptionally common, with average daily consumption by Americans aged 2 and older at 3,400 mg. Overconsumption is linked to many metabolic diseases with and without obesity \[74-76\]. The DGA therefore recommends a maximum intake of 2,300 mg sodium per day, which is equivalent to about one teaspoon of table salt, although the DASH diet targets a maximum of 1,500 mg. Obese individuals who follow these dietary recommendations have shown reduced rates of hypertension, atherosclerosis and lipid-induced oxidative stress and thus, a lowered risk of developing CVD \[77\]. Many studies show that even a moderate reduction in salt intake improves blood pressure both short and long-term. Although perhaps less enjoyable, low-sodium diets seem to be a great dietary approach to manage obesity-associated disorders related to CVD as they are typically low risk and are generally easy to adhere. Another benefit of reducing dietary sodium is that salt intake seems to be a potential risk factor for obesity itself, independent of energy intake \[78\].

**Carbohydrates, Fiber and Cholesterol**

The DASH diet recommends 55% of total daily intake from carbohydrates, including at least 3 servings of whole grains per day. Indeed, evidence from clinical trials demonstrates that obese individuals who increase their intake of whole grains show improvements in many factors associated with cardiovascular health \[79, 80\]. Additionally, DASH targets 30 g of fiber per day for all individuals, which is in line with the DGA for average adults. Fiber is specifically beneficial to heart health through its ability to reduce total and low-density lipoprotein (LDL) cholesterol \[81\]. Interestingly, when compared with a low-carbohydrate diet, a diet high in fiber significantly lowered atherogenic lipids, although both diets were effective for weight loss. It is well known that increased fiber intake also reduces high blood pressure \[82, 83\]. Thus, these dietary components of the DASH diet help to manage obesity-associated CVD through improvements in many known risk factors.

Although the DASH diet does not provide specific recommendations for cholesterol intake, it does target increased consumption of fruits and vegetables and less caloric intake from non-lean meats. The mechanisms underlying the success of these dietary approaches are the reductions in total and LDL cholesterol, increased HDL, and improved
blood pressure \[^{[84, 85]}\]. In fact, following the DASH diet seems to reduce most of the risks associated with the metabolic syndrome which ultimately, contributes to improved cardiovascular health.

Micronutrients

Unsurprisingly, the major micronutrients targeted by the DASH diet are the electrolytes. In addition to sodium (discussed in detail above), potassium, magnesium, and vitamin D are important for proper management of heart health. Obesity is associated with deficiencies of all three, which partially clarifies the mechanisms of obesity-associated hypertension. For instance, in primary hypertension potassium depletion interrupts normal functioning of sodium pumps, increases sympathetic activity and angiotensin II production, and indirectly interferes with calcium signaling \[^{[86]}\]. Vitamin D deficiency, especially when paired with BMI ≥ 30, is also linked to arterial hypertension and coronary artery disease, likely through inappropriate activation of the renin angiotensin-aldosterone system (RAAS) along with other mechanisms \[^{[87, 88]}\]. Magnesium deficiency, commonly seen in the United States, as evidenced by NHANES data from 2001-2010 \[^{[89]}\], is shown to enhance angiotensin-induced aldosterone synthesis and contribute to impaired insulin action \[^{[90, 91]}\]. Thus, interventions to replete low magnesium levels may be key to improving hypertension in diabetic individuals. Indeed, controlled interventions using the DASH diet show repletion of all three micronutrients and subsequently, improvements in several risk factors of CVD \[^{[92-94]}\]. Interestingly, one trial demonstrated that the DASH diet lowered blood pressure in obese hypertensive patients more effectively than an intervention of only potassium, magnesium, and fiber \[^{[95]}\]. The added success of the complete DASH diet was attributed to intake of additional bioactive nutrients such as the antioxidant vitamins C and E, and folate, arginine and lycopene. Additional research is needed to further confirm the effects of these nutrients and determine if others (i.e. phytochemicals, etc) participate in the management of obesity-induced hypertension. Other intervention trials have demonstrated similar beneficial effects following compliance to a DASH diet \[^{[87, 88, 96, 97]}\]. In addition, weight loss of approximately 5% has been shown to significantly reduce and manage the RAAS and positively contribute to reduced blood pressure \[^{[96]}\]. Therefore, dietary approaches to adequately manage obesity-induced hypertension should focus on proper micronutrient intake and at least moderate weight loss.

