Nutritional approaches for managing obesity-associated metabolic diseases

Rachel Botchlett^{1,2}, Shih-Lung Woo¹, Mengyang Liu¹, Ya Pei¹, Xin Guo^{1,3}, Honggui Li¹ and Chaodong Wu¹

¹Department of Nutrition and Food Science, Texas A&M University, College Station, USA

²Pinnacle Clinical Research, Live Oak, USA

³Baylor College of Medicine, Houston, USA

Correspondence
should be addressed
to C Wu

Email
cdwu@tamu.edu

Abstract

Obesity is an ongoing pandemic and serves as a causal factor of a wide spectrum of metabolic diseases including diabetes, fatty liver disease, and cardiovascular disease. Much evidence has demonstrated that nutrient overload/overnutrition initiates or exacerbates inflammatory responses in tissues/organs involved in the regulation of systemic metabolic homeostasis. This obesity-associated inflammation is usually at a low-grade and viewed as metabolic inflammation. When it exists continuously, inflammation inappropriately alters metabolic pathways and impairs insulin signaling cascades in peripheral tissues/organs such as adipose tissue, the liver and skeletal muscles, resulting in local fat deposition and insulin resistance and systemic metabolic dysregulation. In addition, inflammatory mediators, e.g., proinflammatory cytokines, and excessive nutrients, e.g., glucose and fatty acids, act together to aggravate local insulin resistance and form a vicious cycle to further disturb the local metabolic pathways and exacerbate systemic metabolic dysregulation. Owing to the critical role of nutrient metabolism in controlling the initiation and progression of inflammation and insulin resistance, nutritional approaches have been implicated as effective tools for managing obesity and obesity-associated metabolic diseases. Based on the mounting evidence generated from both basic and clinical research, nutritional approaches are commonly used for suppressing inflammation, improving insulin sensitivity, and/or decreasing fat deposition. Consequently, the combined effects are responsible for improvement of systemic insulin sensitivity and metabolic homeostasis.

Key Words

- ▶ metabolism
- ▶ nutrients
- ▶ inflammation
- ▶ obesity
- ▶ metabolic diseases

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Introduction

With the increasing prevalence of obesity worldwide, there is a drastic rise in the incidence of metabolic diseases. Metabolic syndrome, type 2 diabetes mellitus (T2DM)/insulin resistance, and cardiovascular disease are only a few of the obesity-associated diseases that can cause serious health problems (Wilson *et al.* 2002, Bhaskaran *et al.* 2014). Although disturbing physiological metabolism and exacerbating other metabolic problems,

these obesity-associated diseases account for upwards of 1.4 billion dollars spent per year in healthcare costs, in the US alone, for the treatment and management of such diseases (Cawley & Meyerhoefer 2012). Numerous pharmaceuticals are available for treating such disorders; however, it is important for patients/consumers to remember the value and health benefits of food, including both macro- and micronutrients. Nutrients are essential in all aspects of

health, including the absorption and digestion of food, immune function, brain activity, and exercise ability. Not to mention, proper nutrition for maintaining health and staving off metabolic disease could greatly contribute to lower healthcare costs. Therefore, the purpose of this review is to emphasize the importance of nutrients in metabolism and more importantly, summarize how nutritional approaches can be used to support proper health and treat and/or prevent the onset of metabolic disorders, especially those associated with obesity.

Nutrients and the regulation of metabolic homeostasis

All nutrients play various yet vital roles in metabolism. This section briefly highlights the physiological significance of macro- and micronutrients. Discussions include current dietary recommendations, primary metabolic pathways and/or functions in which each nutrient is involved, and examples of major foods that are known to contribute to obesity and/or metabolic diseases or shown to benefit metabolism and support health. Although not a nutrient, gut microbiota is discussed given its importance in regulating metabolic homeostasis.

Carbohydrates

Carbohydrates (CHO) are the primary energy source throughout the body, with multiple tissues and cell types solely depending on CHOs for metabolic needs. For this reason the current acceptable macronutrient distribution range (AMDR) and recommended daily allowance (RDA) for CHOs are 45–65% of total daily calories and 130 g/day, respectively (dietary reference intakes (DRIs), United States Department of Agriculture (USDA)). These values are suggested for males and females of all age groups.

After digestion of dietary CHOs, the resulting monosaccharides (mainly glucose) are converted to energy using three major metabolic pathways: glycolysis, the Krebs cycle, and the electron transport chain. From start to finish, this process accounts for the most efficient breakdown/usage of any macronutrient. Therefore, proper CHO intake not only ensures that cells' energy requirements are met, but also promotes overall metabolic efficiency. In contrast, inadequate intake and/or overconsumption of CHOs can result in metabolic complications. For example, long-term CHO deficiency in healthy/normal weight adults can result in hypoglycemia, muscle atrophy, or ketoacidosis, whereas

overconsumption, in addition to causing weight gain and/or obesity if chronically overconsumed, can lead to disruptions in sleep-wake cycles, increased risk for non-alcoholic fatty liver disease (NAFLD) and insulin resistance (Flowers & Ntambi 2009, He *et al.* 2015b, Neuschwander-Tetri 2013, López-Alarcón *et al.* 2014).

Although over- or under-consumption of CHOs can be detrimental to metabolism, the type of CHO ingested can also differentially affect the health. Complex CHO intake (i.e. starches such as amylose and fibers) is associated with a reduced-risk for metabolic diseases including heart disease, T2DM/insulin resistance, and colon cancer compared to the consumption of primarily simple CHOs (Foster-Powell *et al.* 2002, Jenkins *et al.* 2002, Domínguez Coello *et al.* 2010, Mirrahimi *et al.* 2013, Argiana *et al.* 2015, Turati *et al.* 2014, Sieri *et al.* 2015). Although still a controversial topic, more research is necessary to further define the relationship between simple CHOs and insulin resistance, and/or the onset of metabolic diseases in normal-weight vs. overweight/obese populations. Overall however, results appear to support that reducing simple CHO intake, fructose and sucrose for example, and increasing intake of complex CHOs, especially in the long term, is more supportive of and beneficial to health.

Fats

Unfortunately, when it comes to health and body weight, or more accurately, body image, dietary fats commonly receive a disparaging view. However, fats serve multiple beneficial purposes for health and metabolism. For example, fats provide insulation, drive the absorption of fat-soluble vitamins, serve as primary components in phospholipid bilayers and lipoprotein particles, and provide a long-term energy source when needed. Thus, adequate fat intake is vital for metabolism. No RDA for dietary fats exists but the current AMDR for males and females aged 19 years and older is 20–35% of daily caloric intake (DRIs, USDA). Also included with the adult AMDR is a suggested intake of linoleic acid at 12–17 g/day and α -linolenic acid at 1.1–1.6 g/day, both of which are essential fatty acids and thus, cannot be synthesized innately but only obtained through the diet.

High-fat diets (HFD; daily caloric intake that exceeds body requirements) are indeed detrimental to health as they can be a potent contributor to lipid accumulation throughout the body and thus, can lead to weight gain relatively quickly (Sampey *et al.* 2011, Senthil Kumar *et al.* 2014, Roseno *et al.* 2015). However, more imperative to health and metabolism is the

well-documented association between long-term HFD and the generation of inflammation. For example, it is well established that feeding a saturated fatty acid-enriched HFD to mice causes inflammation in various tissues and organs including the adipose tissue (Xu *et al.* 2003, Huo *et al.* 2010), the liver (Cai *et al.* 2005, Woo *et al.* 2014, Guo *et al.* 2016), small intestine (Guo *et al.* 2013, Botchlett *et al.* 2016), and even the brain (Zhang *et al.* 2008, Tang *et al.* 2015). Significantly, chronic HFD-induced inflammation is now considered as a major factor in the onset of many metabolic disorders including obesity, T2DM, cardiovascular disease and some forms of cancer (Hotamisligil 2006, Terzić *et al.* 2010, Egger 2012). Furthermore, HFD is known to alter the expression of genes involved in metabolic signaling and thus, impair normal metabolic function throughout the body (Choi *et al.* 2013, Banin *et al.* 2014).

Although both overconsumption of total calories and dietary fats can be major driving forces in weight gain/obesity, the type of fat consumed can have significant effects on metabolism and/or the generation of inflammation as well. Numerous studies have indeed provided evidence to support the pro-inflammatory role of saturated fats, compared to unsaturated fats (Milanski *et al.* 2009, Teng *et al.* 2014), and have demonstrated mechanisms of how saturated fats are linked to metabolic diseases. Although intake of unsaturated fats is recommended over saturated (DRIs, USDA), overconsumption of unsaturated fats can also negatively affect health (Azrad *et al.* 2013). Nonetheless, adequate intake of unsaturated fats, i.e. within the AMDR, is shown to be less inflammatory and more beneficial to health compared to that of saturated fats.

Proteins

Dietary proteins/amino acids are only metabolized for energetic needs under extreme conditions, so they primarily benefit health/metabolism in other ways. They provide structure and rigidity to cells, and are necessary for the growth of muscle, bone, and skin, participate in secondary messenger signaling cascades, drive major metabolic pathways such as the Krebs cycle, and play important roles in the metabolism of other macronutrients. As such the current AMDR and RDA for dietary proteins for average adults are 10–35% and 46–56 g/day, respectively (DRIs, USDA).

