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The Journal of the American Nutraceutical Association (ISSN-1521-4524) is published four times annually by the American Nutraceutical Association (ANA). Send all inquiries, letters, and submissions to the ANA Editorial Department at 5120 Selkirk Drive, Suite 100, Birmingham, AL 35242. Contents © 2005 ANA, all rights reserved. Printed in the United States of America. Reproduction in whole or part is not permitted without written permission. It is the responsibility of every practitioner to evaluate the appropriateness of a particular opinion in the context of actual clinical situations. Authors, editors, and the publisher cannot be held responsible for any typographical or other errors found in this journal. Neither the editors nor the publisher assume responsibility for the opinions expressed by the authors.

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In the most recent past issue of JANA, Dr. Robert Krueger authored a short, balanced summary of the April 2004 Report of the Institute of Medicine (IOM) entitled "Dietary Supplements: A Framework for Evaluating Safety." As Dr. Krueger explained, the framework recommended in the IOM report is multifaceted. The report recognizes that most of the nearly 30,000 dietary supplements currently available to the American consumer are safe. That said, the report underscores that questions exist or have been raised about the safety of some supplements, perhaps as many as 10 to 20% of those in the market today. The report describes how various datasets, including the results of animal tests, in vitro evidence, data with respect to interactions, etc., can be used in a science-based approach to determine whether a supplement poses a significant risk to human health. The result is a process for identifying supplement ingredients that may present risks of harm, for prioritizing those ingredients based on potential risk, and for evaluating their safety. Notably to this end, the report raises the concern that the historical use of dietary supplements is not always enough, by itself, to ensure safety even if that historical use is characterized by centuries of consumption or by use in folk medicines.

In the process of developing the framework, the authors of the IOM Report concluded that a number of legal and regulatory barriers impede the collection of safety data. These barriers, according to the report, hamper FDA's ability to protect the public health. Explicit in the report is the conclusion that the Dietary Supplement Health and Education Act of 1994 (DSHEA) unreasonably imposes limits on the quantity and quality of scientific data FDA is able to require with respect to the safety and benefits of dietary supplement ingredients. The report contains the conclusion that: "The constraints imposed on FDA with regard to ensuring the absence of unreasonable risk associated with the use of dietary supplements make it difficult for the health of the American public to be adequately protected."1

The report has not gone unnoticed. Consumer groups have praised it. Even some voices in Congress have weighed in: Senator Durbin, for example, a proponent of amending DSHEA, commented that, in light of the report:

It is now clear that the law should be changed in several key areas — it should require supplement makers to notify the FDA of any serious consequences resulting from these products; some products should be reviewed for safety before being sold; and when evaluating whether sales of a problematic product should be suspended, the FDA should adopt the science-based standard of unreasonable risk rather than the standard of legal certainty that is currently being used.2

The report has its critics as well. Industry groups, for example, question the implications of the report and contend that DSHEA provides FDA more than adequate tools to ensure the safety and proper labeling and promotion of supplement products.

The potential significance of the April 2004 report has been influenced if not heightened by the recent issuance by another IOM committee of an entirely different report critical of dietary supplement regulation in this country. On January 12, 2005, the IOM issued the report "Contemporary and Alternative Medicine in the United States." Characterizing FDA’s regulatory posture under DSHEA with respect to dietary supplements as limited and reactive, the IOM committee preparing this report advances a real concern about the quality of dietary supplements in the United States. The committee summarized its conclusions as follows:

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Product reliability is low, and because patent protection is not available for natural substances there is little incentive for manufacturers to invest resources in improving product standardization. Yet reliable and standardized supplements are needed not only for consumer protection but also for research on safety and efficacy. Without consistent products, research is extremely difficult to conduct or generalize. And without high quality research, medical practitioners cannot make evidence-based recommendations to help guide patients.

