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Review

The Western-style diet: a major risk factor for impaired kidney function and chronic kidney disease

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Odermatt A. The Western-style diet: a major risk factor for impaired kidney function and chronic kidney disease. *Am J Physiol Renal Physiol* 301: F919–F931, 2011. First published August 31, 2011; doi:10.1152/ajprenal.00068.2011.—The Western-style diet is characterized by its highly processed and refined foods and high contents of sugars, salt, and fat and protein from red meat. It has been recognized as the major contributor to metabolic disturbances and the development of obesity-related diseases including type 2 diabetes, hypertension, and cardiovascular disease. Also, the Western-style diet has been associated with an increased incidence of chronic kidney disease (CKD). A combination of dietary factors contributes to the impairment of renal vascularization, steatosis and inflammation, hypertension, and impaired renal hormonal regulation. This review addresses recent progress in the understanding of the association of the Western-style diet with the induction of dyslipidemia, oxidative stress, inflammation, and disturbances of corticosteroid regulation in the development of CKD. Future research needs to distinguish between acute and chronic effects of diets with high contents of sugars, salt, and fat and protein from red meat, and to uncover the contribution of each component. Improved therapeutic interventions should consider potentially altered drug metabolism and pharmacokinetics and be combined with lifestyle changes. A clinical assessment of the long-term risks of whole-body disturbances is strongly recommended to reduce metabolic complications and cardiovascular risk in kidney donors and patients with CKD.

metabolic syndrome; fructose; fat; salt; glucocorticoid

THE KIDNEY IS A HIGHLY VASCULARIZED organ and plays a major role in the maintenance of whole body homeostasis by regulating electrolyte concentrations and blood pressure, lipid metabolism, production and utilization of systemic glucose, degradation of hormones, and excretion of waste metabolites. Dietary compounds and reactive metabolites of endogenous and exogenous chemicals can modulate renal vascularization and metabolism, thereby affecting renal filtration and whole body homeostasis. The chronically elevated ingestion of a combination of high amounts of sugars, salt, and fat and protein from red meat affects multiple metabolic functions and has been associated with a higher incidence of metabolic syndrome, which increases the risk of developing new-onset chronic kidney disease (CKD) (29, 89). Here, recent evidence on the association of the Western-style dietary pattern with the development of kidney disease as well as dietary components and mechanisms involved in the development and progression of kidney disease will be reviewed.

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The Western-Style Diet and Comparison with Other Diets

The transition from a hunter-gatherer type of lifestyle to modern Western society with its tremendous technological advances in food processing led to significant changes in food intake and composition. The Western-style diet, also called the meat-sweet diet or standard American diet, is characterized by an overavailability of food, with high intakes of high-fat foods, high-sugar desserts and drinks, as well as high intakes of red meat, refined grains, and high-fat dairy products (Table 1). The foods are generally highly processed and refined. They are high in saturated fat, trans-fatty acids, sucrose and fructose, proteins from red meat and sodium, but low in monounsaturated (MUFAs) and polyunsaturated fatty acids (PUFAs), plant-derived proteins, and fiber content.

Several epidemiological studies revealed a positive correlation of a Western-style dietary pattern with a higher incidence of obesity, cardiovascular complications, colon cancer, osteoporosis, and CKD (66, 77, 156). A study in a cohort of over 70,000 women, followed for almost 20 years on the impact of dietary patterns derived by factor analysis on the risk of mortality from cardiovascular disease, cancer, and all causes, revealed an increased risk of the Western-style dietary pattern for all end points (66).

In contrast, a prudent dietary pattern (moderate-fat, high-carbohydrate, balanced nutrient reduction; see Table 1) is associated with lower LDL-cholesterol, plasma triglycerides,

Table 1. *Comparison of a Western-style dietary pattern with other diets*

Item/Content	Western	Mediterranean	Moderate Fat, Balanced Nutrient Reduction	(Very) Low Fat, Very High CHO	High Fat, Low CHO, High Protein (Atkins)
Processed red meat	High	Low	Low	Low	High
Poultry, fish	Low	High	Moderate	Moderate	Moderate/low
Cheese	High	High	Low	Low	High
Sugary desserts	High	Low	Low	Low	Low
Sugary drinks	High	Low	Low	Low	Low
Refined grains	High	Low	Moderate/low	Moderate/low	Low
Whole grains	Low	High	High	High	Low
Sodium chloride	High	High	Moderate	Moderate	High
Vegetables	Low	High	High	High	Moderate/low
Fresh fruit	Low	High	High	High	Low
Olive oil	Low	High	Low	Low	Low
High-fat dairy products	High	High	Low	Low	High
Low-fat dairy products	Low	Low	High	High	Low
Content					
% kcal Fat	30–40	30–35	20–30	<10–20	55–65
% kcal CHO	45–55	40–50	55–60	>65	<20
% kcal Protein	15–20	15–20	15–20	10–20	25–30
Average total kcal	2,200	2,200	1,400–1,500*	1,400–1,500*	1,400–1,500*
Saturated fat	High	Low	Low	Low	High
Trans-fat	High	Low	Low	Low	High
MUFA	Low	High	Moderate/low	Low	Low
PUFA	Low	Moderate/low	Moderate	Low	Low
Cholesterol	High	Moderate	Low	Low	High
Dietary fiber	Low	High	High	High	Low

CHO, carbohydrates; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids. Data were extracted from Refs. 1, 4, 18, 50, 56, 68, and 72. *Controlled food intake.

and HDL to total cholesterol (4, 155), with a reduced risk of cardiovascular disease, cancer, and total mortality (66). The beneficial effects of this type of diet, especially when combined with enhanced physical activity, are thought to be due to the controlled food consumption, a lower caloric intake, and a more favorable dietary composition. Based on the known association between the consumption of high amounts of saturated fats and cardiovascular diseases (82, 108, 148), low-fat and very low-fat diets were promoted. Fat-restricted diets are usually high in fiber and water content and provide a high degree of satiety. Such dietary patterns lead to a lower caloric intake and, combined with enhanced physical activity, result in loss of body fat and weight. Plasma triglycerides and LDL-cholesterol are usually reduced by these diets. However, the very low-fat diets often are low in vitamins E and B12 and zinc because of the low animal protein content, thus requiring supplementation (50). Because of the lower caloric intake of the moderate- and low-fat diets, it is difficult to assign observed beneficial effects to specific factors.