Of the twenty essential amino acids, arginine, citrulline and leucine are among the most vital for preventing obesity and/or obesity-related metabolic diseases. For example,

beneficial impacts of L-arginine supplementation include increasing energy expenditure favoring reduced growth of white adipose tissue (WAT) (McKnight *et al.* 2010) whereas dietary L-leucine and L-alanine supplementation reveal similar acute effects on preventing HFD-induced obesity likely by acutely influencing satiety (Freudenberg *et al.* 2013). Citrulline is shown to play an important role as a marker for the onset of diet-induced obesity (Sailer *et al.* 2013) and more recently, exerts a counteractive effect on aging and excess weight-induced metabolic and inflammatory effects in WAT (Joffin *et al.* 2015). Increased intake of dietary leucine shows significant effects on preventing diet-induced obesity and modulating insulin signaling and glucose homeostasis within muscles (Layman & Walker 2006, Zhang *et al.* 2007). Interestingly however, leucine supplementation has the opposite effect when given to already obese rats. Furthermore, obese mice display additional fat accumulation within WAT after supplementation of leucine (Zampieri *et al.* 2014). Consistently, White and coworkers demonstrated that obese rats display higher levels of circulating branched-chain amino acids (BCAA; leucine, isoleucine, and valine) compared with lean control rats. Furthermore, feeding obese rats an isonitrogenous and isocaloric diet in which all three BCAAs were reduced by 45% lowers circulating BCAA to levels observed in control diet-fed lean rats and improves skeletal muscle insulin sensitivity. These results suggest a detrimental role of BCAA in obesity and insulin resistance (White *et al.* 2016). A recent study by Zhenyukh and coworkers also suggest that high levels of BCAA could contribute to the pro-inflammatory and oxidative status (Zhenyukh *et al.* 2017), thereby exerting a deleterious effect. However, there is also evidence suggesting that higher BCAA levels do not have a causal effect on insulin resistance whereas increased insulin resistance appears to increase the circulating fasting BCAA levels (Mahendran *et al.* 2017). Interestingly, a recent prospective study demonstrates that putting individuals with type 2 diabetes and NAFLD on diets high in protein (either animal or plant) increases postprandial levels of BCAA and significantly reduces liver fat independently of body weight, and reduces markers of insulin resistance and hepatic necroinflammation. These results validate the beneficial effects of BCAA on diabetes complicated with NAFLD, which is opposite to a detrimental role of BCAA in insulin resistance. Regardless of the controversy, proper intake of amino acids, in particular arginine, citrulline, and leucine, can greatly maintain health and seemingly prevent the onset of obesity and obesity-related metabolic diseases.

Micronutrients

Although only needed in trace amounts compared to macronutrients, micronutrients are nonetheless vital to metabolism and crucial in maintaining health. The overall group of micronutrients includes all vitamins and minerals, and can therefore be characterized by the varying functions associated with each subgroup. For example, there are electrolytes (sodium, potassium and chloride), antioxidant micronutrients (selenium, vitamins A, C and E), enzyme cofactors (calcium, manganese, copper and molybdenum), and micronutrients that aid in nutrient absorption and/or metabolism (chromium, vitamins A, D and E). With such a wide array of abilities, micronutrients are active in relatively all metabolic pathways/processes including insulin signaling, lipid metabolism, cell differentiation, and the immune response.

Given the obesity epidemic, there is a significant body of literature addressing the relationships between obesity and micronutrients. For example, obesity is shown to be associated with reduced absorption of copper, iron, zinc, and significantly lower the levels of circulating potassium and magnesium (Lukaski *et al.* 2001, Mariosa *et al.* 2008, Sonnweber *et al.* 2012, Suliburska *et al.* 2013, Zaakouk *et al.* 2016). Considering this, deficiencies in any one or combination of micronutrients can greatly contribute to impaired metabolism and likely be detrimental to health. As such, the USDA provides a recommend daily intake for most vitamins and minerals (DRIs, USDA). However, there is also research suggesting that high circulating levels of selenium are associated with increased risk of diabetes independent of obesity (Lu *et al.* 2016). A similar study also indicates that serum vitamin D concentrations are not associated with the risk of the incidence of insulin resistance in Swiss adults (Marques-Vidal *et al.* 2015). In adults with moderate obesity, vitamin D status also appears to be unrelated to insulin resistance (Al Masri *et al.* 2017). In contrast, in the presence of vitamin D deficiency, supplementation of vitamin D for 6 months generates beneficial effects on glycemic control in type 2 diabetic patients with coronary artery disease (Farrokhian *et al.* 2017), suggesting the importance of vitamin D in managing metabolic diseases. Regardless, to date, most randomized intervention trials of micronutrient supplements have failed to show an improvement in meaningful clinical biomarkers, such as improved antioxidant status or benefits to vascular or non-vascular endpoints (Woodside *et al.* 2005). These negative findings, however, should not be considered as evidence to downplay the importance of micronutrients

in disease prevention and health promotion. Instead, it indicates the complexity of micronutrients in the context of battling obesity (Woodside *et al.* 2005), and suggests the necessity of conducting more well-designed, placebo-controlled, and randomized studies in various groups with considerations of age, gender, degree of obesity and ethnicity as biological variables (García *et al.* 2009, Astrup & Bugel 2010).

Diet composition

Although energy density is a critical determinant of nutritional consequences, diet composition appears to be more important in terms of generating profound impact on health. Because of this, a significant amount of studies have examined the effects of healthy diets on metabolic health. In an early isocaloric feeding trial addressing the effects of optimal diets after replacing saturated fats with a diet rich in CHO, protein, or MUFA on blood pressure, Appel and coworkers demonstrated that each of the three diets lowers blood pressure compared with the baseline. Interestingly, partial replacement of CHO with either protein or MUFA further lowers blood pressure and reduces cardiovascular risk (Appel *et al.* 2005). A similar trial by Furtado and coworkers also demonstrated that healthy diets that emphasize CHO, protein, or unsaturated fat reduce plasma total and lipoprotein apo B compared with a typical high-saturated fat diet (Furtado *et al.* 2008). Interestingly, compared with both the CHO diet and unsaturated fat diet, the protein diet generates the most favorable apo B-containing lipoprotein profile and the lowest plasma total apo B concentrations while reducing plasma levels of triglycerides. A recent trial by Gadgil and coworkers further demonstrated that a diet that partially replaces CHO with unsaturated fat may improve the insulin sensitivity in a population at risk for cardiovascular disease (Gadgil *et al.* 2013). Clearly, these randomized trials provide convincing evidence supporting the importance of diet composition in managing metabolic diseases.

Microbiota

Distinct microbial populations span relatively every part of the human body, including the lungs, nasal passages, vagina, and intestine, and all play their own unique role in maintaining health (Cho & Blaser 2012). The intestinal microbial community is especially vital to metabolic homeostasis as it participates in nutrient absorption and maintaining the health of the intestinal tract. Specifically,

intestinal microbiota aid in the production of bioactive compounds and some essential nutrients and metabolites and, arguably their most beneficial role within the intestinal environment, generate short-chain fatty acids (SCFA) (Natarajan & Pluznick 2015). Although pathogenic bacteria are also present, within normal/healthy hosts diseased/inflammatory states are efficiently regulated and do not negatively alter metabolism.

However, alterations within the microbial community have been implicated in the onset of diet-induced metabolic disorders (Cani *et al.* 2008, Turnbaugh *et al.* 2008, Turnbaugh & Gordon 2009, Suez *et al.* 2014). Specifically, changes to the normally-occurring gut bacteria are associated with reduced metabolite and/or peptide production, impaired nutrient absorption, diminished SCFA production, and a proinflammatory state (Cani *et al.* 2008, Samuel *et al.* 2008, Ding *et al.* 2010, Ridaura *et al.* 2013, Heinritz *et al.* 2016). Several studies have even indicated that HFD-induced dysbiosis promotes intestinal inflammation that precedes obesity and other metabolic diseases (Bleau *et al.* 2015, Ding *et al.* 2010). Thus, it seems alterations to healthy microbial populations can both contribute to and be a result of diet-induced obesity and/or a variety of metabolic diseases. Maintaining a healthy flora is therefore essential in treating and/or staving off such disease states. Indeed, many studies have now demonstrated positive effects from a variety of therapeutics or interventions to combat obesity, diabetes, and others (He *et al.*, Sáez-Lara *et al.* 2016).

Nutrients, epigenetics, and genetics

The interplays among nutrients, epigenetics, and genetics have been increasingly studied by many researchers, and are detailed by numerous reviews. Additionally, nutrients or nutrient metabolism can be significantly influenced by genetic factors; although nutrients, *per se*, have limited roles in altering genetics. Now, it is convincing that nutrients, e.g., nutrients that alter one carbon metabolism, are capable of altering epigenetics to influence the status of health and/or diseases. Indeed, various nutritional approaches are shown to act through, at least in part, modulating epigenetics to bring about beneficial effects, in particular anti-cancer effects (Bishop & Ferguson 2015). Unlike anti-cancer approaches, there are relatively fewer nutritional approaches that may be used for managing obesity and related metabolic diseases. However, it would be of particular importance in targeting maternal nutrition to reduce the incidence of future offspring obesity.