DIET COMPOSITION FOR MANAGING OBESITY-RELATED CHRONIC LIVER DISEASES

Obesity significantly increases the incidence of NAFLD, with hepatic fat deposition (steatosis) being the primary feature. Simple steatosis may be benign, but progresses to non-alcoholic steatohepatitis (NASH) when the liver exhibits overt inflammatory damage. NASH is now considered as one of the most common causes of terminal liver diseases including liver cirrhosis and hepatocellular carcinoma. Due to the close relationship between obesity and NAFLD, most dietary approaches used for obesity management are also applicable to NAFLD \[^{[98, 99]}\].

Fat Content

It is accepted that inflammation drives the progression from simple steatosis to NASH. Accordingly, anti-inflammatory nutritional approaches have been considered for managing NAFLD. In 2012, the Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association stated that omega-3 fatty acids may be beneficial for NAFLD; although it was not recommended to treat NAFLD \[^{[98]}\]. Six years later, the Guideline regarding omega-3 fatty acids remains the same \[^{[99]}\]. This guideline, interestingly, can be interpreted in an either positive or negative way. On the one hand, there is lack of convincing clinical evidence to consistently support the effect of omega-3 fatty acids on improving or reserving liver histology and serum ALT \[^{[100]}\]. On the other hand, supplementation with omega-3 fatty acids brings about beneficial effects on NAFLD. For example, treatment with docosahexaenoic acid (DHA) plus
Eicosapentaenoic acid (EPA) for 15-18 months is associated with a decrease in liver fat content; although the treatment did not improve fibrosis scores [103]. Moreover, a significant number of studies using rodent models of NAFLD have attributed the beneficial effects of omega-3 fatty acids to mechanisms varying from decreasing hepatic inflammation [102] and suppression of liver oxidative stress [103] to attenuating the TGFβ-Smad3 pathway [104]. It should be noted that omega-3 fatty acids are also beneficial to obesity-associated insulin resistance. As such, the systemic benefits of omega-3 fatty acids are expected to also account for its anti-NAFLD effect.

Antioxidants

During NASH, oxidative stress is viewed as a critical factor underlying the development of hepatocellular damage. Given this, vitamin E has been used to treat NASH [105-107]. The results consistently support the effects of vitamin E on reducing ALT and improving fibrosis scores in NASH patients. Based on convincing evidence, vitamin E has been continuously recommended to treat non-diabetic adults with biopsy-proven NASH [98, 99]. However, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis [98, 99].

**DIET COMPOSITION AND IMPACT BEYOND NUTRIENT RATIOS**

While a number of nutrients have been considered to treat obesity-associated metabolic disease, it is worth noting that diet composition appears to be more important in terms of generating profound impact on health. As supported by evidence from studies of either animal or human subjects, differences in diet composition have been shown to alter biomarkers related to metabolic diseases varying from metabolites to lifespan [108-110].

**Low Protein and High Carbohydrate Diet**

The benefits of CR have been previously reviewed [5]. Interestingly, recent evidence also suggests that altering diet composition, but not energy intake, is sufficient enough to modulate life span and metabolic aspects. For instance, upon altering primarily protein and carbohydrate amount, Solon-Biet et al. demonstrated that replacing protein with carbohydrate is capable of optimizing longevity and health in mice likely by suppressing hepatic mammalian target of rapamycin (mTOR) [109]. A similar study in mice further indicated that low protein and high carbohydrate diet under ad libitum conditions generates metabolic benefits comparable with those achieved by CR [110]. To be noted, these findings were made from mice under CR or ad libitum conditions, which are different from obese or diseased conditions. Indeed, in terms of managing metabolic diseases, high protein and low carbohydrate (HPLC) diet, but not low protein high carbohydrate (LPHC) diet, is more beneficial. In support of this, certain studies involving human subjects with stage 1 hypertension have shown that partial substitution of carbohydrate with either protein or monounsaturated fat can lower blood pressure, improve lipid levels, and reduce estimated cardiovascular risk [108]. Thus, the benefits and optimal use of HPLC vs. LPHC diet appear to be dependent on the presence (or absence) of diseases.