A contrary approach of a high-fat/low-carbohydrate/high-protein diet was promoted by Dr. Robert Atkins (Table 1). To achieve low-carbohydrate content, the intake of fruits, vegetables rich in starch, and beans and grain products are avoided, and the diet is characterized by its high content of meat, cheese, and fatty dairy products. The low-carbohydrate diet leads to a loss of weight during the initial period of the dietary regimen, probably by the lower caloric intake compared with the Western-style diet (50). However, some weight is regained afterward and the overall weight loss is comparable with that of other diets of controlled caloric intake. Moreover, the Atkins-type diet may be nutritionally inadequate because of limited intake of vitamins E, C, and B6, thiamine, folic acid, calcium, magnesium, and iron (36). The fact that the body has to produce energy almost exclusively from fat and protein leads to elevated blood uric acid concentrations and ketosis. There are serious concerns on potential risks of this type of diet for cardiac, bone, liver, and renal function because of the high amounts of saturated fat, trans-fatty acids, cholesterol, and proteins from red meat (134).

A better comparison of different dietary patterns is allowed at similar caloric intake, e.g., the Western-style diet and the Mediterranean diet. The Mediterranean diet (of southern Italian and Greek inhabitants) is characterized by high contents of plant foods, fresh fruits, fish, and poultry, dairy products, and olive oil as the main source of fat. Red meat, saturated fat, and trans-fatty acids are low. The high content of MUFAs such as oleic acid and the antioxidant and anti-inflammatory effects of olive oil may be responsible at least in part for the observed lower risk of coronary heart disease (35). The adherence to a Mediterranean diet was found to exert protective effects against type 2 diabetes in a study including more than 13,000 students from the University of Navarra (Spain) (102). During the 4-yr follow-up period, a high adherence to the diet showed an 80% relative reduced risk of developing diabetes. Furthermore, a meta-analysis of prospective cohort studies found an association of adherence to a Mediterranean diet with a lower risk of cancer, cardiovascular disease, and Parkinson's and Alzheimer's diseases (123, 130). The high intake of fibers, vegetables, and virgin oil for preparing foods, and the intake of polyphenols from a moderate consumption of red wine, were considered as the major protective dietary factors. A meta-analysis of 50 studies covering over a half-million individuals indicated an association of adherence to a Mediterranean diet with lower blood pressure, blood sugar, and triglycerides (80).

Although high sodium chloride intake is considered an important risk factor for developing hypertension, cardiovascular disease, and renal disease, and despite the high salt content of the Mediterranean diet (salted fish, capers, olives,

anchovies, cheese), adherence to this diet was found to improve renal artery circulation and lower the renal-resistive index, independent of changes in insulin sensitivity (143). These observations indicate that a combination of dietary factors is responsible for the adverse effects of the Western-style diet on renal function.

Association of the Western-Style Diet and Metabolic Disease with CKD

The National Health and Nutrition Examination Survey (NHANES) revealed an association of obesity with albuminuria and an increased incidence of CKD, independent of diabetes and hypertension (149). A recent report on the Nurses' Health Study, a prospective observational cohort study including over 3,000 women, revealed an increased risk of microalbuminuria at a higher dietary intake of animal fat and two or more servings per week of red meat (94). Moreover, in a subgroup analysis with available data on dietary pattern and urinary albumin-to-creatinine ratios, the investigators found that high scores for a Western-style dietary pattern correlated directly with microalbuminuria and a rapid decline of estimated glomerular filtration rate (93). They further showed that the strict adherence to the Dietary Approach to Stop Hypertension (DASH) diet (corresponding to a moderate-fat, balanced nutrient reduction pattern; Table 1) led to a lower risk of rapid estimated glomerular filtration rate decline, but there was no association with microalbuminuria. The diabetic status had no effect on these associations. These observations indicate that the Western-style diet causes an impairment of renal vascular function, inflammation and subsequent microalbuminuria, and a rapid decrease in kidney function, whereas the DASH-style diet exerts protective effects. The investigators included elderly white women only; therefore, it will be important to conduct similar investigations in cohorts of men of different ages and younger women as well as individuals other than Caucasians.

Increasing evidence indicates that metabolic syndrome is especially critical for kidney donors due to the limited functional capacity of the remaining kidney, emphasizing the need for lifestyle recommendations and renoprotective and cardioprotective programs for kidney donors (49, 119, 120). Obesity and nephron reduction can promote a decrease in glomerular filtration rate and an increase in proteinuria (119). Nondiabetic patients on hemodialysis presented with decreased body fat area and subcutaneous fat mass but increased visceral fat and altered serum lipid profiles, suggesting that reduced kidney function leads to fat redistribution and/or altered adipocyte differentiation (111). This underscores the importance of the kidney for lipid homeostasis.

The role of impaired kidney function in a situation of nutrient overload has been investigated in rats. Laboratory rats are kept in small cages, and, in contrast to their natural habitat, show very limited physical activity. Thus ad libitum feeding represents a situation of nutrient overload and lack of physical activity, resembling the disturbed nutrient availability/physical activity balance in humans in Western societies. Zhao et al. (157, 158) found a close relationship between renal function and blood lipids in uninephrectomized Sprague-Dawley rats on standard rodent chow ad libitum. The animals were studied for up to 10 mo, when they developed end-stage renal disease. Uninephrectomy resulted in lipodystrophy of subcutaneous and visceral adipose depots with lipid depletion, adipocyte dedifferentiation, and lipid peroxidation. These changes were followed by hypercholesterolemia with elevated total cholesterol, LDL, HDL, and triglyceride levels, and they occurred before the development of glomerulosclerosis and chronic renal failure (Fig. 1). Interestingly, renal but not hepatic 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase was increased, suggesting that the renal enzyme may be responsible for hypercholesterolemia in these animals. Uninephrectomized rats had significantly less fat in the perirenal capsule, omentum, mesenteries, and abdominal walls. The perirenal fat, consisting in healthy rats mainly of heat-protecting white adipose tissue (104), was mainly replaced by heat-producing brown adipose tissue. Furthermore, ectopic fat accumulation combined with chronic inflammatory infiltrates was observed in liver, pancreas, and adrenals of uninephrectomized rats. These findings demonstrate that reduced kidney function in rats fed ad libitum leads to severe disturbances in lipid homeostasis. Most of the observed changes, including the chronic renal failure, could be prevented by the angiotensin-converting enzyme (ACE) inhibitor lisinopril, indicating involvement of the renin-angiotensin-aldosterone system (RAAS) (136, 157). The association between experimental glomerulosclerosis and hyperlipidemia and the deposition of lipid in glomeruli emphasizes that an intact glomerular function is essential for maintaining lipid homeostasis (157, 158).