Pathology of metabolic dysfunction

Many factors can contribute to impaired local and/or systemic metabolic signaling and in turn, augment the onset of metabolic diseases. This section briefly focuses on the pathology of three primary dysfunctions related to diet-induced obesity. Tissue specific pathologies as well as nutritional interventions to reduce their onset are discussed in subsequent sections. Also, the highlights of nutrition and metabolic dysfunction are summarized in Fig. 1 (see text for detail).

Inflammation/inflammatory responses

Inflammation is the principal response of the body invoked to deal with injuries and infections. As an acute or short-term adaptive response, inflammation is a crucial component of tissue repair and vital for maintaining cell viability and function. However, long-term consequences of prolonged inflammation are often associated with metabolic disorders, such as insulin resistance, fatty liver disease, T2DM, atherosclerosis and some cancers (Wellen & Hotamisligil 2003, Zimmermann *et al.* 2011). Substantial evidence now links obesity with inflammation (Emilsson *et al.* 2008, Hardy *et al.* 2011). Unlike acute inflammation, which is usually localized to the site of injury (Warren *et al.* 2010), obesity-associated inflammation is a low-grade, chronic state (Neels & Olefsky 2006). Furthermore, inflammation in obesity is a systemic progression that involves the activation of several inflammatory pathways, and the subsequent generation of proinflammatory cytokines, which can contribute to the dysfunction of multiple organ/organ systems (Ouchi *et al.* 2010, Lumeng & Saltiel 2011).

Many factors, including diet, play a role in promoting the inflammatory processes. Excess intake of overall or saturated fat and calories for example can activate inflammatory pathways in cells by nutrient-sensing and cytokine signaling mechanisms (Arkan *et al.* 2005), both of which occur by the stimulation of cell surface receptors including toll-like receptors (TLRs), and/or cytokine receptors such as intracellular pathogen sensing NOD-like receptors. Furthermore, these pathways can converge and activate other pro-inflammatory pathways including the mitogen activated protein kinase (MAPK), c-jun N-terminal kinase (JNK), extracellular regulated kinase (ERK), P38 MAPK, the inhibitor κ B kinase (IKK), and protein kinase C (PKC) pathways (Mogensen 2009, Saxena & Yeretssian 2014). After stimulation of such pathways,

Figure 1

Obesity, inflammation and metabolic dysregulation. During obesity, nutrient overload initiates or exacerbates inflammation in the intestine, adipose tissue and liver. Inflammation, in turn, impairs functions of the liver, adipose tissue and skeletal muscle to critically contribute to the development of insulin resistance and metabolic dysregulation via working with or without excessive free fatty acids (in particular saturated fatty acids). The interactions between nutrients and host cells e.g., intestinal cells and adipocytes, also generate factors that exert profound actions the brain to alter feeding behaviors, the dysregulation of which contributes significantly to positive energy balance (not depicted). IEC, intestine epithelial cells; IEL, intestine epithelial lymphocytes; DC, dendritic cells; FFA, free fatty acids, and M1/M2, macrophage (MΦ) polarization.

activated transcription factors including nuclear factor kappa beta (NFκB) can further direct the inflammatory response by binding target gene promoters in the nucleus and in turn lead to the translation of inflammatory cytokine and chemokine genes to activate or enhance the immune responses (Fan *et al.* 2005).

Fat deposition

As discussed above, intake of dietary fats is vital to overall health and normal functioning of many metabolic pathways. Following intake, digestion and absorption of dietary fats, triglycerides are formed within the small intestine, packaged into lipoprotein particles, and transported to the liver. During this process triglycerides can be hydrolyzed and converted into glycerol and free fatty acids (FFAs). This is necessary for FFAs to enter adipocytes, be re-esterified into triglycerides, and stored. This overall process is the primary pathway for fat deposition in the adipose tissue and continues as dietary fats are consumed.

When caloric intake chronically exceeds the body's requirements however, fat deposition can be amplified (Speakman 2004). In some cases, excess intake of any one macronutrient can also result in such consequences (Ambrosini *et al.* 2012, Hörnell *et al.* 2013, Moslehi *et al.* 2015, Carreiro *et al.* 2016). It seems that multiple mechanisms exist for how overnutrition stimulates this process. For example, many studies have reported increased expressions of genes involved in the

fat deposition and/or decreased expressions of genes that regulate beta oxidation following overnutrition (Hudgins *et al.* 2000, Guo *et al.* 2016). Overnutrition with an HFD is a particularly common cause of weight gain/obesity as it is shown to contribute to both subcutaneous and visceral WAT deposition (Kubant *et al.* 2015). In addition, HFD feeding is associated with morphological changes in the intestine, including an increased number and length of villi (Sukhotnik *et al.* 2004, Dailey 2014), which ultimately increases the efficiency of fat absorption and assimilation into the body (Tchernof & Després 2013). The combination of enlarged WAT and increased intestinal fat absorption culminates in HFD-induced obesity, which is correlated with abnormal lipid metabolism and dyslipidemia, increased oxidative stress and inflammation, increased intestinal permeability, and a decrease in systemic insulin sensitivity (Huo *et al.* 2010, Kim *et al.* 2012, Guo *et al.* 2013, Botchlett *et al.* 2016).

Insulin resistance

Insulin resistance is a pathophysiological condition in which physiological levels of insulin do not adequately produce an insulin response in insulin-sensitive target tissues including adipose, skeletal muscle, and the liver (Fig. 1). One of the major molecular mechanisms underlying insulin resistance is the defects in the insulin signaling pathway (Morino *et al.* 2006). For example,

impaired/altered activation of a member of the family of insulin receptor substrates (IRS), specifically IRS-1, can greatly contribute to systemic insulin resistance. Inflammation/proinflammatory cytokines are widely known to interfere with the insulin signaling pathway, including suppression/interference of IRS-1 and IRS-2 (White 2003). Given that diet-induced inflammation can promote the expression and release of multiple inflammatory stimuli, it is now highly implicated in reduced insulin action/insulin resistance (Hirosumi *et al.* 2002, Hotamisligil 2006).

HFDs, in particular, interfere with several sites in the insulin signaling cascade. For example, HFD reduces insulin receptor (IR) and IRS1/2 expression and/or phosphorylation (Liu *et al.* 2015), impairs the phosphorylation of PI3K (Zierath *et al.* 1997), and decreases the translocation of the glucose transporter GLUT4 to the cell membrane (Zierath *et al.* 1997). HFD feeding also directly contributes to insulin resistance in the adipose tissue through adipocyte hypertrophy. One major consequence when adipocytes become overly enlarged is increased secretion of FFAs. Excess FFAs enter the bloodstream and accumulate in various tissues causing steatosis and systemic insulin resistance. For example, increased FFAs impair the insulin signal in muscle (Kim *et al.* 2002) and markedly stimulate hepatic gluconeogenesis (Chu *et al.* 2002), which contribute to increased glucose production and an exacerbated hyperglycemic phenotype. Moreover, excess FFAs are toxic to pancreatic beta cells and can cause reduced insulin production (Shimabukuro *et al.* 1998). HFD can also directly impair lipid metabolism. Specifically, it leads to reduced lipolysis through inhibition of 5' AMP-activated protein kinase (Barroso *et al.* 2011) and increased lipid accumulation via increased expression of fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC) (Guo *et al.* 2016), all of which can intensify systemic insulin resistance.

Nutritional approaches for suppression of obesity-association inflammation

Over the recent decades, as the rates of health disparities and metabolic diseases have increased, researchers have investigated the mechanisms underlying the onset of such conditions. It is now relatively well understood that inflammation is a primary causal factor in many diseases, especially those associated with diet/overnutrition, such as obesity. This section will discuss dietary interventions/

nutrients that prevent and/or regulate inflammation specifically within the adipose tissue (Fig. 2), liver (Fig. 3), and intestine (Fig. 4).

Suppression of adipose tissue inflammation

Under normal conditions, the adipose tissue responds to insulin properly, which includes inhibition of lipolysis and stimulation of glucose uptake and fat deposition. However, pathological states such as diet-induced obesity, cause excessive tissue expansion and dysfunction, leading to insulin resistance and subsequently, increased lipolysis and generation of FFA. In such states, several proinflammatory pathways including JNK, IKK, NFκB, cyclic AMP-responsive element-binding protein H (CREBH) are triggered, and ROS are generated (Hotamisligil & Erbay 2008, Huo *et al.* 2010). Adipocytes in turn secrete cytokines in response to enhanced inflammatory signaling, including tumor necrosis factor alpha (TNFα), interleukin (IL)-1, IL-6, resistin, and monocyte chemoattractant protein-1 (MCP-1). In addition to adipocytes, the adipose tissue also contains numerous immune cells that are activated during proinflammatory/disease states. For example, in obesity there is increased macrophage infiltration into the adipose tissue and more importantly, a phenotypic switch from anti-inflammatory, M2, to proinflammatory, M1, macrophages. Newly recruited macrophages, together with the adipose tissue proinflammatory resident macrophages, promote further secretion of cytokines and chemokines. This low-degree, chronic inflammation in the adipose tissue plays an important role in the development of systemic insulin resistance, and can lead to metabolic and cardiovascular diseases (Berg & Scherer 2005).