Together, the two IOM reports present an open challenge to the adequacy of DSHEA in assuring that consumers receive, on a consistent basis, safe and beneficial dietary supplement products. Dr. Krueger has, quite rightly, invited objective commentary on the issues. This, however, is not as easy a task as one would wish. As I have noted in this space before, for decades, federal regulation of dietary supplement products has been characterized by friction and mutual distrust between regulatory authorities, FDA in particular, and dietary supplement manufacturers. One perspective, troubled by excesses in claims and questions with respect to safety, has advocated careful, paternalistic regulation. The other perspective, focusing on the promotion of affordable non-pharmaceuticals for good health and healthy lifestyles, has advocated for allowing consumers to make choices about the preventive health care programs best suited for them.

In passing DSHEA, Congress sought to bring "balance" and "common sense" to the longstanding debate. Recognizing that many consumers place increased reliance on non-traditional health care programs, the framers of DSHEA assumed the safety of the vast majority of dietary supplements and focused on "empowering" consumers to make choices about such non-traditional programs on the basis of "data from scientific studies." IOM reports are characterized, often legitimately, as the product of "ivory tower" science and, as a result, are at odds with the practical realities of both regulation and product development and marketing. The April 2004 and January 2005 IOM reports present an open challenge, whether a more precise focus on safety is appropriate and whether the goal of "empowerment" that the framers of DSHEA assumed and sought, respectively, are being achieved today. The ball is in the industry’s court to respond to the report, not with the old saws of the past or available legal and policy arguments, but rather with as modern and self-critical a data-based assessment as can be mustered.

REFERENCES:
4. See legislative history of the Dietary Supplement Health Education Act, Public Law 103-417 [S784]; October 25, 1994, Section 2(14) ("dietary supplements are safe within a broad range of intake and safety problems with the supplements are relatively rare").
5. Id., Section 2(8).
THE METABOLIC SYNDROME


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INTRODUCTION

The pandemic of obesity in the United States predicts major increases in the incidence of the metabolic syndrome (MS), type 2 diabetes mellitus (DM), coronary artery disease (CAD), myocardial infarction (MI), cerebrovascular accidents (CVA), generalized atherosclerosis (AS) and the total burden of cardiovascular disease (CVD). Genetic predisposition, environmental and lifestyle factors are the predominant contributors to the MS. Lifestyle factors such as physical inactivity and unhealthy and unbalanced nutritional consumption of excess calories, simple refined carbohydrates with a high glycemic index and load, high saturated fat (SF), high trans fats (TF) and reduced exercise contribute to the escalating rates of obesity and MS. The MS and obesity are contributing to major economic and public health concerns and problems that mandate aggressive, urgent and dedicated identification, prevention, treatment and education of patients and health care providers as well as other public, private and governmental agencies.

The MS most definitely represents a constellation of cardiovascular (CV) risk factors determined predominantly by the degree of insulin resistance (IR). The continuum of risk associated with each CV risk factor, as well as the additive or synergistic effect on total CV risk, will be discussed in the context of assessing and reducing global CV risk.

This paper will, however, primarily review the pathophysiology, diagnosis, prevention and nonpharmacologic treatment of the metabolic syndrome and its components based on the premise of first promoting education regarding the criteria, symptoms and multi-faceted treatments of the MS, and then entrusting the medical community with forming doctor/patient partnerships in health care with the goal of bringing this devastating and increasingly prevalent disease spectrum under control.
DEFINITIONS

The metabolic syndrome has been variously defined and validated by at least four separate organizations6,7,8,9,10,11,12 including National Cholesterol Education Program’s Adult Treatment Panel III (NCEP-ATP-III),6,7,8,9 World Health Organization (WHO),11 American Association of Clinical Endocrinologists (AACE)12 and the European Society of Hypertension, European Society of Cardiology, International Society of Hypertension (ESH/ESC/ISH) (Table 1, 2).10