Interindividual behavioral differences, environmental interactions, and the complex mixture of dietary factors make the identification of specific risk factors of the Western-style diet and the elucidation of mechanisms of metabolic and renal diseases a challenging task. Four major risk factors, i.e., animal fat, animal protein, sugar, and sodium chloride, are discussed below in more detail, including recent insight into mechanisms contributing to impaired kidney function.

A High-Fat Diet as a Risk Factor for CKD

The Western-style diet is high in animal fat with high levels of saturated fats and trans-fatty acids. A cross-sectional study (Reasons for Geographic and Racial Differences in Stroke Study; REGARDS), including more than 19,000 adults >45 yr of age, found a significant association between saturated fat intake and hyperalbuminuria (95). Other subtypes of fat such as PUFAs and trans-fatty acids were associated neither with hyperalbuminuria nor with estimated glomerular filtration rate. Another study (Blue Mountains Eye Study), including 2,600

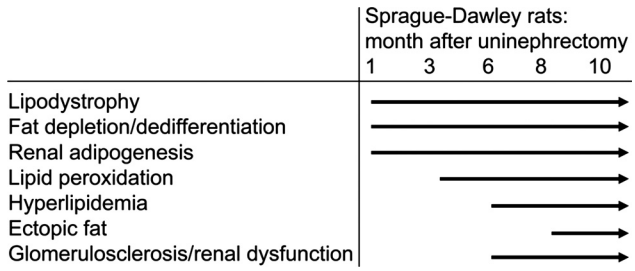

Fig. 1. Impaired lipid metabolism following uninephrectomy in rats (the figure is modified from Ref. 158). Sprague-Dawley rats were uninephrectomized at 3 mo of age and fed with standard rodent chow ad libitum. Rats were euthanized at 10 mo for biochemical and histopathological analyses.

participants >50 yr of age, analyzed the impact of the consumption of PUFAs and fish on the prevalence of CKD (62). A significantly lower incidence of CKD was observed for participants in the highest quartile of long-chain n-3 PUFA intake and of fish consumption compared with those in the lowest quartile of intake. In contrast, total n-3 PUFA and total n-6 PUFA were not significantly associated with CKD. An association of the intake of cholesterol and of total, saturated, monounsaturated, and trans-fat with an increased risk of renal cell carcinoma was found by another study (69). The intakes of PUFAs, n-3 and n-6 PUFAs, were not associated, but high fiber intake was inversely associated with the risk of renal cell carcinoma. These observations emphasize the importance of the composition of dietary fat regarding adverse effects on metabolic and renal functions.

A large number of studies in rodents address potential mechanisms responsible for the Western-style diet-induced development of kidney disease (Fig. 2). Most of them are based on animals on high-fat diet. Nevertheless, a clear assignment of the observed effects to specific dietary factors is often difficult due to the type of diet used in treated vs. control animals. The adverse effects of dietary saturated fats on kidney function, however, are supported by several recent studies. Streptozotocin-induced diabetic rats fed a lard diet containing high amounts of saturated fats for 11 days showed elevated levels of plasma ketone, total cholesterol, and triglycerides compared with rats fed a diet where the fat content of lard was replaced by PUFA-rich rapeseed oil (154). The lard-fed animals had higher albuminuria and renal triglyceride levels, with a positive correlation between these two factors. Furthermore, they had increased renal sterol-regulatory element binding protein (SREBP)-1 levels compared with rapeseed oil-treated rats. Thus saturated fats may promote the progression of diabetic nephropathy while PUFAs may exert protective effects. Adverse effects are also known for high dietary cholesterol. Marked glomerular hypertrophy was observed in uninephrectomized rats challenged with a high-cholesterol diet (117). Inhibition of HMG-CoA reductase by statins was found to preserve renal function in ⅝ nephrectomized rats, indicating a key role of the kidney in cholesterol homeostasis (58, 78).

The adverse effects of high dietary fat content were confirmed in a study on obese *fa/fa* Zucker rats (43). The high-fat group was treated for 10 wk with a diet consisting of 35% kcal from fat, 15% kcal from protein, and 50% kcal from carbohydrates, compared with 13, 30, and 60%, respectively, in standard chow of control animals. Saturated fat, MUFAs, and PUFAs were 6.6, 15, and 10% for the high-fat diet compared with 1.6, 1.6, and 2.5% for standard chow, respectively. High-fat diet-treated rats developed proteinuria, had reduced plasma HDL, and showed higher levels of total renal cortical reactive oxygen species (ROS), plasma lipids, insulin, C-reactive protein, and blood urea nitrogen. Markers of inflammation (TNF-α and NF-κB) and oxidative stress (NADPH oxidase) were significantly higher in the renal cortex of obese Zucker rats on a high-fat diet compared with controls. The membrane-permeable radical scavenger 2-hydroxy-2,2,6,6-tetramethyl piperidine-*N*-oxyl (tempol) attenuated these effects, indicating that prevention of oxidative stress is beneficial at an early phase of diabetic nephropathy (Fig. 2). Similarly, inflammatory markers and oxidative stress markers were significantly increased in the renal cortex of Sprague-Dawley rats treated for 6 wk with a high-fat diet (58% fat-derived calories and a total of 5.4 kcal/g, compared with normal chow with 12% fat-derived calories and a total of 3.3 kcal/g) (44). Infusion of angiotensin II by osmotic pumps and high-fat feeding for another 4 wk potentiated oxidative stress and renal inflammation, without further exacerbating vascular dysfunction.

The role of hyperlipidemia-induced inflammation in the development of glomerular injury was demonstrated in a study with Apo E(−/−) mice on a high-fat diet (normal chow supplemented with 15% cacao butter, 1.25% cholesterol, and 0.5% sodium cholate) for 4 wk (140). These mice showed significantly elevated levels of the proinflammatory cytokines TNF-α and IL-6. Treatment with anti-IL-6 receptor antibody significantly reduced renal inflammation, lipid accumulation, mesangial cell proliferation, and the progression of proteinuria.

