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Literature Review

An Overview of the Identification and Management of the Metabolic Syndrome in Chiropractic Practice

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Abstract

Objective: This article presents an overview of metabolic syndrome (MetS), which is a collection of risk factors that can lead to diabetes, stroke, and heart disease. The purposes of this article are to describe the current literature on the etiology and pathophysiology of insulin resistance as it relates to MetS and to suggest strategies for dietary and supplemental management in chiropractic practice.

Methods: The literature was searched in PubMed, Google Scholar, and the Web site of the American Heart Association, from the earliest date possible to May 2014. Review articles were identified that outlined pathophysiology of MetS and type 2 diabetes mellitus (T2DM) and relationships among diet, supplements, and glycemic regulation, MetS, T2DM, and musculoskeletal pain.

Results: Metabolic syndrome has been linked to increased risk of developing T2DM and cardiovascular disease and increased risk of stroke and myocardial infarction. Insulin resistance is linked to musculoskeletal complaints both through chronic inflammation and the effects of advanced glycosylation end products. Although diabetes and cardiovascular disease are the most well-known diseases that can result from MetS, an emerging body of evidence demonstrates that common musculoskeletal pain syndromes can be caused by MetS.

Conclusions: This article provides an overview of lifestyle management of MetS that can be undertaken by doctors of chiropractic by means of dietary modification and nutritional support to promote blood sugar regulation.

Introduction

Metabolic syndrome (MetS) has been described as a cluster of physical examination and laboratory findings

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that directly increases the risk of degenerative metabolic disease expression. Excess visceral adipose tissue, insulin resistance, dyslipidemia, and hypertension are conditions that significantly contribute to the syndrome. These conditions are united by a pathophysiological basis in low-grade chronic inflammation and increase an individual's risk of cardiovascular disease, type 2 diabetes mellitus (T2DM), and all-cause mortality.[1]

The National Health and Nutrition Examination Survey (NHANES) 2003-2006 estimated that approximately 34% of United States adults aged 20 years and more had MetS.[2] The same NHANES data found that 53% had abdominal adiposity, a condition that is closely linked to visceral adipose stores. Excess visceral adiposity generates increased systemic levels of proinflammatory mediator molecules. Chronic, low-grade inflammation has been well documented as an associated and potentially inciting factor for the development of insulin resistance and T2DM.[1]

NHANES 2003-2006 data showed that 39% of subjects met criteria for insulin resistance. Insulin resistance is a component of MetS that significantly contributes to the expression of chronic, low-grade inflammation and predicts T2DM expression. T2DM costs the United States in excess of $174 billion in 2007.[3] It is estimated that 1 in 4 adults will have T2DM by the year 2050.[3] Currently, more than one third of US adults (34.9%) are obese,[4] and, in 2008, the annual medical cost of obesity was $147 billion.[4,5] This clearly represents a health care concern.

The pervasiveness of MetS dictates that doctors of chiropractic will see a growing proportion of patients who fit the syndrome criteria.[6] Chiropractic is most commonly used for musculoskeletal complaints believed to be mechanical in nature;[6] however, an emerging body of evidence identifies MetS as a biochemical promoter of musculoskeletal complaints such as neck pain, shoulder pain, patella tendinopathy, and widespread musculoskeletal pain.[7–13] As an example, the cross-linking of collagen fibers can be caused by increased advanced glycation end-product (AGE) formation as seen in insulin resistance.[14] Increased collagen cross-linking is observed in both osteoarthritis and degenerative disc disease,[15] and reduced mobility in elderly patients with T2DM has also been attributed to AGE-induced collagen cross-linking.[16,17]

A diagnosis of MetS is made from a patient having 3 of the 5 findings presented in Table 1. Fasting hyperglycemia is termed impaired fasting glucose and indicates insulin resistance.[18,19] An elevated hemoglobin A1c (HbA1c) level measures long-term blood glucose regulation and is diagnostic for T2DM when elevated in the presence of impaired fasting glucose.[3,18]

Table 1 Diagnostic Predictors for MetS[20]

Predictor	Abnormal value
Impaired fasting glucose	>100 mg/dL
Triglycerides	>150 mg/dL
HDL cholesterol	<50 for women; <40 for men
Blood pressure	>130/85
Waist circumference	≥36" for women; ≥40" for men

HDL, high-density lipoprotein.