All include hypertension, dyslipidemia (high triglyceride, low HDL, dense LDL), obesity (elevated waist circumference, increased body mass index [BMI], waist/hip ratio [WHR]) and hyperglycemia, whereas microalbuminuria is an additional component of the MS in the WHO guidelines (Table 1).11 This definition takes into consideration that the MS originates from both insulin resistance and activation of vascular inflammatory mechanisms related to increased oxidative stress, vascular endothelial dysfunction, thrombosis and atheroembolic disease. The ESH/ESC/ISH guidelines add C-reactive protein > 1.0 mg/dL due to its thrombosis and atheroembolic disease. The Third National Health and Nutrition Examination Survey (NHANES III) found that 34% of women and 42% of men with microalbuminuria had the MS (p < 0.0001) and compared with "prediabetes," EWET identified more persons with hyperinsulinemia, dyslipidemia, hyperuricemia, hyperglycemia and diabetes (RR 3.2).

Currently, few clinicians measure waist circumference (WC) in their clinical practices. There is no systematic and continuous effort from any organization to inform practicing physicians about the potential usefulness of WC measurement. There are no standardized and calibrated normal ranges for WC, and cutoffs associated with equivalent risks vary with age, sex and ethnicity. For example, the World Health Organization (WHO) has suggested lower cutoffs for Asians living in the Pacific region.18 On the basis of a public health survey of 55,563 persons, Lin et al.19 suggested that the WC cutoffs for Asians living in Taiwan should be even lower than the WHO recommendation. Further observations are required to ascertain whether the WC cutoffs should be different for whites living in Ireland than for whites living in other geographic areas or for blacks, Hispanics and caucasians.20 The methods for WC measurements have varied in previous studies. The lack of a standardized measuring protocol for WC is understandably a concern for clinicians who are trying to determine which reference values to use to interpret WC results.

Identification of type II DM vs. impaired glucose tolerance (IGT) also creates a whole new CV risk category and perhaps should not be included in the requirements for MS as suggested by WHO.11 Type II DM is a CAD equivalent in men in the Framingham Study (10-year risk for CAD > 20%)21 and is a CVA risk equivalent in women in the Women’s Pooling Project.22 The Oxford Study based on the UK Prospective Diabetes Study (UKPDS) database differs from Framingham in that it includes a measure of glycemia and duration of DM, which is underestimated by Framingham, that more accurately predicts CAD and CVA.23

Microalbuminuria is a component of the MS in WHO, but not ATP-III guidelines. Based on numerous studies, microalbuminuria should now be considered a major criteria for MS.24 The Third National Health and Nutrition Examination Survey (NHANES III) found that 34% of women and 42% of men with microalbuminuria had the MS (p < 0.0001).24 Hypertension and hyperglycemia had the strongest correlation with microalbuminuria. A FBG > 110 mg% was highly correlated with microalbuminuria. It is well established that microalbuminuria is a strong predictor of CV morbidity and mortality25,26 and is related to hypertension,27 central adiposity,28 renal dysfunction,24,29 vascular endothelial damage, increased vascular permeability and is, thus, an early indicator of atherosclerosis.29

Levels of C-reactive protein (HS-CRP) are more strongly associated with metabolic syndrome than BMI, but were not independently associated with three-year risk of death or major adverse CV events such as MI, CVA or CHF.30 The MS, but not BMI, predicts future CV risk in women.30
INCIDENCE AND PREVALENCE

It is estimated that over 22% (range 21.8 to 23.7%) of the adult U.S. population (over 47 million adults) have MS and the incidence is rapidly increasing each year\textsuperscript{31,32} (Figure 1). Mexican Americans, especially Hispanic men, African American women and the elderly have the highest incidence, reaching over 40% by age 60 years in all ethnic groups, but is lowest in blacks of both genders\textsuperscript{31,32} (Figure 1). During the past three decades, the prevalence of obesity has doubled from 15% to over 30%.\textsuperscript{33,34} Approximately 66% of the U.S. population is now either overweight (BMI > 25) or obese (BMI > 30), which has paralleled the increased prevalence of the MS.\textsuperscript{33,34} The MS was present in 4.6%, 22.4% and 59.6% of normal weight, overweight and obese men, respectively, and a similar distribution was observed in women.\textsuperscript{32}