Recently, Okamura et al. (112) reported reduced levels of activated NF-κB and oxidative stress in mice deficient of the class B scavenger receptor CD36 that had unilateral ureteral obstruction and that were placed on a high-fat diet (15.8% total

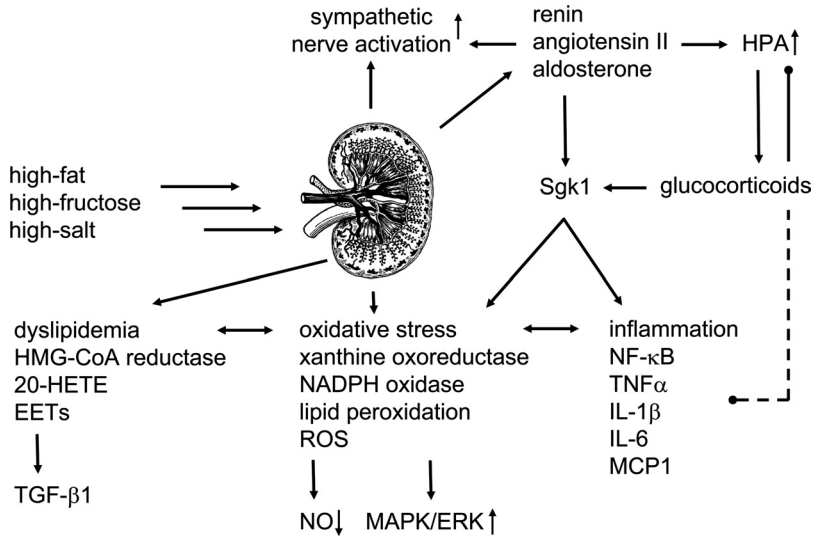

Fig. 2. Impact of the Western-style diet on relevant factors in the kidney. 20-HETE, 20-hydroxyeicosatetraenoic acid; COX-2, cyclooxygenase-2; EETs, epoxyeicosatrienoic acids; MCP1, macrophage attractant protein-1; NO, nitric oxide; ROS, reactive oxygen species; Sgk1, serum and glucocorticoid-dependent kinase-1; TGF-β1, transforming growth factor-β1.

fat, 1.25% cholesterol and 0.5% sodium cholate) for 7 wk. These mice showed significantly decreased accumulation of interstitial myofibroblasts, suggesting that CD36 exacerbates inflammation and oxidative stress and promotes fibrogenesis in CKD.

Another key modulator of renal lipid accumulation is SREBP1. Moreover, SREBP1 enhances the activity of proinflammatory cytokines and profibrotic growth factors. Whereas C57BL/6J mice on a high-fat diet [60% kcal saturated fat (lard) diet] became obese, hyperglycemic, and hyperinsulinemic and showed elevated levels of SREBP1 and SREBP2, A/J mice showed normal SREBP levels and were resistant to high-fat feeding (74). Importantly, deletion of SREBP1 in the C57BL/6J strain prevented renal triglyceride accumulation, renal inflammation, glomerulosclerosis, and proteinuria. Activation of the farnesoid X receptor (FXR) attenuated triglyceride accumulation, by modulating the synthesis and oxidation of fatty acids, and improved almost all features of impaired renal function (75, 151), suggesting that FXR activation may represent a therapeutic approach for treatment of patients with metabolic syndrome and CDK.

A study on Dahl salt-sensitive rats suggested a key role for transforming growth factor-β1 (TGF-β1) in the development of glomerular injury by increasing glomerular permeability for albumin through the inhibition of glomerular 20-hydroxyeicosatetraenoic acid (20-HETE) production (37). In line with these findings, Luo et al. (100) found increased TGF-β1 levels and decreased glomerular expression of CYP4A (required for 20-HETE production) and CYP2C and CYP2J [required for epoxyeicosatrienoic acid (EET) synthesis] in streptozotocin-treated rats (100). These effects were observed under a normal and high-fat diet. Induction of glomerular CYP4A and 20-HETE formation by clofibrate reduced TGF-β1 levels and ameliorated proteinuria. The hyperglycemia-mediated stimulation of TGF-β1 and the decreased glomerular 20-HETE and EET production are among the earliest changes in the development of proteinuria.

High-fat feeding dogs (supplementing standard food with an additional 0.5–0.9 kg of cooked beef fat/day) for 10 wk led to significantly increased kidney and total body weight, mean arterial blood pressure, and heart rate, accompanied by induction of TGF-β1 and other proinflammatory cytokines and profibrotic factors in the medullary interstitium, along with enhanced glomerular filtration rate and higher renal plasma flow (63). Moreover, plasma renin was significantly elevated in high fat-fed dogs, supporting the evidence for an activation of the RAAS by the Western-style diet. Increased systolic blood pressure and glucose intolerance were measured in spontaneously hypertensive rats on a high-fat diet (45% kcal from fat, 20% kcal from protein and 35% kcal from carbohydrate compared with 16, 26, and 58%, respectively, for normal chow) for 12 wk (31). The high-fat diet enhanced renal renin and angiotensin II production as well as angiotensinogen and ACE; however, there was no difference in circulating lipids, renin, and aldosterone according to diet. These observations reveal that important tissue-specific changes precede systemic alterations. Importantly, the angiotensin receptor blocker candesartan and the antioxidant tempol prevented high-fat-diet-induced renal steatosis and hypertension. In another study using spontaneously hypertensive rats on a high-fat diet, tempol and simvastatin were found to reduce oxidative stress, improve renal endothelial function, and decrease glomerular injury (86). While tempol also attenuated the increased production of the chemokine monocyte chemoattractant protein-1 (MCP-1), simvastatin had no effect.

Another important mechanism includes the stimulation of sympathetic nerve activity by increased visceral fat accumulation. A study of New Zealand rabbits fed a high-fat diet ad libitum for 4 wk (standard rabbit chow supplemented with 5% lard and 5% soy oil) had increased visceral fat, higher mean arterial pressure, heart rate, and plasma norepinephrine (116). Renal sympathetic nerve activity was 50% higher in high fat-fed rabbits and correlated with plasma leptin levels. Interestingly, intracerebroventricular leptin administration increased mean arterial blood pressure in high fat-fed and control rabbits, but the stimulation of renal sympathetic nerve activity was more pronounced in high fat-fed animals and they had less cFos-expressing neurons in regions important for appetite and sympathetic action of leptin, suggesting a marked selective leptin resistance in these animals.