The emerging evidence demonstrates that we cannot view musculoskeletal pain as only coming from conditions that are purely mechanical in nature. Doctors of chiropractic must demonstrate prowess in identification and management of MetS and an understanding of insulin resistance as its main pathophysiological feature. The purposes of this article are to describe the current literature on the etiology and pathophysiology of insulin resistance as it relates to MetS and to suggest strategies for dietary and supplemental management in chiropractic practice.

Methods

PubMed was searched from the earliest possible date to May 2014 to identify review articles that outlined the pathophysiology of MetS and T2DM. This led to further search refinements to identify inflammatory mechanisms that occur in the pancreas, adipose tissue, skeletal muscle, and hypothalamus. Searches were also refined to identify relationships among diet, supplements, and glycemic regulation. Both animal and human studies were reviewed. The selection of specific supplements was based on those that were most commonly used in the clinical setting, namely, gymnema sylvestre, vanadium, chromium and α-lipoic acid.

Discussion

Insulin Resistance Overview

Under normal conditions, skeletal muscle, hepatic, and adipose tissues require the action of insulin for cellular glucose entry. Insulin resistance represents an inability of insulin to signal glucose passage into insulin-dependent cells. Although a genetic predisposition can exist, the

etiology of insulin resistance has been linked to chronic low-grade inflammation.[1] Combined with insulin resistance-induced hyperglycemia, chronic low-grade inflammation also sustains MetS pathophysiology.[1]

Two thirds of postprandial blood glucose metabolism occurs within skeletal muscle via an insulin-dependent mechanism.[18,19] Insulin binding to its receptor triggers glucose entry and subsequently inhibits lipolysis within the target tissue.[21,22] Glucose enters skeletal muscles cells by way of a glucose transporter designated Glut4.[18] Owing to genetic variability, insulin-mediated glucose uptake can vary more than 6-fold among nondiabetic individuals.[23]

Prolonged insulin resistance leads to structural changes within skeletal muscle such as decreased Glut4 transporter number, intramyocellular fat accumulation, and a reduction in mitochondrial content.[19,24] These events are thought to impact energy generation and functioning of affected skeletal muscle.[24] Insulin-resistant skeletal muscle is less able to suppress lipolysis in response to insulin binding.[25] Subsequently, saturated free fatty acids accumulate and generate oxidative stress.[22] The same phenomenon within adipose tissue generates a rapid adipose cell expansion and tissue hypoxia.[26] Both these processes increase inflammatory pathway activation and the generation of proinflammatory cytokines (PICs).[27]

Multiple inflammatory mediators are associated with the promotion of skeletal muscle insulin resistance. The PICs tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), and IL-6 have received much attention because of their direct inhibition of insulin signaling.[28–30] Since cytokine testing is not performed clinically, elevated levels of high-sensitivity C-reactive protein (hsCRP) best represent the low-grade systemic inflammation that characterizes insulin resistance.[31,32]

Insulin resistance–induced hyperglycemia can lead to irreversible changes in protein structure, termed glycation, and the formation of AGEs. Cells such as those of the vascular endothelium are most vulnerable to hyperglycemia due to utilization of an insulin-independent Glut1 transporter.[33] This makes AGE generation responsible for most diabetic complications,[15,33,34] including collagen cross-linking.[15]

If unchanged, prolonged insulin resistance can lead to T2DM expression. The relationship between chronic low-grade inflammation and T2DM has been well characterized.[35] Research has demonstrated that patients with T2DM also have chronic inflammation within the pancreas, termed insulitis, and it worsens hyperglycemia due to the progressive loss of insulin-producing β cells.[36–39]

Visceral Adiposity and Insulin Resistance

Caloric excess and a sedentary lifestyle contribute to the accumulation of subcutaneous and visceral adipose tissue. Adipose tissue was once thought of as a metabolically inert passive energy depot. A large body of evidence now demonstrates that excess visceral adipose tissue acts as a driver of chronic low-grade inflammation and insulin resistance.[27,34]

It has been documented that immune cells infiltrate rapidly expanding visceral adipose tissue.[26,40] Infiltrated macrophages become activated and release PICs that ultimately cause a phenotypic shift in resident macrophage phenotype to a classic inflammatory M1 profile.[27] This vicious cycle creates a chronic inflammatory response within adipose tissue and decreases the production of adipose-derived anti-inflammatory cytokines.[43] As an example, adiponectin is an adipose-derived anti-inflammatory cytokine. Macrophage-invaded adipose tissue produces less adiponectin, and this has been correlated with increasing insulin resistance.[26]