Old age, postmenopausal status, Mexican American ethnicity, higher body mass index, current smoking, low household income, high carbohydrate intake, no alcohol consumption and physical inactivity were associated with increased odds of the metabolic syndrome.\textsuperscript{32} The MS is at epidemic proportions and will become endemic in the future due to the increasing prevalence of obesity, an aging population and an increasing proportion of high-risk ethnic minorities. An additional 12 million adults will likely develop the MS as a result of aging alone by the year 2022. The recent NHANES IV data substantiate the continued increases in obesity and MS rates in the U.S.\textsuperscript{35}

TOTAL CARDIOVASCULAR MORBIDITY AND MORTALITY

The total CV, CAD morbidity and mortality and all cause mortality dramatically increases with duration of the MS, and the Kaplan-Meier Hazard Curves separate early from patients without MS and continue to diverge over time\textsuperscript{36} (Figures 2, 3, 4). In an 11.4 year study (Kuppio Heart Study), men with the metabolic syndrome as defined by NCEP were 2.9 (95% confidence interval [CI], 1.2 – 7.2) to 4.2 (95% CI, 1.6 – 10.8) times more likely and, as defined by the WHO, 2.9 (95% CI, 1.2 – 6.8) to 3.3 (95% CI, 1.4 – 7.7) times more likely to die of CHD after adjustment for conventional cardiovascular risk factors. The metabolic syndrome as defined by the WHO was associated with 2.6 (95% CI, 1.4 – 5.1) to 3.0 (95% CI, 1.5 – 5.7) times higher CVD mortality and 1.9 (95% CI, 1.2 – 3.0) to 2.1 (95% CI, 1.3 – 3.3) times higher all-cause mortality. The NCEP definition less consistently predicted CVD and all-cause mortality. Factor analysis using 13 variables associated with metabolic or cardiovascular risk yielded a metabolic syndrome factor that explained 18% of the total variance. Men with loadings on the metabolic factor in the highest quartile were 3.6 (95% CI, 1.7 – 7.9), 3.2 (95% CI, 1.7 – 5.8) and 2.3 (95% CI, 1.5 – 3.4) times more likely to die of CHD, CVD and any cause, respectively.\textsuperscript{36}

METABOLIC SYNDROME AND INSULIN RESISTANCE: PROGRESSIVE DISORDERS

Insulin resistance (IR) can be identified in children prior to the development of the dyslipidemia, hypertension and hyperglycemia that occur later in life.\textsuperscript{37} It is likely that insulin resistance and MS are polygenic disorders with major lifestyle influences that determine its biochemical and clinical expression. A tabular and graphic representation of insulin resistance in the development of the MS, glucose intolerance and type 2 DM are shown in Table 4 and Figure 5.\textsuperscript{37} Insulin resistance is present for many years prior to the development of hyperglycemia. Initially, IR is compensated with pancreatic hyperinsulinemia to maintain a normal serum glucose (with decreased hepatic insulin clearance and augmented post-hepatic insulin delivery in abdominally obese subjects). However, pancreatic beta cell exhaustion cannot meet IR demands over time resulting in IGT and clinical DM. A constellation of metabolic and biochemical disturbances characteristic of the MS occur during this time such as dyslipidemia, glucose intolerance, hypertension, microalbuminuria, endothelial dysfunction, vascular inflammation, a prothrombotic milieu and premature CAD.\textsuperscript{37}

VASCULAR ENDOTHELIUM, ENDOTHELIAL DYSFUNCTION AND THE METABOLIC SYNDROME

The blood vessel becomes the primary and central organ in the pathogenesis of cardiovascular disease, dyslipidemia, metabolic syndrome and hypertension. The blood vessel consists of the intima (endothelium and connective tissue), the media (vascular smooth muscle, a protein matrix of elastin and collagen, and an internal elastic lamina), and the adventitia with strong fibrous tissue to maintain vessel shape.\textsuperscript{38}

The vascular endothelium is the largest endocrine organ and the largest organ in the body.\textsuperscript{39} It is 14,000 ft\textsuperscript{2} in surface area, the size of 6 tennis courts in square area and 5 times the heart size in mass with a total weight of about 2 kilograms.\textsuperscript{39,40,41,42,43,44} It is a metabolically active organ with endocrine, paracrine, autocrine and intracrine functions.