The contribution of increased renal sympathetic activity to the development of obesity and hypertension has been demonstrated by bilateral renal denervation that greatly attenuated sodium retention and hypertension in obese dogs on a high-fat diet (regular food supplemented with 0.7 kg cooked beef fat/day) for 5 wk (79) Moreover, late-stage diet-induced obese mice showed significantly attenuated effects of an intraperitoneal or intracerebroventricular injection of leptin on food intake and body weight (105). Renal responses were preserved, but lumbar and brown adipose tissue sympathetic nerve activity responses were attenuated, indicating tissue-specific alterations in the sympathetic nerve activity responses in diet-induced obese mice.

Although a direct comparison of different animal studies is often difficult due to variations in the species used, the dietary composition, treatment, and duration, several factors and therapeutic interventions that modulate renal function have been identified (Table 2).

A Protein-Rich Diet and Impaired Kidney Function

The Western-style diet and low-carbohydrate, high-protein diets such as the Atkins diet are particularly high in fat and

Table 2. *Dietary factors and therapeutic interventions modulating renal function*

Dietary Fat Affecting Renal Function	Effect on Renal Function
Saturated fatty acids	−
Trans-fatty acids	−
PUFAs	+
Cholesterol	−
Therapeutic intervention:	
HMG-CoA inhibitor (statins)	+
Radical scavenger (tempol)	+
Anti-IL-6 receptor antibody	+
FXR agonists	+
Angiotensin receptor blockers	+
Angiotensin-converting enzyme inhibitors	+
PPAR-α agonists	+
MR antagonists	+

HMG, hydroxy-3-methylglutaryl; FXR, FX receptor; PPAR, peroxisome proliferator-activated receptor; MR, mineralocorticoid. +Beneficial effects; − adverse effects.

proteins from red meat. The excessive consumption of red meat has been associated with an increased risk of colon cancer (57, 153), coronary heart disease (81), and impaired kidney function (85). Replacement of animal protein by vegetable protein significantly reduced death from coronary heart disease in a study over 15 years including about 30,000 women (81). The Nurses' Health Study reported an association of animal protein intake with renal function decline in women already presenting with mild kidney function impairment but not in women with normal kidney function (85). Renal function decline was observed with animal protein-rich diets but not with plant protein-rich diets, emphasizing the importance of the source of protein (and fat) rather than the amount regarding adverse health consequences.

Serum creatinine levels and estimated glomerular filtration rate did not change in individuals with normal renal function after 1 yr of a low-carbohydrate diet with higher protein (35% kcal from protein compared with 24%) and fat intake (61% compared with 30%) (21). However, convincing evidence indicates that reduced protein intake favorably affects disease progression in patients with stage 3–4 CKD and delays the time to renal death (28). Reduced blood urea levels and proteinuria in CKD patients on low- and very low-protein diets delay kidney function decline; however, a close monitoring of these patients including supplementation of certain nutrients is required. Reduced kidney function is found in ~40% of diabetic patients (34). Thus high intakes of red meat represent a risk for further deterioration of kidney function in this patient population (2).

Moreover, consumption of high amounts of animal proteins leads to a marked acid load to the kidney and has been associated with the development of kidney stones (118). High meat protein intakes result in increased dietary acid loads and compensatory increases in renal acid excretion and ammonia production, leading to metabolic acidosis with a higher risk for tubulointerstitial injury (146). Restricted protein intake is therefore recommended for the prevention of recurrent kidney stones and the progression of kidney function decline (59).

Association of Sugar Consumption with Hyperuricemia, Oxidative Stress, and Impaired Kidney Function

Sugar consumption steadily has increased in the Western world during the last few decades. Especially, the excessive consumption of high-sugar soft drinks is considered to cause adverse metabolic effects (22). The use of sucrose, a disaccharide consisting of fructose and glucose, and high-fructose corn syrup, a mixture of 55% free fructose and 45% free glucose, have been associated with the occurrence of hypertension and hyperuricemia in adolescents (54, 73, 109). The acute ingestion of fructose but not glucose resulted in elevated blood pressure (22), and fructose ingestion was accompanied by increased intracellular and circulating uric acid (114). Furthermore, the prolonged ingestion of a high-fructose diet caused reduced insulin sensitivity, weight gain with visceral obesity, hypertriglyceridemia, and postprandial dyslipidemia (54, 125, 126, 132). Importantly, a recent study found decreased inflammatory parameters (high sensitivity C-reactive protein, soluble intercellular adhesion molecule), fasting serum insulin levels, and blood pressure in patients with stage 2 and 3 CKD upon switching from a regular to a low-fructose diet for 6 wk (24).

The Atherosclerosis Risk in Communities Study revealed an association of high consumption of sugar-sweetened soda with prevalent hyperuricemia and CKD but not with increased incidence (16). Although fructose has been recommended to diabetic patients because it does not enhance blood glucose levels (10, 25, 145), there is strong evidence that fructose, but not glucose, accelerates the development of metabolic syndrome and the progression of CKD (55). The intake of two or more high-sugar content beverages has been associated with an increased risk of impaired glomerular filtration and proteinuria (128). High fructose consumption was further associated with an increased risk for kidney stones (138) and gout (30).

Various cell-based and rodent studies provided important mechanistic insight into fructotoxicity. In rats, pair feeding a very high-fructose diet (60% fructose) for 6 wk induced renal hypertrophy with tubular cell proliferation and low-grade tubulointerstitial injury (107). The same diet resulted in reduced renal function with proteinuria, accelerated glomerulosclerosis, tubular atrophy, tubulointerstitial inflammation, interstitial collagen disposition, and peritubular monocyte-macrophage infiltration in the rat remnant kidney model (⅝ nephrectomy) (55). Rats were treated for 6 wk before ⅝ nephrectomy, and the dietary regimen was continued for another 11 wk. The expression of osteopontin, α-smooth muscle actin, ectodermal dysplasia 1 (ED-1), and interstitial collagen IV increased significantly in kidneys from fructose-treated animals but not in dextrose-treated rats, and impaired renal functions were not observed in rats fed a high-glucose diet. Other investigators reported that a high-fructose diet can induce most disturbances characteristic of metabolic syndrome such as insulin resistance, hypertriglyceridemia, visceral obesity, inflammation, oxidative stress, hyperuricemia, glomerular hypertension, reduced renal blood flow, and preglomerular-vascular disease (106). Importantly, these effects were not observed in rats pair fed with glucose or starch.