Hypothalamic Inflammation and Insulin Resistance

Eating behavior in the obese and overweight has been popularly attributed to a lack of will power or genetics. However, recent research has demonstrated a link between hypothalamic inflammation and increased body weight.[41,41]

Centers that govern energy balance and glucose homeostasis are located within the hypothalamus. Recent studies demonstrate that inflammation in the hypothalamus coincides with metabolic inflammation and an increase in appetite.[43] These hypothalamic centers simultaneously become resistant to anorexigenic stimuli, leading to altered energy intake. It has been suggested that this provides a neuropathological basis for MetS and drives a progressive increase in body weight.[41]

Central metabolic inflammation pathologically activates hypothalamic immune cells and disrupts central insulin and leptin signaling.[41] Peripherally, this has been associated with dysregulated glucose homeostasis that also impairs pancreatic β cell functioning.[41,44] Hypothalamic inflammation contributes to hypertension through similar mechanisms, and it is thought that central inflammation parallels chronic low-grade systemic inflammation and insulin resistance.[41–44]

Clinical Correlates of Diet-Induced Inflammation and Insulin Resistance

Feeding generally leads to a short-term increase in both oxidative stress and inflammation.[41] Total

calories consumed, glycemic index, and fatty acid profile of a meal all influence the degree of postprandial inflammation. It is estimated that the average American consumes approximately 20% of calories from refined sugar, 20% from refined grains and flour, 15% to 20% from excessively fatty meat products, and 20% from refined seed/legume oils.[45] This pattern of eating contains a macronutrient composition and glycemic index that promote hyperglycemia, hyperlipemia, and an acute postprandial inflammatory response.[46] Collectively referred to as postprandial dysmetabolism, this proinflammatory response can sustain levels of chronic low-grade inflammation that leads to excess body fat, coronary heart disease (CHD), insulin resistance, and T2DM.[28,29,47]

Recent evidence suggests that several MetS criteria may not sufficiently identify all individuals with postprandial dysmetabolism.[48,49] A 2-hour oral glucose tolerance test (2-h OGTT) result greater than 200 mg/dL can be used clinically to diagnose T2DM. Although MetS includes a fasting blood glucose level less than 100 mg/dL, population studies have shown that a fasting glucose as low as 90 mg/dL can be associated with an 2-h OGTT level greater than 200 mg/dL.[49] Further, a recent large cohort study indicated that an increased 2-h OGTT was independently predictive of cardiovascular and all-cause mortality in a nondiabetic population.[48] Mounting evidence indicates that postprandial glucose levels are better correlated with MetS and predicting future cardiovascular events than fasting blood glucose alone.[41,48]

Fasting triglyceride levels generally correlate with postprandial levels, and a fasting triglyceride level greater than 150 mg/dL reflects MetS and insulin resistance. Contrastingly, epidemiologic data indicate that a fasting triglyceride level greater than 100 mg/dL influences CHD risk via postprandial dysmetabolism.[48] The acute postprandial inflammatory response that contributes to CHD risk includes an increase in PICs, free radicals, and hsCRP.[48,49] These levels are not measured clinically but, monitoring fasting glucose, 2-hour postprandial glucose and fasting triglycerides can be used as correlates of postprandial dysmetabolic and low-grade systemic inflammation.

MetS and Disease Expression

Diagnosis of MetS has been linked to an increased risk of developing T2DM and cardiovascular disease over the following 5 to 10 years.[1] It further increases a patient's risk of stroke, myocardial infarction, and death from any of the aforementioned conditions.[1] Facchini et al[47] followed 208 apparently healthy, nonobese subjects for 4 to 11 years while monitoring the incidence of clinical events such as hypertension, stroke, CHD, cancer, and T2DM. Approximately one fifth of participants experienced clinical events, and all of these subjects were either classified as intermediately or severely insulin resistant. It is important to note that all of these clinical events have a pathological basis in chronic low-grade inflammation,[50] and no events were experienced in the insulin-sensitive groupings.[47]