One proposed dietary intervention for reducing obesity-associated adipose tissue inflammation is intake of long-chain (LC) omega-3 (n-3) polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). First, they are precursors to resolvins and protectins, endogenous chemical compounds for the withdrawal of proinflammatory cytokines (Bannenberg *et al.* 2005). Secondly, LC n-3 PUFAs can bind G protein-coupled receptor 120 (GPR120) and repress macrophage-induced inflammation and promote insulin sensitivity (Oh *et al.* 2010). Thirdly, EPA and DHA give rise to series 3 prostaglandins that are less inflammatory compared to series 2, normally derived from arachidonic acid (Calder 2010). In fact, in *db/db* mice, a rodent model for diet-induced diabetes, mice

Figure 2

Nutritional approaches for managing obesity-associated metabolic impairments in the liver. AMPK, AMP-activated protein kinase; GLUT2, glucose transporter 2; IKK, I κ B kinases; IR, insulin receptor; IRS1/2, insulin receptor substrate 1/2; JNK, c Jun N-terminal kinase; KC, Kupffer cell; n-3 PUFA, omega-3 polyunsaturated fatty acid; NF κ B, nuclear factor kappa beta; M1, proinflammatory macrophage; M2, anti-inflammatory macrophage; PDK, phosphoinositide-dependent kinase; PI3K, phosphoinositide 3-kinase; pPAR α , peroxisome proliferator-activated receptor alpha; ROS, reactive oxygen species; SOD, superoxide dismutase; TG, triglyceride; TGF β , transforming growth factor beta; TNF α , tumor necrosis factor alpha; Vit D, vitamin D; Vit E, vitamin E.

supplemented with n-3 PUFA showed significantly reduced macrophage infiltration into the adipose tissue and reduced JNK phosphorylation compared with HFD alone, or HFD supplemented with n-6 PUFA (Todoric *et al.* 2006). In addition to regulating systemic inflammation, n-3 LC PUFAs can also prevent hyperplasia and hypertrophy in the adipose tissue, and induce adiponectin secretion and mitochondrial biogenesis in adipocytes (Kopecky *et al.* 2009).

Although the results from basic nutrition research are promising and encouraging, there is also increasing evidence validating the efficacy of nutritional approaches for suppressing the adipose tissue inflammation. As indicated by the results from a human trial by Itariu and coworkers, treatment of severely obese nondiabetic patients with LC n-3 PUFAs for 8 weeks decreased proinflammatory biomarkers in both visceral and subcutaneous adipose tissues, as well as circulating levels of IL-6 (Itariu *et al.* 2012). This anti-inflammatory effect of LC n-3 PUFAs, however, was not associated with a decrease in body weight and

improvement of insulin sensitivity. A similar trial showed that treatment of insulin-resistant, nondiabetic subjects with n-3 fatty acids for 12 weeks decreased adipose tissue macrophages, increased capillaries, and reduced MCP-1 expression (Spencer *et al.* 2013). Consistently, treatment with n-3 fatty acids did not significantly alter body weight and systemic insulin sensitivity. Although the effects of supplementation of n-3 fatty acids on reducing body weight remained controversial (see 'Adipose tissue and reduction of adiposity' section), there appears to be no doubt that n-3 fatty acids are capable of reducing inflammation, including that in the adipose tissue. Additional to n-3 fatty acids, monounsaturated fatty acids (MUFAs) also exhibit anti-inflammatory effects. As supporting evidence, a parallel controlled-feeding trial in abdominally overweight subjects revealed that consumption of a MUFA diet for 8 weeks caused a more anti-inflammatory profile in the adipose tissue comparing to consumption of a saturated fatty acid diet (van Dijk *et al.* 2009). Unlike PUFA, MUFA diets appear to be more promising in improving insulin

Figure 3

Nutritional approaches for managing obesity-associated metabolic impairments in the small intestine. AMPK, AMP-activated protein kinase; FFAs, free fatty acids; GLUT4, glucose transporter 4; IKK, IκB kinases; IR, insulin receptor; IRS1/2, insulin receptor substrate 1/2; JNK, c Jun N-terminal kinase; M1, proinflammatory macrophage; M2, anti-inflammatory macrophage; MCP-1, monocyte chemoattractant protein 1; n-3 PUFA, omega-3 polyunsaturated fatty acid; NFκB, nuclear factor kappa beta; PDK, phosphoinositide-dependent kinase; PI3K, phosphoinositide 3-kinase; pPARα, peroxisome proliferator-activated receptor alpha; ROS, reactive oxygen species; SIRT1, sirtuin 1; SOD, superoxide dismutase; TG, triglyceride; TGFβ, transforming growth factor beta; TNFα, tumor necrosis factor alpha.

sensitivity (see 'Nutritional approaches for insulin sensitization' section).

Another dietary component with anti-inflammatory actions is polyphenolic compounds that inhibit NFκB and MAPK inflammatory pathways, and activate the AMPK pathway in the adipose tissue. Curcumin, derived from rhizomes of the plant *Curcuma longa* (turmeric), is a major polyphenol investigated for this purpose. In fact, *in vitro* studies have demonstrated that curcumin inhibits hydrogen peroxide (H₂O₂)-induced oxidative damage and reduces apoptotic death in human bone marrow-derived mesenchymal stem cells (Yagi *et al.* 2013). Specifically, it appears that curcumin inhibits the generation of ROS via alteration of the PI3K/AKT/mTOR signaling pathway and subsequent inhibition of FOXO1 translocation to the nucleus (Han *et al.* 2012). In endothelial cells, curcumin protects from oxidative injury through blocking Notch signaling that in turn reduces cell apoptosis (Yang *et al.* 2013). Further, within macrophages curcumin is reported to decrease expressions of NFκB and

IL-1β (Du *et al.* 2013). Systemically, *in vivo* studies using rats have shown significantly decreased TNF-α and IL-6 levels after treatment with 50 mg/kg per day of curcumin (Alghasham *et al.* 2013). Similarly, Kant and coworkers showed that treatment with 0.3% (400 μL) curcumin not only reduced inflammatory cytokines, but also promoted wound contraction and increased expressions of anti-inflammatory molecules such as IL-10 and anti-oxidant enzymes such as superoxide dismutase, catalase and GPx (Kant *et al.* 2014). Given the premise of anti-oxidants in suppressing proinflammatory responses, a significant amount of human trials have been performed to examine the effects of mixed fruit and vegetable supplements on inflammatory biomarkers. As summarized by the review article by Esfahan and coworkers, most studies have validated the beneficial effects of daily consumption of fruits and vegetables on suppressing inflammation (Esfahani *et al.* 2011). However, most studies also have limitations related to the diversity of studies and study population.

Figure 4

Summary of nutritional approaches for managing obesity-associated metabolic dysregulation. Most of the currently used approaches are shown to be effective at suppressing inflammation, improving insulin sensitivity, and/or decreasing fat deposition. At the integrative level, the combined effects on key metabolic tissues including the intestine, the liver, adipose tissue and muscle bring about improvement of metabolic dysregulation. In addition, nutritional approaches should be combined with healthy life style, e.g., sufficient physical activity and appropriate circadian clock rhythms of daily life, to maximize the beneficial effects (not depicted). n-3 PUFA, omega-3 polyunsaturated fatty acid; Vit D, vitamin D; Vit E, vitamin E.

Suppression of liver inflammation

The liver is a complex organ composed of various cell populations including hepatocytes and Kupffer cells (KCs). During both acute and chronic liver inflammation, activated KCs promote the generation of proinflammatory cytokines via activation of JNK and NFκB signaling pathways. This manifestation of inflammation is especially true with obesity as increased circulating levels of FFAs are well known activators of KCs. Chronic overnutrition/HFD intake, and subsequent chronic activation of proinflammatory pathways, could also trigger a fibrotic response as the generation of myofibroblasts is triggered to replace damaged/dead hepatocytes. This irreversible damage signifies the onset of declining hepatic function in disease states including obesity.

Many researchers have investigated dietary factors to combat and/or regulate inflammation within the liver. In particular, n-3 PUFAs, palmitoleic acid, and vitamins E and D have known beneficial effects. Systemically, intake of n-3 PUFA is associated with reduced circulating proinflammatory markers including CRP, cytokines, proinflammatory eicosanoids, and others (Schwab & Serhan 2006). Studies using experimental models of liver injury have specifically shown that n-3 PUFAs are able to prevent liver necroinflammatory injury through decreasing liver oxidative stress and DNA damage (González-Pérez *et al.* 2006). In addition, n-3 PUFAs are also known agonists of peroxisome proliferator activated receptor α (PPAR α) (Zúñiga *et al.* 2011), which is known to inhibit NFκB activity (Huang *et al.* 2016). Recently, it has been reported that the activation of liver PPAR α by

n-3 PUFAs is able to increase the PPAR α /NFκB interaction, thereby reducing the expression of proinflammatory cytokines (Zúñiga *et al.* 2011). It seems that n-3 PUFAs exert this effect in KCs through activation of GPR120, a putative receptor for n-3 fatty acids (Oh *et al.* 2010). These effects in turn decrease activation/phosphorylation of JNK and NFκB, as well as stimulate the phenotypic shift from M1 to M2 macrophages, to concomitantly reduce the generation of inflammation.