Hyperuricemia is considered to play a causal role in fructose-induced metabolic disease (32, 54, 73, 106, 109, 122). Fructose is metabolized by >50% in the liver. The remainder is taken up and metabolized mostly by adipocytes and renal proximal tubular cells of the S3-segment by the fructose transporter Glut-5 (135). Unlike glucose, fructose primarily undergoes phosphorylation by fructokinase, also known as ketohexokinase, to form fructose-1-phosphate, which is further converted by aldolase B to dihydroxyacetone and glyceraldehyde (Fig. 3). Thereby, fructokinase bypasses the tightly regulated glycolytic control by phosphofructokinase, which can result in ATP depletion and degradation of adenine nucleotides to uric acid via xanthine oxidoreductases. Experiments in cultured human renal proximal HK-2 cells demonstrated that fructokinase is responsible for fructose-dependent ATP depletion (32). Silencing of fructokinase prevented ATP depletion and abolished the observed induction of MCP-1 upon incubation of the cells with fructose-containing medium. The fructose-mediated induction of MCP-1 was prevented by coincubation of cells with *N*-acetylcysteine, the cell-permeable superoxide scavenger (MnTMPyP), the NADPH oxidase inhibitor apocynin, or the xanthine oxoreductase inhibitor allopurinol, suggesting that MCP-1 production is dependent on superoxide generation. Elevated uric acid levels and/or oxidants formed by xanthine oxoreductase activity are thought

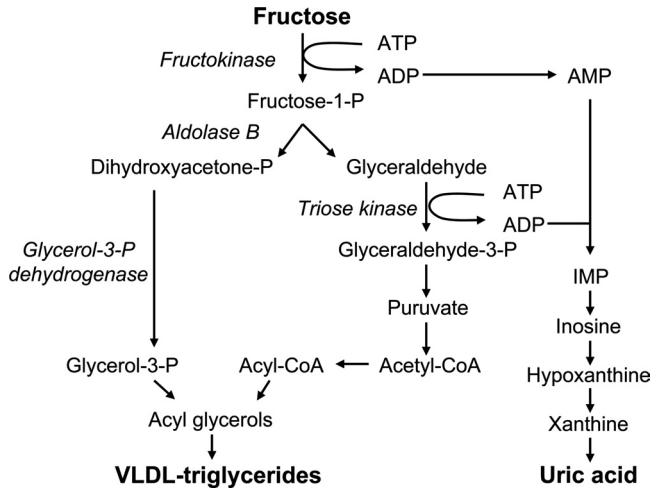

Fig. 3. Metabolism of fructose and the formation of triglycerides and uric acid.

to be responsible for ROS production and the redox-dependent proinflammatory effect (76, 101, 121).

Association of High Intakes of Sodium Chloride with CKD

High-salt intake is a well-accepted risk factor for the development of proteinuria and kidney disease (41, 147), and it accelerates disease progression in patients with CKD. A randomized double-blinded study in black hypertensive patients showed a 19% reduction of urinary protein excretion upon reducing salt intake from 10 to 5 g/day (137). Another study comparing blacks, whites, and Asians with mild hypertension revealed decreased proteinuria in all three ethnic groups upon a more modestly reduced salt intake from 9.7 to 6.5 g/day (65). The recent study by Lin et al. (94) indicates that reduced sodium chloride intake may lower the risk of estimated glomerular filtration rate decline. In addition, high salt intake has been associated with elevated urinary calcium excretion and the formation of kidney stones. A decrease in hypercalciuria and the reoccurrence of kidney stones have been observed after a reduction of salt consumption (17). A lower risk of kidney stones was also observed in a study on the DASH-style diet, containing low/moderate sodium chloride (139). Thus lower intakes of sodium chloride positively influence blood pressure and calcium homeostasis.

Potential Mechanisms of Adverse Metabolic Effects of a Combination of High-Fructose/High-Sodium Chloride Diets

An important link between a high-fructose/high-salt diet and hypertension has been demonstrated in a series of experiments with transgenic animals. Prolonged ingestion of fructose promotes salt and fructose absorption in the small intestine and in renal proximal tubules through coordinated activity of the fructose transporter Glut5, the chloride/bicarbonate exchanger Slc26A6, and the sodium/proton exchanger NHE-3 (131). When mice were fed a high-fructose diet for 5 days, wild-type animals showed a sixfold increase in blood fructose levels (11). In contrast, blood fructose levels were not altered in Glut5(−/−) mice; however, they developed hypotension as a result of volume depletion on the high-fructose diet. The fact that fructose did not stimulate intestinal salt absorption in Glut5(−/−) mice indicates that fructose exerts its stimulatory effects after Glut5-mediated uptake. The high-fructose/high-salt diet results in a salt overload from enhanced intestinal and renal absorption (129) .

Like Glut5, Slc26A6 and NHE-3 also localize to the apical membrane of renal proximal tubular cells (Fig. 4), and they play an important role in fructose-stimulated salt absorption (84, 115, 124, 150, 152). Increased renal salt excretion was observed in Slc26A6(−/−) mice fed a high-fructose diet, and these mice failed to develop hypertension on a high-fructose diet compared with wild-type mice. Importantly, a low-salt diet completely abrogated fructose-stimulated hypertension (27), underscoring the adverse effects of the combination of a high-fructose/high-salt diet.

The expression of sugar and salt transporters is modulated by glucocorticoids. In rats, Glut5 expression is induced by fructose but only after weaning begins at 14 days of age (40).