Insulin resistance is linked to musculoskeletal complaints both through chronic inflammation and the effects of AGEs. Advanced glycation end-products have been shown to extensively accumulate in osteoarthritic cartilage and treatment of human chondrocytes with AGEs increased their catabolic activity.[51] Advanced glycation end-products increase collagen stiffness via cross-linking and likely contribute to reduced joint mobility seen in elderly patients with T2DM.[52] Compared to nondiabetics, type II diabetic patients are known to have altered proteoglycan metabolism in their intervertebral discs. This altered metabolism may promote weakening of the annular fibers and subsequently, disc herniation.[53] The presence of T2DM increases a person's risk of expressing disc herniation in both the cervical and lumbar spines.[17,54] Patients with T2DM are also more likely to develop lumbar stenosis compared with nondiabetics, and this has been documented as a plausible relationship between MetS risk factors and physician-diagnosed lumbar disc herniation.[55–57]

There are no specific symptoms that denote early skeletal muscle structural changes. Fatty infiltration and decreased muscle mitochondria content are observed within age-related sarcopenia[58]; however, it is still being argued whether fatty infiltration is a risk factor for low back pain.[59,60]

Clinical management of MetS should be geared toward improving insulin sensitivity and reducing chronic low-grade inflammation.[1] Regular exercise without weight loss is associated with reduced insulin resistance, and at least 30 minutes of aerobic activity and resistance training is recommended daily.[61,62] Although frequently considered preventative, exercise, dietary, and weight loss interventions should be considered alongside pharmacological management in those with MetS.[1]

Data regarding the exact amount of weight loss needed to improve chronic inflammation are inconclusive. In overweight individuals without diagnosed MetS, a very-low-carbohydrate diet (<10% calories from carbohydrate) has significantly reduced plasma inflammatory markers (TNF-α, hsCRP, and IL-6) with

as little as 6% reduction in body weight.[63,64] Individuals who meet MetS criteria may require 10% to 20% body weight loss to reduce inflammatory markers.[65] Interestingly, the Mediterranean Diet has been shown to reduce markers of systemic inflammation independent of weight loss[65] and was recommended in the American College of Cardiology and American Heart Association Adult Treatment Panel 4 guidelines.[66]

A growing body of research has examined the effects of the Spanish ketogenic Mediterranean diet, including olive oil, green vegetables and salads, fish as the primary protein, and moderate red wine consumption. In a sample of 22 patients, adoption of the Spanish ketogenic Mediterranean diet with 9 g of supplemental salmon oil on days when fish was not consumed has led to complete resolution of MetS.[67] Significant reductions in markers of chronic systemic inflammation were seen in 31 patients following this diet for 12 weeks.[68]

A Paleolithic diet based on lean meat, fish, fruits, vegetables, root vegetables, eggs, and nuts has been described as more satiating per calorie than a diabetes diet in patients with T2DM.[69] In a randomized crossover study, a Paleolithic diet resulted in lower mean HbA1c values, triglycerides, diastolic blood pressure, waist circumference, improved glucose tolerance, and higher high-density lipoprotein (HDL) values compared to a diabetes diet.[70] Within the context of these changes, a referral for medication management may be advisable.

Irrespective of name, a low-glycemic diet that focuses on vegetables, fruits, lean meats, omega-3 fish, nuts, and tubers can be considered anti-inflammatory and has been shown to ameliorate insulin resistance.[49,71–73] Inflammatory markers and insulin resistance further improve when weight loss coincides with adherence to an anti-inflammatory diet.[70] A growing body of evidence suggests that specific supplemental nutrients also reduce insulin resistance and improve chronic low-grade inflammation.

Key Nutrients That Promote Insulin Sensitivity

Research has identified nutrients that play key roles in promoting proper insulin sensitivity, including vitamin D, magnesium, omega-3 (n-3) fatty acids, curcumin, gymnema, vanadium, chromium, and α-lipoic acid. It is possible to get adequate vitamin D from sun exposure and adequate amounts of magnesium and omega-3 fatty acids from food. Contrastingly, the therapeutic levels of chromium and α-lipoic acid that affect insulin sensitivity and reduce insulin resistance cannot be obtained in food and must be supplemented.

Vitamin D, Magnesium, Omega-3 Fatty Acids, and Curcumin

Vitamin D, magnesium, and n-3 fatty acids have multiple functions, and generalized inflammation reduction is a common mechanism of action.[74–80] Their supplemental use should be considered in the context of low-grade inflammation reduction and health promotion, rather than as a specific treatment for MetS or T2DM.