Palmitoleate, a MUFA, has recently been discovered to exert anti-inflammatory effects in the liver (Guo *et al.* 2012). For example, palmitoleate serves to reduce the liver inflammatory status in an animal model of HFD-induced insulin resistance seemingly by reducing NFκB signaling in macrophages (Guo *et al.* 2012). Similar results have also recently been reported by Souza and coworkers. Specifically, palmitoleic acid supplementation in mice resulted in reduced liver proinflammatory cytokine production of IL-1 β , IL-12, and TNF α , all of which was associated with reduced NFκB signaling and decreased TLR4 expression (Souza *et al.* 2014).

Vitamin E is well known for its anti-inflammatory ability throughout the body. In the liver, vitamin E acts at the propagation phase of lipid peroxidation to donate a hydrogen group, affectively neutralizing the free radical. The vitamin E itself is then converted to tocopheroxyl radical, which reacts with other peroxy radicals to form non-radical products. This ability of vitamin E is especially important in non-alcoholic steatohepatitis (NASH), a condition commonly associated with obesity, where increased levels of oxidative stress within hepatocytes

trigger the formation of proinflammatory cytokines such as TNF α , TGF β , and IL-8. In fact, supplementation with vitamin E in an animal model of NASH significantly reduced NF κ B signaling and the expression of markers for cell apoptosis such as Bax and Bcl-2 (Nan *et al.* 2009). Vitamin D, although most widely known for its role in calcium homeostasis, recently has also been shown to exert anti-inflammatory properties within the liver. For example, vitamin D supplementation in mice resulted in increased expression of antioxidant molecules including glutathione peroxidase and superoxide dismutase (George *et al.* 2012). Further, vitamin D supplementation in a rodent model for NASH lead to a decrease in the progression of liver inflammation, as shown by an improvement in liver histology (Nakano *et al.* 2011). This study also reported that phototherapy elevated levels of the active form of vitamin D which contributed to a reduction in hepatocyte apoptosis and reduced gene expressions of several proinflammatory cytokines. Interestingly, vitamin D deficiency is associated with increased TLR4 expression in the liver. Roth and coworkers suggested that this effect is due to a shift in microbiota following vitamin D deficiency, which causes an increase in bacterial translocation and thus, increased endotoxin exposure within the liver (Roth *et al.* 2012). Unlike animal studies, there are limited human trials studying the effects of dietary interventions on liver inflammation. However, the anti-inflammatory effects generated by nutritional approaches, i.e., PUFAs, MUFAs, and anti-oxidants, may also lead to suppression of liver inflammation in human subjects.

Suppression of intestine inflammation

Several disease states can lead to the development of inflammation in the small intestine. Physical damage, bacterial, viral or parasitic infections, or severe disorders such as Crohn's disease can all contribute to increased inflammation as the responding immune system involves macrophage recruitment and T-cell activation, both of which stimulate inflammatory cytokine pathways. Much research also implicates obesity in inflammatory cytokine production in the small intestine. Diet-induced models of obesity, particularly HFD feeding studies in rodent models using saturated fats, are especially powerful to induce an obese phenotype relatively quickly. Results from such studies show that chronic HFD feeding directly contributes to the generation of inflammation in the small intestine through increased TLR4 expression (de La Serre *et al.*

2010), phosphorylation of JNK (Guo *et al.* 2013) and IKK (Arkan *et al.* 2005), and mRNA levels of IL-6 and TNF α (Guo *et al.* 2013). Interestingly, TLR4 and NF κ B expressions are also increased after only short-term HFD (Wang *et al.* 2013). In addition, HFD-induced obesity also seems to indirectly contribute to small intestinal inflammation via changes in the gut microbial composition. Specifically, several mouse studies have demonstrated a shift in the ratio of *Firmicutes* to *Bacteroidetes* populations (Turnbaugh *et al.* 2006, Turnbaugh *et al.* 2008). This shift leads to increased production of LPS, which generates inflammation locally through stimulation of the TLR4 signaling pathway, and can contribute to systemic inflammation and worsen the obese phenotype (Cani *et al.* 2008). HFD-induced dysbiosis is also associated with reduced levels of intestinal alkaline phosphatase (IAP) (de La Serre *et al.* 2010), which normally functions to detoxify LPS. Changes in microbiota could also alter SCFA concentrations which, when lacking, may promote small intestinal inflammation as reviewed by de Besten and coworkers (den Besten *et al.* 2013). Collectively, these findings indicate that diet-induced obesity contributes to small intestinal inflammation via both direct and indirect mechanisms.

Many adults suffer from intestinal discomfort, whether from minor conditions or diagnosed diseases. Current dietary interventions to reduce intestine inflammation and thus, lessen the pain associated with such conditions include treatment with both macro- and micronutrients. For example, in rodent models of colitis and/or *in vitro* studies investigating anti-inflammatory therapeutics milk oligosaccharides, PUFAs, and polyphenolic compounds such as flavonoids are shown to significantly reduce intestinal inflammation (Lara-Villoslada *et al.* 2006, Vezza *et al.* 2016). Given this, it is a logic extension to use dietary approaches for protecting against obesity-associated intestinal inflammation. Indeed, there is an ongoing clinical trial in obese and non-obese individuals testing the ability of low-fat dairy yogurt to improve gastrointestinal health and reduce chronic inflammation (ClinicalTrials.gov Identifier: NCT01686204). Regardless of the outcomes, targeting intestinal inflammation to maintain metabolic homeostasis or correct metabolic dysregulation via nutritional approaches is increasingly attracting research attention. Among established anti-inflammatory dietary components, n-3 PUFAs are shown to decrease obesity-associated intestinal inflammation, evidenced by its effects on suppressing Th1/Th17 cells (Monk *et al.* 2012). In addition to dietary components, pre- and probiotics can

prevent HFD-induced shifts in the intestinal microbiota (Heo *et al.* 2016). In fact, following HFD feeding treatment with probiotics can actually return the microbial community to its original pre-diet distribution (Heo *et al.* 2016). Given the vast diversity of the human microbiome across subjects/patients, a few interventions will certainly not benefit everyone. Thus, continued research is further investigating additional nutritional therapeutics for HFD-induced/obesity-associated inflammation within the intestinal environment.

Over the past several decades, a number of human trials have focused on the efficacy of various dietary components on intestine inflammation and related diseases, in particular inflammatory bowel disease (IBD). However, to date, there are limited trials examining the effects of nutritional approaches for suppressing obesity-related intestine inflammation. This may be due to the fact that it is a relatively new concept that obesity-related intestine inflammation precedes and correlates with insulin resistance (Ding *et al.* 2010, Du *et al.* 2015). However, it is expected that in the future more trials will specifically address whether and how diets suppress intestine inflammation in the context of preventing or reversing obesity-related metabolic dysregulation.

Nutritional approaches for reducing fat deposition

In non-diseased physiological states, with balanced nutrient and caloric intake, fat deposition is closely regulated and well-managed within the adipose tissue. However, with abnormal metabolism and/or diseases, such as obesity, fat deposition can become uncontrolled, induce inflammation, and occur outside of adipocytes. This section focuses on nutrient/dietary interventions to prevent against the onset of impaired/abnormal lipid metabolism and fat deposition within the adipose tissue, liver, and intestine (Figs. 2, 3, and 5).

Adipose tissue and reduction of adiposity

To support proper/healthy fat deposition, it is recommended to consume complex carbohydrates and lean protein, and limit saturated fat intake. In addition, several functional foods are thought to contribute to healthy fat deposition. Curcumin for example, increases the levels of activated AMPK which in turn decreases the ACC activity, which is a master regulator of lipogenesis.

Inactivity of ACC results in elevated carnitine palmitoyl transferase 1 (CPT1) activity and subsequently, increased LC fatty acid β -oxidation. Curcumin also inhibits the expression of PPAR γ and C/EBP α , which are the key transcription factors involved in adipogenesis and lipogenesis within the adipose tissue. By suppressing the differentiation of pre-adipocytes into adipocytes, curcumin can also suppress the enlargement of adipocytes/adipose tissue and thus, potentially help in staving off weight gain and/or obesity (Aggarwal 2010).

Resveratrol, a non-flavanol polyphenol found in red wine, is another functional food with beneficial abilities in combating diet-induced obesity. Specifically, resveratrol is involved in the downregulation of lipogenesis via increasing levels of SIRT 1 and PPAR γ coactivator 1 α (PGC1 α) (Higashida *et al.* 2013). SIRT 1 represses PPAR γ and thus, serves to inhibit adipogenesis and triggers lipolysis in mature fat cells (Picard *et al.* 2004). PGC1 α helps to regulate mitochondrial biogenesis and oxidative metabolism, which increases rates of β -oxidation in the adipose tissue and can lead to reduced body fat (Liang & Ward 2006).