**High Protein and Low Carbohydrate Diet**

As mentioned above, HPLC diet is beneficial for subjects with certain health issues associated with metabolic syndrome. This is true when the ratios of macronutrients are within a relatively balanced range. For example, a trial that examined the effect of altering the composition of a DASH diet indicated that each of the three diets in which saturated fats were replaced by carbohydrate, protein, or mono-unsaturated fatty acids was able to lower blood pressure compared with baseline [111]. In this study, the composition of carbohydrate: fat: protein is 58: 27:
15 for the carbohydrate diet, 48: 27: 25 for the protein diet, and 48: 37: 15 for the unsaturated fat diet [111]. Similarly, the trial by Furtado et al. demonstrated that the protein diet generates the most favorable benefits on plasma lipoprotein profile and the lowest plasma total apoB concentrations while reducing plasma levels of triglycerides [112]. Additional to lowering blood pressure and plasma apoB levels, partially replacing carbohydrate with unsaturated fat also improves systemic insulin sensitivity [113]. These results not only validate the benefits of replacing saturated fats with carbohydrate, protein, and/or unsaturated fat, but also demonstrate that the protein diet appears to be able to maximize benefits relative to the carbohydrate diet and/or unsaturated fat diet. The underlying mechanisms by which the protein diet is superior are not clear. However, it is likely that the protein diet, at the given diet composition, does not induce mTOR activation as does the HPLC diet [109]. Also, it cannot be ruled out that altering diet composition likely generates distinct effects on human subjects versus laboratory mice. The latter are normally maintained by diet with carbohydrate: fat: protein composition of 62.1: 13.2: 24.6.

**Low Carbohydrate, Low Protein, and High Fat diet**

As indicated by many studies, low carbohydrate, low protein, and high fat diets (ketogenic diet) have been considered to manage obesity and associated problems including T2DM [114, 115]. This diet is very different from the aforementioned diets. In the context of weight loss, ketogenic diet appears to act through preventing an increase in appetite, and this effect is attributable to ketosis [116]. Ketogenic diet also reduces insulin secretion. This in turn favors whole body fat oxidation and contributes to weight loss [115]. Ketogenic diet also exerts a glucose-lowering effect, which is more pronounced than that achieved by a conventional low caloric diet [114]. Additional to reducing body weight and lowering glucose levels, ketogenic diet may also benefit heart health. The latter is attributable to, at least in part, the effect of ketogenic diet on improving dyslipidemia and hypertension [115].

Although it displays metabolic benefits, ketogenic diet may also cause some unwanted effects. This, indeed, is well illustrated by a study in which the effects of standard diet, Western high-fat diet, and ketogenic diet on metabolic aspects were examined in laboratory mice [117]. In this study, diet compositions were (carbohydrate: fat: protein) 62.1: 13.2: 24.6 for standard diet, 40.7: 40.6: 18.7 for Western diet, and 0.4: 95.1: 4.5 for ketogenic diet. As expected, Western diet caused the greatest increase in body weight whereas ketogenic diet caused the lowest. Also, Western diet, at either 6 week or 12 week duration, caused significant increase in body fat content. Interestingly, mice on a ketogenic diet consumed more calories compared with mice on a chow diet or Western diet. Clearly, these results confirmed the benefits of ketogenic diet on managing body weight. In relation to Western diet, ketogenic diet is anti-lipogenic. However, over a time period of 12 weeks, ketogenic diet caused hepatic steatosis and inflammation, which is associated with hepatic endoplasmic reticulum stress. A similar study using mice further indicated that long-term ketogenic diet leads to reduced β- and α-cell mass and failed to produce weight loss [118]. Thus, long term ketogenic diet is associated with increased risk for NAFLD and T2DM. However, neither of the two studies investigated the effect of ketogenic diet on obese mice. Thus, additional research is needed to examine whether ketogenic diet produces unwanted effects in obese mice similar to those in lean mice. Nonetheless, caution is needed when considering ketogenic diet as a nutritional intervention, particularly over long periods of time.

**CONCLUSION**

Healthy nutrition is effective in terms of managing obesity and related metabolic diseases. While much attention is paid to the benefits achieved by altering the content of healthy nutrients, it may be time to shift the focus to diet composition which is likely of particular importance in managing obesity and other related metabolic diseases. Consistently, diets with balanced nutrients that are capable of generating metabolic benefits should be considered as the primary approach for managing obesity and metabolic disease. In addition, when using a dietary approach it
is also important to monitor off-target effects, such as unwanted side effects, while focusing on the target goals of weight loss and systemic metabolic benefits.

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DECLARATION OF CONFLICTING INTEREST

The authors have no conflicts of interest (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript.

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