Evidence pertaining to the precise role of vitamin D in MetS and insulin resistance is inconclusive. Increasing dietary and supplemental vitamin D intake in young men and women may lower the risk of MetS and T2DM development,[81] and a low serum vitamin D level has been associated with insulin resistance and T2DM expression.[82] Supplementation to improve low serum vitamin D (reference range, 32-100 ng/mL) is effective, but its impact on improving central glycemia and insulin sensitivity is conflicting.[83] Treating insulin resistance and MetS with vitamin D as a monotherapy appears to be unsuccessful.[82,83] Achieving normal vitamin D blood levels through adequate sun exposure and/or supplementation is advised for general health.[84–86]

The average American diet commonly contains a low magnesium intake.[80] Recent studies suggest that supplemental magnesium can improve insulin sensitivity.[81,82] Taking 365 mg/d may be effective in reducing fasting glucose and raising HDL cholesterol in T2DM,[83] as well as normomagnesemic, overweight, nondiabetics.[84]

Diets high in the omega-6 fat linoleic acid have been associated with insulin resistance[85] and higher levels of serum proinflammatory mediator markers including IL-6, IL-1β, TNF-α, and hsCRP.[87] Supplementation to increase dietary omega-3 fatty acids at the expense of omega-6 fatty acids has been shown to improve insulin sensitivity.[88–90] Six months of omega-3 supplementation at 3 g/d with meals has been shown to reduce MetS markers including fasting triglycerides, HDL cholesterol, and an increase in anti-inflammatory adiponectin.[91]

Curcumin is responsible for the yellow pigmentation of the spice turmeric. Its biological effects can be characterized as antidiabetic and antiobesity via down-regulating TNF-α, suppressing nuclear factor κB activation, adipocytokine expression, and leptin level modulation,.[92–95] Curcumin has been reported to activate peroxisome proliferator-activated receptor-γ, the nuclear target of the thiazolidinedione class of antidiabetic drugs,[93] and it also protects hepatic and pancreatic cells.[92,93] Numerous studies have reported

weight loss, hsCRP reduction, and improved insulin sensitivity after curcumin supplementation.[92–95]

There is no established upper limit for curcumin, and doses of up to 12 g/d are safe and tolerable in humans.[96] A randomized, double-blinded, placebo-controlled trial (N = 240) showed a reduced progression of prediabetes to T2DM after 9 months of 1500 mg/d curcumin supplementation.[97]

Curcumin,[98] vitamin D,[84] magnesium,[91] and omega-3 fatty acids[80] are advocated as daily supplements to promote general health. A growing body of evidence supports the views of *Gymnema sylvestre*, vanadium, chromium, and α-lipoic acid should as therapeutic supplements to assist in glucose homeostasis.

G sylvestre

Gymnemic acids are the active component of the *G sylvestre* plant leaves. Gymnemic acids are the active component of the *G sylvestre* plant leaves. Studies evaluating *G sylvestre*'s effects on diabetes in humans have generally been of poor methodological quality. Experimental animal studies have found that gymnemic acids may decrease glucose uptake in the small intestine, inhibit gluconeogenesis, and reduce hepatic and skeletal muscle insulin resistance.[99] Other animal studies suggest that gymnemic acids may have comparable efficacy in reducing blood sugar levels to the first-generation sulfonylurea, tolbutamide.[100]

Evidence from open-label trials suggests its use as a supplement to oral antidiabetic hypoglycemic agents.[96] One quarter of patients were able to discontinue their drug and maintain normal glucose levels on an ethanolic gymnema extract alone. Although the evidence to date suggests its use in humans and animals is safe and well tolerated, higher quality human studies are warranted.

Vanadyl Sulfate

Vanadyl sulfate has been reported to prolong the events of insulin signaling and may actually improve insulin sensitivity.[101] Limited data suggest that it inhibits gluconeogenesis, possibly ameliorating hepatic insulin resistance.[100,101] Uncontrolled clinical trials have reported improvements in insulin sensitivity using 50 to 300 mg daily for periods ranging from 3 to 6 weeks.[101–103] Contrastingly, a recent randomized, double-blind, placebo-controlled trial found that 50 mg of vanadyl sulfate twice daily for 4 weeks had no effect in individuals with impaired glucose tolerance.[104] Limited clinical and experimental data exist supporting the use of vanadyl sulfate to improve insulin resistance, and further research is warranted regarding its safety and efficacy.