It appears that caloric restriction (CR) is a powerful and effective approach for reducing body weight, as well as adiposity (see 'Caloric restriction' section). Additional to CR, both PUFAs and MUFAs are shown to alter body fat composition or even reduce fat mass. For example, in a small-size human study involving healthy adults, substitution of fish oil for visible fats in a control diet (52% carbohydrates, 16% protein, 32% fat; polyunsaturated:saturated (P:S 0.2)) for 3 weeks reduced body fat mass (Couet *et al.* 1997). Similarly, in a trial examining the effects of dietary oils, supplementation with conjugated linoleic acid (CLA), but not safflower oil (SAF) for 36 weeks significantly reduced body mass index and total adipose mass without altering lean mass (Norris *et al.* 2009). In overweight or obese children, supplementation of CLA also reduced body fatness (Racine *et al.* 2010). However, there are also many studies that could not support an exact anti-obesity role for n-3 PUFAs in overweight/obese subjects, which suggest the necessity of conducting more large-scale and long-term clinical trials (Du *et al.* 2015). Compared with PUFAs, MUFAs appear to be more promising in terms of reducing fat mass. As supporting evidence, the results of a 6-month randomized and controlled trial involving nondiabetic overweight or obese men and women revealed that MUFA diets allowed less body fat regain than did the control diet (Due *et al.* 2008). More interestingly, consumption of an isocaloric

Figure 5

Nutritional approaches for managing obesity-associated metabolic impairments in adipose tissue. AMPK, AMP-activated protein kinase; FFAs, free fatty acids; GLUT4, glucose transporter 4; IKK, IκB kinases; IR, insulin receptor; IRS1/2, insulin receptor substrate 1/2; JNK, c Jun N-terminal kinase; M1, proinflammatory macrophage; M2, anti-inflammatory macrophage; MCP-1, monocyte chemoattractant protein 1; n-3 PUFA, omega-3 polyunsaturated fatty acid; NFκβ, nuclear factor kappa beta; PDK, phosphoinositide-dependent kinase; PI3K, phosphoinositide 3-kinase; pPARα, peroxisome proliferator-activated receptor alpha; ROS, reactive oxygen species; SIRT1, sirtuin 1; SOD, superoxide dismutase; TG, triglyceride; TGFα, transforming growth factor beta; TNFα, tumor necrosis factor alpha.

MUFA-rich diet prevented central fat redistribution induced by a CHO-rich diet in insulin-resistant subjects (Paniagua *et al.* 2007). In future trials, it may be important to examine the anti-obesity effects of mixed diets.

Brown adipose tissue and promotion of thermogenesis

Brown adipose tissue (BAT) is unique from the more abundant WAT primarily in its ability to generate heat via thermogenesis. Within the mitochondria of BAT, uncoupling protein 1 (UCP1) allows hydrogen ion flux directly from the inner membrane to the matrix, without activating ATP synthase. BAT contains significantly more mitochondria compared to WAT, which equates to more nutrient energy converted to heat, which then elevates glucose metabolism and increases the production of energy. Therefore, more BAT theoretically means more energy expenditure and/or weight loss. However, humans lose a significant amount of BAT as they mature from infants to adults. Nonetheless, nutrients and foods to

increase BAT is a popular research focus for reducing and/or preventing diet-induced obesity.

Some research has indicated that BAT can be activated or stimulated by dietary components, particularly those in spicy foods. For example, non-pungent analogs of capsaicin (capsinoids) are reported to activate BAT in adult humans (Yoneshiro *et al.* 2012, Yoneshiro *et al.* 2013). One suggested mechanism is that thermogenesis is increased via stimulation of the transient receptor potential vanilloid receptor (TRPV1) (Szallasi *et al.* 1999) and upregulation of UCP1 (Yoneshiro *et al.* 2013). In addition, ingestion of capsinoids increases energy expenditure significantly, even in as short as 30 min (Saito 2013). Specifically, consumption of 2.56 mg capsaicin per meal can counteract the unfavorable decrease in energy expenditure during negative energy balance and can boost fat oxidation (Janssens *et al.* 2013). There are many vanilloids with structures similar to capsaicin, such as piperine found in pepper, gingerols, shogaol, and 6-paradol found in ginger. All of these compounds are

also shown to act as agonists for TRPV1 and recruit BAT for thermogenesis (Saito 2013). Thus, repeated ingestion of these compounds could potentially contribute to repeated stimulation of BAT thermogenesis in humans. Continued research to investigate other activators of BAT is of significant interest.

The discovery of beige adipocytes led to the consideration of promoting the development of beige adipocytes in WAT (browning) as a new avenue for management of metabolic disease (Bartelt & Heeren 2014). In addition, a great number of studies have advanced the understanding of the molecular mechanisms underlying browning. To date, however, there is no effective browning-based therapeutic approach for managing obesity and related metabolic diseases. Consistently, Abdullahi and coworkers raised the concern that the notion of browning is supposedly beneficial may be inadequate (Abdullahi & Jeschke 2016).

Liver and reduction of steatosis

The liver is a major metabolic organ involved in fat metabolism. Although a major role of the liver under normal/healthy conditions is not to store fat, it is responsible for a significant amount of *de novo* lipogenesis, including esterification of dietary fatty acids derived from chylomicron remnants, and plasma non-esterified fatty acids (NEFA) derived from adipose tissue lipolysis. Beta-oxidation and triglyceride export in the form of very-low density lipoprotein (VLDL) also occur within the liver. Thus, in pathological states, such as overnutrition and/or diet-induced obesity, dysregulation of any of these processes could lead to abnormal fat deposition in the liver. In fact, excessive fat deposition could pose significant physiological consequences that could lead to metabolic diseases such as alcoholic and non-alcoholic fatty liver diseases.

Several nutrients have been found to protect against excessive hepatic fat deposition. These nutrients include methionine, choline, n-3 PUFAs, and folic acid. Both methionine and choline play important roles in the endogenous synthesis of phosphatidylcholine (Corbin & Zeisel 2012), one of the components of VLDL, and thus, the export of triglycerides from the liver. Indeed, mice fed a methionine and choline-deficient diet (MCD) develop severe hepatic steatosis (Anstee & Goldin 2006). In fact, MCD diet is so potent that it is now used to fed mice as a model for *in vivo*/diet-induced liver damage. As discussed in a previous section, one of the primary benefits of n-3

PUFAs is its anti-inflammatory ability. However, n-3 PUFAs exert additional effects within the liver. As ligands of PPAR α , which is a nuclear receptor for genes involved in β -oxidation, n-3 PUFAs have been shown to increase hepatic β -oxidation via upregulation of fatty acid binding protein (FABP) and CPT1 (Bordoni *et al.* 2006, Jump 2008). In addition, n-3 PUFAs are shown to decrease hepatic lipogenesis by reducing the expression and maturation of sterol regulatory element binding protein-1c (SREBP-1c), thereby downregulating the transcription of hepatic lipogenic genes such as ACC and FAS (Howell *et al.* 2009, Jump 2008). Lastly, because folic acid is a cofactor in the synthesis of 5-aminoimidazole-4-carboxamide 1- β -D-ribofuranoside (AICAR), which is an activator of AMPK, there is recent evidence suggesting that folic acid may be protective against hepatic steatosis. The likely mechanism seems that folic acid decreases lipogenesis via increasing activation of AMPK (Buettner *et al.* 2010), which in turn reduces expression and/or activity of ACC. However, further validations are necessary to confirm these effects of folic acid.

Although basic research has generated a huge body of knowledge regarding nutritional regulation of the pathogenesis of steatosis, there are limited trials examining dietary interventions on hepatic fat deposition. Given the beneficial effects of dietary approaches for reducing body weight and adiposity, it is also interesting to examine if the same approaches result in beneficial effects on hepatic steatosis. Indeed, there is an ongoing randomized controlled trial to examine whether consumption of a Mediterranean diet reduce liver fats (Papamiltiadous *et al.* 2016). There is a hope that more of this type of trials will be performed in near future.

Intestine and improvement of fat metabolic homeostasis

The digestion and absorption of triglycerides in the intestine is a complex progression involving emulsification, hydrolysis of fatty acid ester bonds, and aqueous dispersion of lipolytic products, and mainly occurs in the proximal jejunum and distal parts of the ileum. The major products of triglyceride digestion, monoglycerides and fatty acids, are absorbed by enterocytes through simple diffusion by using micelles, which delivers the products from within the intestinal lumen to the intestinal microvilli. Once absorbed, products are re-synthesized into triglycerides within the smooth endoplasmic reticulum before excretion into the lymphatics system. This process occurs repeatedly, as dietary fats are consumed, and in healthy

individuals does not seem to pose any negative metabolic affects. During the digestion and absorption processes, chylomicrons deliver dietary fats, and thus play a prominent role in fat homeostasis. Due to this, increasing evidence from animal studies has indicated that limiting the rate of intestinal triglyceride synthesis and/or altering chylomicron response could modulate gut hormone secretion, lipid metabolism, and systemic energy balance (Yen *et al.* 2015).

Following overnutrition however, and particularly overnutrition with fat, research shows altered intestinal morphology including increased height and number of microvilli, jejunal mucosal weight, and total protein content (Dailey 2014). Consequently, these effects culminate not only in increased absorptive surface area but increased efficiency of fatty acid absorption within the intestine. Although it is unclear if this effect alone impairs metabolism or stimulates pro-inflammatory mechanisms within the intestine, it does show that overnutrition with HFD significantly impacts the small intestine and subsequently, can contribute to increased circulating fatty acids/triglycerides. As discussed previously, this in turn can lead to increased fat deposition (i.e. weight gain and/or obesity) and the stimulation of pro-inflammatory signaling in distal tissues. Furthermore, it is well documented that HFD directly contributes to intestinal inflammation (de La Serre *et al.* 2010, Guo *et al.* 2013), which in turn can impair nutrient assimilation (Semrin *et al.* 2006). This review discusses dietary options to combat intestinal inflammation in other sections (see 'Suppression of intestine inflammation' and 'Intestine and Insulin-sensitization' section); however, at present it is unclear whether dietary components such as phytoactive chemicals, fibers, and/or antioxidant vitamins/minerals can help protect against HFD-induced excessive fat absorption, alterations in intestinal morphology, and/or reverse impairments to nutrient absorption. Continued research to investigate any benefit of such nutrients in this manner would be greatly beneficial in further understanding the underlying mechanisms of HFD-induced/obesity-associated metabolic impairments and more importantly, combat such disturbances to potentially protect normal/healthy intestine function. Nonetheless, to support the intestinal and overall health it is recommended to consume a diet low in fat and high in foods such as bran cereal fiber, vegetables, fruits, and tea (Weisburger 1997, Ley *et al.* 2014, Via & Mechanick 2016) (DRIs, USDA).