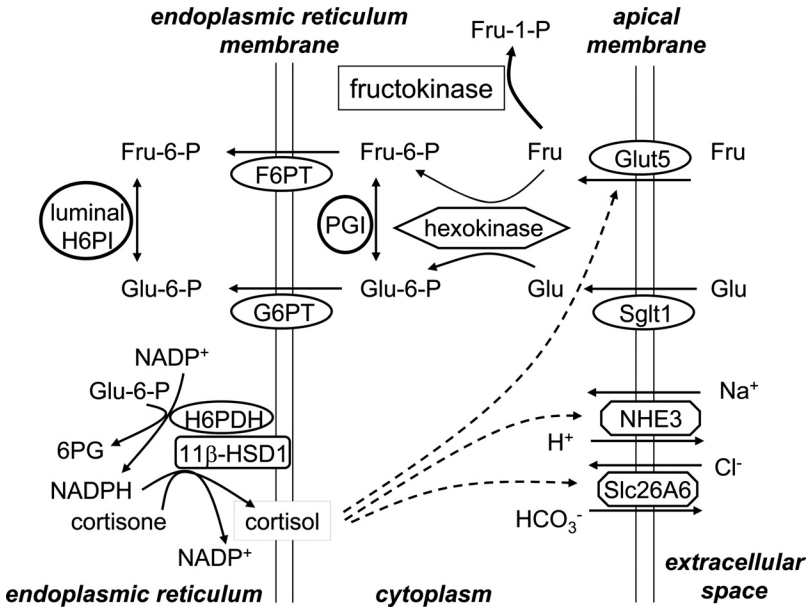

Fig. 4. Schematic model of a cell in the S3 segment of the renal proximal tubulus. 11β-HSD1, 11β-hydroxysteroid dehydrogenases 1; 6PG, 6-phosphogluconate; Fru, fructose, Fru-6-P, fructose-6-phosphate, F6PT, fructose-6-phosphate transporter of the endoplasmic reticulum membrane; Glu, glucose; Glu-6-P, glucose-6-phosphate, G6PT, glucose-6-phosphate transporter of the endoplasmic reticulum membrane; H6PDH, hexose-6-phosphate dehydrogenase; H6PI, luminal hexose-6-phosphate isomerase; PGI, phosphogluco-isomerase.

Glucocorticoids sensitize the neonatal intestine to fructose induction of intestinal Glut5 function. Glucocorticoids also modulate NHE-3 expression and activity. A rapid increase in the cell surface expression of NHE-3 as a result of enhanced exocytosis has been observed in cell-based experiments upon addition of glucocorticoids (15). Chronically elevated glucocorticoids are considered to stimulate NHE-3 mRNA and protein expression, thereby driving increased sodium transport activity. It has been shown that insulin regulates volume and acid-base homeostasis by increasing NHE-3 expression (53) and that glucocorticoids enhance the effect of insulin by induction of serum and glucocorticoid dependent kinase-1 (Sgk1) (83). Elevated angiotensin II production and Sgk1 activity at high glucose concentrations may further stimulate NHE-3 expression. Silencing of Sgk1 in renal proximal tubular cells reduced the angiotensin II-induced NHE-3 expression by 50% and abolished the increases in sodium uptake in angiotensin II-treated cells (133).

The glucocorticoid-dependent stimulation of insulin-induced NHE-3 expression seems to be abolished by intracellular lipid accumulation (13). Incubation of opossum kidney cells with a mixture of long-chain fatty acids led to accumulation of intracellular lipids with a concomitant concentration-dependent reduction in NHE-3 activity and ammonium excretion. NHE-3 has an important role in mediating ammonium excretion. This observation is in line with the observed impaired regulation of NHE-3 activity in renal steatosis and decreased ammonium excretion in Zucker diabetic fatty rats (14). Patients with metabolic syndrome have a higher risk of uric acid-mediated nephrolithiasis as a result of decreased urinary pH and impaired ammonium secretion (38, 39, 113). Further studies in vivo and in cultured cells are required to elucidate the impact of acute and chronic exposure to high concentrations of fat, sugars, and salt and the combinations of them on glucocorticoid sensitivity and on glucocorticoid-dependent regulation of sugar and salt transporters.

Potential Role of Impaired Corticosteroid Regulation in Western-Style Diet-Induced Adverse Effects on Kidney Function

The Western-style diet can lead to disturbances of glucocorticoid and mineralocorticoid action by distinct mechanisms. As mentioned above, the prolonged ingestion of a high-fat/high-fructose/high-salt diet results in an activation of the RAAS. The resulting elevation of aldosterone levels causes proinflammatory and profibrotic effects in the kidney and in other tissues such as the heart (12, 23, 52). Elevated aldosterone causes endothelial dysfunction and promotes oxidative stress and the expression of proinflammatory factors by a sodium- and mineralocorticoid receptor (MR)-dependent mechanism in the kidney (23). Clinical studies in rather low numbers of CKD patients revealed that MR blockade results in decreased proteinuria (reviewed in Ref. 20). Clearly, studies in large numbers of patients and consideration of dietary factors are needed to elucidate the adverse effects mediated by corticosteroids.

Liu et al. (97) provided evidence for an MR- and extracellular signal-regulated kinase kinase (MEK)-dependent stimulation of the proliferation of rat mesangial cells in high-glucose medium. Proapoptotic and mitogenic aldosterone-dependent effects that could be reduced by both MR antagonists and free radical scavengers were observed in cultured human mesangial cells (103). Furthermore, rats treated for a prolonged period of time with aldosterone showed enhanced mesangial cell proliferation and expansion of the mesangium (110). Thus elevated aldosterone levels, particularly in the presence of high salt and high glucose intake, may cause mesangial cell damage, independent of hemodynamic effects.

A recent mechanistic study with cultured and primary renal cortical collecting duct cells found that aldosterone resulted in a Sgk1-dependent activation of NF-κB with increased expression of proinflammatory NF-κB target genes including MCP1, plasminogen activator inhibitor, IL-1β, and IL-6 (92). Proinflammatory cytokines affect local corticosteroid signaling by modulating 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes. 11β-HSD2, converting active (cortisol, corticosterone) to inactive glucocorticoids (cortisone, 11-dehydrocorticosterone) and rendering specificity of MR for aldosterone in tissues such as renal cortical collecting ducts, distal colon, and excretory glands, is downregulated by the proinflammatory cytokines TNF-α, IL-1β, and IL-6 (33, 67, 87, 88, 144). It is well documented that reduced 11β-HSD2 activity results in glucocorticoid-dependent MR activation in renal cortical collecting ducts, causing salt retention and ultimately leading to hypertension (reviewed in Refs. 48 and 51).