Chromium

Diets high in refined sugar and flour are deficient in chromium (Cr) and lead to an increased urinary excretion of chromium.[105,106] The progression of MetS is not likely caused by a chromium deficiency,[107] and dosages that benefit glycemic regulation are not achievable through food.[106,108,109]

A recent randomize, double-blind trial demonstrated that 1000 μg Cr per day for 8 months improved insulin sensitivity by 10% in subjects with T2DM.[110] Cefalu et al[110] further suggested that these improvements might be more applicable to patients with a greater degree of insulin resistance, impaired fasting plasma glucose, and higher HbA1c values. Chromium's mechanism of action for improving insulin sensitivity is through increased Glut4 translocation via prolonging insulin receptor signaling.[109] Chromium has been well tolerated at 1000 μg/d,[105] and animal models using significantly more than 1000 μ Cr per day were not associated with toxicological consequences.[109]

α-Lipoic Acid

Humans derive α-lipoic acid through dietary means and from endogenous synthesis.[111] The foods richest in α-lipoic acid are animal tissues with extensive metabolic activity such as animal heart, liver, and kidney, which are not consumed in large amounts in the typical American diet.[111] Supplemental amounts of α-lipoic acid used in the treatment of T2DM (300-600 mg) are likely to be as much as 1000 times greater than the amounts that could be obtained from the diet.[112]

Lipoic acid synthase (LASY) appears to be the key enzyme involved in the generation of endogenous lipoic acid, and obese mice with diabetes have reduced LASY expression when compared with age-and sex-matched controls.[111] In vitro studies to identify potential inhibitors of lipoic acid synthesis suggest a role for diet-induced hyperglycemia and the PIC TNF-α in the down-regulation of LASY.[113] The inflammatory basis of insulin resistance may therefore drive lowered levels of endogenous lipoic acid via reducing the activity of LASY.

α-Lipoic acid has been found to act as insulin mimetic via stimulating Glut4-mediated glucose transport in muscle cells.[110,114] α-Lipoic acid is a lipophilic free radical scavenger and may affect glucose homeostasis through protecting the insulin receptor from damage[114] and indirectly via decreasing nuclear factor κB–mediated TNF-α and IL-1 production.[110] In

postmenopausal women with MetS (presence of at least 3 ATPIII clinical criteria) 4 g/d of a combined inositol and α-lipoic acid supplement for 6 months significantly improved OGTT scores by 20% in two thirds of the subjects.[114] A recent randomized double-blinded placebo-controlled study showed that 300 mg/d α-lipoic acid for 90 days significantly decreased HbA1c values in subjects with T2DM.[115]

Side effects to α-lipoic acid supplementation as high as 1800 mg/d have largely been limited to nausea.[116] It may be best to take supplemental α-lipoic acid on an empty stomach (1 hour before or 2 hours after eating) because food intake reportedly reduces its bioavailability.[117] Clinicians should be aware that α-lipoic acid supplementation might increase the risk of hypoglycemia in diabetic patients using insulin or oral antidiabetic agents.[117]

Limitations

This is a narrative overview of the topic of MetS. A systematic review was not performed; therefore, there may be relevant information missing from this review. The contents of this overview focuses on the opinions of the authors, and therefore, others may disagree with our opinions or approaches to management. This overview is limited by the studies that have been published. To date, no studies have been published that identify the effectiveness of a combination of a dietary intervention, such as the Spanish ketogenic diet, and nutritional supplementation on the expression of the MetS. Similarly, this approach has not been studied in patients with musculoskeletal pain who also have the MetS. Consequently, the information presented in this article is speculative. Longitudinal studies are needed before any specific recommendations can be made for patients with musculoskeletal that may be influenced by the MetS.

Conclusion

This overview suggests that MetS and type 2 diabetes are complex conditions, and their prevalence is expected to increase substantially in the coming years. Thus, it is important to identify if the MetS may be present in patients who are nonresponsive to manual care and to help predict who may not respond adequately.

We suggest that diet and exercise are essential to managing these conditions, which can be supported with key nutrients, such as vitamin D, magnesium, and omega-3 fatty acids. We also suggest that curcumin, *G sylvestre*, vanadyl sulfate chromium, and α-lipoic acid could be viewed as specific nutrients that may be taken during the process of restoring appropriate insulin sensitivity and signaling.

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