Nutritional approaches for insulin sensitization

Alongside obesity, rates of diabetes have also drastically risen over the previous decades. In fact, the CDC currently estimates that 29 million Americans have diabetes, with roughly 95% of these cases being T2DM. As such, much research has investigated how to combat the onset of such a disorder both systemically and in specific tissues. Therefore, this section discusses specific consequences of insulin resistance and provides examples of successful nutrient interventions that help regulate impaired insulin signaling and/or protect against the onset of T2DM systemically. In this section, the mechanistic insights are focused on key tissues/organs that are essential for the regulation of systemic insulin sensitivity (Figs. 2, 3, and 5).

Systemic effects

T2DM/insulin resistance if not monitored can be very dangerous. Abnormal insulin signaling and thus, insufficient glucose uptake can be disastrous to many cell types and tissues that require glucose as a primary source of energy, such as the brain, red blood cells, and kidneys. Further, insulin resistance is known to impair normal metabolic signaling in primary tissues involved in glucose homeostasis. For example, in skeletal muscle, the major organ for glucose utilization, impaired insulin signaling leads to reduced glycogen synthesis (Nikoulina *et al.* 2001) which can greatly contribute to hyperglycemia. T2DM, especially when paired with obesity, can also severely interfere with normal nutrient-sensing mechanisms (Breen *et al.* 2011) and lipid metabolism (Harmel *et al.* 2014). All of these systemic impairments in turn exacerbate T2DM, and can lead to a vicious cycle of insulin resistance and metabolic dysfunction.

Several micronutrients are known to improve systemic insulin signaling in humans, even in the presence of obesity. For example, supplementation with vitamins D and E helps improve homeostasis model assessments of insulin resistance (HOMA-IR) scores (Manning *et al.* 2004, Belenchia *et al.* 2013, Talaei *et al.* 2013), which is indicative of overall improved insulin sensitivity. High doses of thiamin/vitamin B1 (Luong & Nguyen 2012, Alaei Shahmiri *et al.* 2013) and several minerals (Jayawardena *et al.* 2012, Rodríguez-Moran & Guerrero-Romero 2014) are also suggested to prevent or slow the progression of hyperglycemia toward diabetes. Other

dietary components have also recently been implicated in the management of obesity-related diseases in rodent models of obesity. Specifically, polyphenolics such as apple extract and the green tea extract epigallocatechin-3-gallate (EGCG) serve to not only lower HOMA-IR scores but exert anti-obesogenic properties as well (Brown *et al.* 2009, Santamarina *et al.* 2015).

In a study involving insulin-resistant human subjects, consumption of cod protein diet for 4 weeks was shown to cause a significant increase in insulin sensitivity in relative to consumption of a similar diet containing lean beef, pork, veal, eggs, milk, and milk products (Ouellet *et al.* 2007). Although encouraging, the study, however, could not completely rule out a contribution of n-3 PUFAs to the improvement in insulin sensitivity; however, n-3 PUFAs did not improve insulin sensitivity in several trials (Itariu *et al.* 2012, Spencer *et al.* 2013). As fat mass correlates well with systemic insulin resistance, many trials also analyzed changes in insulin sensitivity while examining dietary effects on weight loss. This was particularly true for trials involving MUFAs as described in section 'Adipose tissue and reduction of adiposity' (Paniagua *et al.* 2007, Due *et al.* 2008). Overall, the insulin-sensitizing effects of nutritional approaches are highly associated with its effects on suppressing inflammation and/or reducing fat deposition.

Adipose tissue and insulin-sensitization

Under normal conditions, the adipose tissue secretes a regulated amount of adipokines, such as leptin and adiponectin, both of which are involved in neuroendocrine control of appetite and behavior of food intake. Dietary fat is stored in the adipose tissue as triglycerides, which consequently leads to decreased circulating FFAs. However, in pathological states such as overnutrition and particularly, overnutrition-induced obesity, increased triglyceride deposition in adipocytes leads to abnormal adipocyte metabolism and increased secretion of adipokines. Particularly, there are increased secretions of MCP-1 (Sartipy & Loskutoff 2003) and other cytokines including TNF α and IL-1 β , secreted by both adipocytes and recruited macrophages. Increased levels of these cytokines are highly associated with increased lipolysis and decreased triglyceride synthesis. Consequently, elevated circulating FFAs damage pancreatic beta cells and reduce insulin secretion, and exacerbate hyperglycemia of T2DM.

Given that obesity is highly linked with T2DM, research to fully understand the pathology and/or

focus on preventative/therapeutic benefits has greatly increased. Therefore, investigating dietary factors that may protect against the development of insulin resistance is paramount. Interestingly, both DHA and resveratrol are known to decrease angiogenesis within the adipose tissue and improve insulin sensitivity, primarily through activation of SIRT1 (Luo *et al.* 2016), which is a deacetylase that regulates expressions of genes involved in insulin secretion and adipocyte metabolism, among others. Furthermore, Chardonnay grape seed flour, which contains high amounts of flavonoids, is shown to ameliorate obesity and insulin resistance, and improve glucose tolerance in diet-induced obese mice via the modulation of genes within the adipose tissue (Seo *et al.* 2015). The potential use of additional functional food components for combating insulin resistance in the adipose tissue will be interesting to investigate, particularly for any potential combination therapeutic treatments.

Hepatic regulation of insulin resistance

In the liver, normal insulin signaling transduces a cascade of actions that properly stimulate or inhibit glucose and fat metabolism, including stimulating glycolysis, glycogenesis, and lipogenesis, while inhibiting gluconeogenesis and glycogenolysis. During insulin resistance however, the signaling molecules within these cascades become impaired/inhibited by various factors including inflammatory mediators such as TNF- α , IL-6, and IL-1 β and result in a loss of insulin signaling (Hirosumi *et al.* 2002, Gregor & Hotamisligil 2011).

However, dietary factors again prove to be beneficial in regulating these metabolic pathways. Specifically, fatty acids and micronutrients protect against insulin resistance in the liver both preventing the loss of insulin signaling molecules and reducing the generation of inflammation. For instance, n-3 PUFAs are shown to increase the liver expression of IRS-1 and GLUT2 (Hein *et al.* 2012 & Bargut *et al.* 2014), and also decrease the liver inflammatory status, via increased production of resolvins, to improve insulin sensitivity (González-Pérez *et al.* 2009). Similar to n-3 PUFAs, palmitoleate is also shown to improve insulin sensitivity at both hepatic and systemic levels in mice (Guo *et al.* 2012). This insulin-sensitizing effect is attributable to, at least in part, the anti-inflammatory effect of palmitoleate. However, palmitoleate supplementation increases hepatic lipogenic program through enhancing the transcription activity of SREBP1c, leading to an increase in hepatic

fat deposition. Although processing unwanted effects, palmitoleate, in combination with other nutrients, may still offer benefits similar to those achieved by Mediterranean diets (Mashek & Wu 2015). Additional to fatty acids, vitamin D can also improve the hepatic insulin resistance likely by improving the inflammatory status of immune cells such as macrophages (Sung *et al.* 2012). Some evidence suggests that folic acid may also have this effect (Buettner *et al.* 2010); however, further investigations to fully understand the mechanisms of folic acid are warranted.

Intestine and insulin-sensitization

It is now well established that inflammation can significantly contribute to insulin resistance, both systemically and within specific tissues. This is also true within the small intestine. Overnutrition with saturated fat can be particularly causative (Rivellese *et al.* 2002) as saturated fat can stimulate multiple pro-inflammatory mechanisms. For instance, TLR4 expression, which is shown to be a key factor in the development of insulin resistance in many insulin-sensitive tissues, is increased in response to high saturated fat intake in small intestine. The interactions between HFD and bacterial populations with the intestinal tract are also associated with insulin resistance. For example, mice with conventional bacteria fed on HFD express significantly higher levels of TNF α , a well-known inhibitor of insulin signaling, compared to germ-free mice fed on the same diet (Ding *et al.* 2010). Furthermore, it has been shown that short-term HFD feeding leads to the translocation of commensal bacteria from the intestine to adipose tissue, which contributes to the development of inflammation and HFD-induced systemic hyperglycemia (Amar *et al.* 2011). Thus, the intestine can both directly and indirectly contribute to the development of systemic insulin resistance within the diet-induced obese model, as it not only exhibits impaired insulin signaling itself, but also serves as a mediator for the onset of insulin resistance in distal tissues.