In contrast, the glucocorticoid-activating enzyme 11β-HSD1 is enhanced by the proinflammatory cytokines TNF-α, IL-1β, and IL-6 (26, 33, 45, 46, 64, 71, 141). Chronically elevated 11β-HSD1 activity has been associated with various adverse metabolic effects (7, 142). 11β-HSD1 is highly expressed in the liver, adipose tissue, adrenals, and macrophages. It is also found at high levels in renal proximal tubular cells (19, 60, 61); however, its role in the kidney remains unclear. Chronically elevated 11β-HSD1 expression is likely to exert adverse effects on glucose and lipid metabolism in these cells. The S3 segment of the proximal tubule plays an important role in glucose and fructose reuptake from the urinary filtrate. It has been observed in diabetic animals that hyperglycemia leads to glucosuria due to limited reuptake of filtered glucose; however, a gradual increase in the maximal renal tubular transport rate can blunt the increased glucose excretion in chronic hyperglycemia (96).

Studies in Akita mice (impaired insulin production) with an additional deletion of Sgk1 provided evidence for a role of Sgk1 in the stimulation of renal tubular glucose transport in diabetic kidneys (3). Urinary excretion of glucose as well as fluid, sodium, and potassium was increased in Akita/sgk1(−/−) mice. As a compensatory response, circulating aldosterone concentrations were increased in these mice. In healthy kidneys, Sgk1 is expressed in glomeruli and aldosterone-sensitive distal tubules (98); however, expression was found in proximal tubules in diabetic nephropathy (90). Thus elevated levels of aldosterone upon RAAS activation and glucocorticoids due to enhanced 11β-HSD1 upon induction by proinflammatory cytokines are expected to activate Sgk1 in proximal tubular cells, thereby stimulating glucose uptake from the urinary filtrate and contributing to hyperglycemia.

It has been shown that a high-fat/high-salt diet stimulated renal Sgk1 expression in mice (70). Importantly, fluid intake, urinary flow rate, and urinary sodium chloride excretion was significantly increased in sgk1(−/−) mice, and blood pressure was elevated in wild-type but not sgk1(−/−) mice (70). These

experiments demonstrate an important role of Sgk1 in the hypertensive effects of a combined high-fat/high-salt diet, probably by the combined action in glomeruli, distal tubules, and proximal tubular cells.

The Western-style diet may affect glucocorticoid metabolism not only at the transcriptional level. A high-sugar-containing diet may enhance local glucocorticoid activation by increasing the availability of the reduced cofactor NADPH in the endoplasmic reticulum (ER). The 11β-HSD1-dependent cortisol generation requires the cosubstrate NADPH, which is generated in the ER by H6PDH (Fig. 4) (6, 8). H6PDH activity depends on the availability of glucose-6-phosphate in the ER, thereby representing a coupling between nutrient status and hormonal regulation (5, 9, 91). Cell-based experiments have shown that increasing glucose concentrations stimulate 11β-HSD1 oxoreductase activity and that a NADPH/$NADP^+$ ratio of 10 or greater is required for efficient activity (42). Furthermore, glucose stimulates the expression of both 11β-HSD1 and H6PDH, at least in hepatocytes (47).

Recently, we found that replacing glucose by fructose in the culture medium was sufficient to drive 11β-HSD1 oxoreductase activity in transfected HEK-293 cells (unpublished observations). In fact, fructose was even somewhat more efficient than glucose to stimulate 11β-HSD1 activity. In experiments with isolated microsomes fructose-6-phosphate was sufficient to stimulate 11β-HSD1 oxoreductase activity (127). The results suggested that fructose-6-phosphate was transported into the ER independently of the known glucose-6-phosphate translocase of the ER membrane (G6PT), followed by the isomerization to glucose-6-phosphate by a yet unidentified enzyme (Fig. 4). Both fructose-6-phosphate transport and fructose-6-phosphate isomerase activity were found in microsomes derived from liver, adipose tissue, kidney, and HEK-293 cells. These observations suggest that a high-sugar diet stimulates local glucocorticoid activation by the 11β-HSD1/H6PDH complex.

Moreover, a recent study with rats fed ad libitum with 16% solutions of sucrose, fructose, or glucose and chow and water reported two- and threefold higher 11β-HSD1 mRNA levels within 24 h in liver and adipose tissue. Hepatic 11β-HSD1 mRNA levels were suppressed by 60% or more after 1 wk for all sugar diets, revealing time- and sugar type-dependent differences in the regulation of local glucocorticoid metabolism (99).

The contribution of fructose to glucocorticoid activation is especially relevant in nonhepatic tissues expressing Glut5, which mediates insulin-independent fructose transport. The prominent expression of 11β-HSD1 and H6PDH in the epithelial cells of the proximal tubules in the juxtamedullary cortex coincides with the expression of Glut5 (19, 60, 61, 135). It was shown that a high-fructose diet in Sprague-Dawley rats induces fructokinase and Glut5 expression (107). The impact of fructose on renal glucocorticoid metabolism remains to be explored. Interestingly, 11β-HSD1 is also highly expressed in renal medullary interstitial cells, where it colocalizes with the prostaglandin E_2-synthesizing enzyme cyclooxygenase-2 (COX-2) (19, 60, 61). Because glucocorticoids downregulate the expression of COX-2, 11β-HSD1 likely plays a role in the modulation of renal inflammation (61).

Conclusions

A chronic nutrient overload causes various tissue-specific and systemic metabolic dysfunctions that increase the risk of kidney damage and promote CKD. Especially, the combination of high amounts of saturated fat, fructose, and salt promotes dyslipidemia, hormonal disturbances, oxidative stress, inflammation, and fibrosis with impaired glomerular function and hypertension. Future research has to elucidate the contribution by different kidney cell types as well as the cross talk between kidney cells, adipocytes, and immune cells. For mechanistic studies, suitable human cell lines are still lacking and single-cell as well as multicellular systems need to be established. The risk of the Western-style diet for kidney donors has to be further investigated. Carefully designed animal experiments and clinical studies have to address the acute and chronic effects caused by the Western-style diet and elucidate the respective contribution of caloric intake, content of fat, fructose and salt, as well as age, sex, physical activity, and other factors such as smoking and psychological stress. Therapeutic interventions have to consider altered drug metabolism and hormonal regulation. Successful therapy should aim at the simultaneous modulation of several targets to lower oxidative stress and inflammation, reduce cholesterol and fatty acid synthesis, inhibit the RAAS, and improve hormonal sensitivity. The most successful interventions, however, will include lifestyle changes consisting of a combination of enhanced physical activity and improved dietary regimens.

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I apologize that I could not reference all contributions in this field due to space limitations.

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