Regarding interventions to alleviate insulin resistance through targeting the small intestine, it seems the best approach is to reduce/prevent the generation of inflammation. Ingestion of vitamin E for example helps reduce the formation of free radicals within the intestine and thus, attenuates lipid peroxidation and protein oxidation to thereby reduce inflammation (Shirpoor *et al.* 2007). Additional dietary treatments to reduce intestine inflammation are discussed above in section 'Suppression of Intestine Inflammation'. However, non-dietary

treatments have been suggested as well. For example, direct treatment with anti-inflammatory cytokines can greatly improve the intestinal environment and protect against systemic insulin resistance. Specifically, interleukin 22 (IL-22) not only decreases endotoxemia and inflammation, but also serves to preserve the gut mucosal barrier and improve the systemic insulin sensitivity (Wang *et al.* 2014). IL-22 expression and/or activity are reduced in the obese phenotype (Wang *et al.* 2014) therefore, treatment with this cytokine in patients with obesity-associated insulin resistance could drastically improve their impaired metabolic state. In addition, it is recently well documented that an HFD also induces phenotypic shifts within the intestinal microbiome that in turn, contribute to the development of obesity and systemic insulin resistance (Turnbaugh *et al.* 2006, Cani *et al.* 2008, Cani *et al.* 2009, Patrice & Nathalie 2009). Therefore, interventions to retain commensal bacterial populations can also regulate the generation of inflammation and onset of insulin resistance. In fact, many studies have demonstrated that prebiotics and/or probiotics can counteract the negative metabolic effects and associated metabolic disorders induced by HFD (Everard *et al.* 2011, Park *et al.* 2013, Toral *et al.* 2014, Wang *et al.* 2015a).

Feeding behavior and physical activity

The most effective way to prevent obesity-related metabolic diseases appears to be to prevent the development of obesity or to promote weight loss. Many pharmaceutical and herbal products exist for weight loss, promising 'fast results' or 'rapid weight loss'. Unfortunately no 'quick fix' for weight loss exists. Healthy weight loss however, although a slower process, is greatly beneficial for overall health and metabolism and more importantly, is more sustainable. The most effective interventions to achieve such weight loss, and prevent weight gain in the already overweight/obese, are caloric restriction and physical activity. This section will discuss each intervention and outline the specific metabolic benefits each has to offer.

Caloric restriction

Caloric restriction (CR) involves negative energy balance short of malnutrition or deficiency of essential nutrients. It is a dietary intervention that can improve health and extend the life span in many species, including rodents, primates and humans (Heilbronn & Ravussin 2003, Colman *et al.* 2014). In addition to inducing weight-loss,

CR is shown to improve glycemic control and insulin sensitivity in obese diabetic patients (Wing *et al.* 1994, Markovic *et al.* 1998). Similar results were also obtained in a randomized controlled trial involving obese infertile women (Becker *et al.* 2015). Even in non-obese healthy adults, 2-year CR results in 10% weight loss without negatively altering life quality (Martin *et al.* 2016). Similarly in healthy adults, Sparks *et al.* demonstrated that 12-month CR does not improve muscle mitochondrial functions, but appears to significantly decrease plasma levels of insulin and tends to decrease plasma levels of glucose, which likely indicate improvement of insulin sensitivity (Sparks *et al.* 2017). Of interest, CR *per se* is a significant factor in generating metabolic benefits during weight loss in obese and diabetic patients (Wing *et al.* 1994). A similar study has further suggested that the beneficial effects of CR on insulin action and glycemic control are related to changes in individual macronutrients. The latter is different from weight loss, whose beneficial effects are related to changes in abdominal fat (Markovic *et al.* 1998). According to accumulating evidence, it seems that CR is beneficial in this manner for both obese and normal-weight subjects, with and without diabetes. For example, one study found that obese, non-diabetic human adults on an acute CR diet for 5 days had improved skeletal muscle insulin sensitivity via enhanced insulin signaling molecules (Wang *et al.* 2012). In addition, studies demonstrate that CR can also protect cardiovascular/endothelial function in obesity. For example, short-term CR of 80% in obese rats ameliorates impaired endothelial function and reduces systolic blood pressure *ad libitum* (García-Prieto *et al.* 2015). The likely mechanism seems that reduced caloric and/or nutrient intake stimulates endothelial AMPK activity and subsequently leads to activation of the PI3K-Akt-eNOS pathway. CR also improves ventricular hypertrophy, fibrosis, and diastolic dysfunction, and decreases the expression of angiotensin converting enzyme and angiotensin II type 1A receptor genes in the heart of obese rats (Takatsu *et al.* 2013).

Given that inflammation is a major underlying factor of obesity and obesity-related diseases, much research has also investigated how CR may regulate the generation of inflammation. For instance, CR is viewed as a way to counter systemic inflammation caused by the adipose tissue expansion (Ye & Keller 2010). To date, many studies have investigated this using both human and animal models of HFD-induced obesity, given the association between overnutrition and inflammation and/or the onset of obesity. Widespread results show that CR reduces HFD-induced proinflammatory markers, such as

proinflammatory cytokines and NF κ B, and the production of oxidative stress (Park *et al.* 2012, Wasinski *et al.* 2013). These findings are also true in clinical studies on diabetic, morbidly obese patients. For example, acute CR (400 kCal less/day) for 7 days reduced inflammation, improved insulin sensitivity and improved renal function (Giordani *et al.* 2014). However, it should be noted that CR could cause adverse effects in some populations, such as the elderly or low BMI, diabetic patients receiving insulin (Darmon *et al.* 2010). Nonetheless, careful consideration and proper physician supervision should always be taken for any individual following such a diet plan (Buchowski *et al.* 2012, Bhardwaj *et al.* 2013, Takatsu *et al.* 2013, Tomada *et al.* 2013).

Physical activity and caloric restriction

Physical activity significantly increases energy expenditure and therefore is commonly used an intervention for weight loss and/or preventing weight gain. This intervention is especially beneficial for obese individuals (Jakicic & Otto 2005, Fock & Khoo 2013, Baillot *et al.* 2015, Chin *et al.* 2016), who commonly lead an overall sedentary lifestyle. In fact, physical activity is the most highly recommended intervention to prevent and slow weight gain, and lower BMI in obese children (Alkon *et al.* 2014, Bautista-Castaño *et al.* 2004, Lee *et al.* 2012). Furthermore, physical activity is not only beneficial for weight loss. A vast number of studies have demonstrated that physical activity is greatly beneficial in maintaining and promoting overall health via increased cardiovascular efficiency, insulin signaling in skeletal muscle, and in young individuals in preventing osteoporosis (Bassuk & Manson 2005, Borer 2005, Klein *et al.* 2004, Roberts *et al.* 2006).

Due to the beneficial abilities of CR and physical activity, independently, in preventing and/or combating obesity and obesity-associated disorders, numerous studies have investigated the effect of a combination intervention on such disorders. Unsurprisingly, results of such studies demonstrate positive results. For example, exercise and CR together can help lower the obesity index by reducing visceral fat, reduce levels of serum biomarkers such as LDL and triglycerides, and decrease inflammatory indicators (Ekuni *et al.* 2014, Vissers *et al.* 2013). Further, a combined intervention can reduce cardiovascular risks in obese individuals diagnosed with metabolic syndrome (Dutheil *et al.* 2013). Several studies report that a combination of exercise and CR exerts more beneficial effects than either physical activity or CR alone (Wang *et al.* 2015b). Such combination interventions are also useful approaches for

preventing the complications of NAFLD, commonly seen in the obese (Nseir *et al.* 2014).

Childhood obesity

Obesity remains a global epidemic. Alarming, the percentage of children with obesity in the United States has more than tripled since the 1970s, based on the Childhood Obesity Facts released by the CDC. The situation is even worse in developing countries including China, where the percentage of childhood obesity increases much greater and faster. Given the difficulty in reducing body weight once obesity is established, it is considered as an urgent need to initiate prevention and treatment of obesity in children (Dehghan *et al.* 2005). As demonstrated by numerous studies, total diet and physical activity level of a child critically determine a child's body weight. Therefore, nutrition approaches are crucial for prevention of childhood obesity. It is equally important to establish and enforce programs to increase physical activities in both pre-school and school-age children. The pertinent details have been described elsewhere, and are not discussed here.

Conclusion

The increase in the incidence of obesity makes obesity and its related metabolic diseases a huge problem in public health. Over the past several decades, mounting evidence obtained from both basic and clinical research has much advanced our understanding of the pathogenesis of metabolic diseases and led to the validation and application of nutritional approaches for managing metabolic diseases. As described above, nutritional approaches are commonly used for suppressing inflammation, improving insulin sensitivity, and/or decreasing fat deposition (Fig. 5). Although promising, the current approaches are also challenged by existing and new issues, e.g., poor long-term efficacy and reproducibility, and increased prevalence of childhood obesity. Another significant challenge is that human studies, in relation to animal studies, often have limitations in methodologies, which prevents performing insightful experiments to establish cause-and-effect relationships. To solve the issues, many efforts are needed to enhance the nutrition research. In particular, basic and clinical nutrition research is needed to extensively investigate how various diet compositions differentially alter metabolic homeostasis. There is also a

need to conduct long-term randomized and controlled trials to firmly establish the beneficial effects of nutritional approaches. Furthermore, how such factors may differ within the context of childhood and adolescent obesity is of paramount importance. Lastly, it might be a time now for a philosophic change: to use nutritional approaches, together with healthy lifestyle at all ages, for promoting health and preventing obesity and metabolic diseases, not for treating metabolic diseases.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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