The vascular endothelium under normal, healthy physiologic conditions forms a continuous sheet of organized monolayer polyhedral cells that becomes disorganized at extremes of hemodynamic shear stress (hypotension and hypertension).\textsuperscript{39,40,41}

Endothelial cells create a conduit that regulates blood flow through the tissues. Small vessels and capillaries consist primarily of endothelial cells, while larger vessels have additional components including connective tissue and smooth muscle that add strength and tone to the vessel.\textsuperscript{39,40,41}

The endothelium, which forms a barrier between the blood and the tissues, is a living organ with multiple functions. The endothelial cells are tightly interlocked so that
passage of products from the blood occurs through the endothelial cell. These cells are both a passive filter and a metabolically active organ that secretes substances into and out of the blood and into the underlying vascular smooth muscle, which regulates the local milieu.39,40,41,42,43,44

ENDOTHELIAL FUNCTION

The strategic location of the endothelium allows specific modulation of elements in the blood and vascular smooth muscle cell (Figure 6).42,44 Modulation in the circulating blood controls platelet function, coagulation, monocyte and leukocyte adhesion and inflammation. Modulation of the vascular smooth muscle cells (VSMC) determines permeability, contractile state, proliferative or growth response, migratory response and redox state (Figure 7). The endothelium maintains vascular health by a carefully controlled balance of "good" or "bad" mediators (Figure 8).42,44

Endothelial activation and subsequent responses are shown in Figure 8.45 Activation of endothelial receptors can stimulate nitric oxide (NO) synthase (NOS) with the production of NO and cyclooxygenase (COX), which produces prostacyclin (PGI2) from arachidonic acid (AA) and can lead to the release of endothelium-derived hyperpolarizing factor (EDHF). NO causes relaxation by activating the formation of cyclic GMP (cGMP) from guanosine triphosphate (GTP) by soluble guanylate cyclase (SGC). Prostacyclin (PGI2) causes relaxation by activating adenylate cyclase (AC) leading to the formation of cyclic AMP (cAMP). EDHF produces hyperpolarization and relaxation by opening K+ channels. Any increase in cytosolic calcium causes the release of relaxing factors. In certain blood vessels, contracting substances can be released from the endothelial cells, which include superoxide anions (O2-), thromboxane A2 (TXA2), endoperoxides and possibly endothelin-1 (ET-1). Thromboxane A2 and endoperoxides activate specific receptors (TX/Endo) on the vascular smooth muscle, as does ET1. Such activation causes an increase in intracellular Ca2+ leading to contraction. The production of ET-1 (catalyzed by endothelin converting enzyme [ECE]) can be augmented by angiotensin II (ATII), vasopressin (VP) or thrombin (T). The neurohumoral mediators, which induce the release of endothelium-derived relaxing factors (and sometimes contracting factors) through activation of specific endothelial receptors include: acetylcholine (ACh); adenosine diphosphate (ADP); bradykinin (BK); endothelin (ET); adrenaline (A); serotonin (5HT); thrombin (T); vasopressin (VP).

NITRIC OXIDE: CARDIOVASCULAR EFFECTS

Nitric oxide is the most powerful endogenous vasodilator. It maintains basal vascular tone, but is also produced and released both tonically and under stimulation.41,45,46,47,48,49 It inhibits the atherosclerotic process, lowers blood pressure and improves insulin resistance. Nitric oxide is synthesized in the endothelium and vascular smooth muscle by nitric oxide synthase with a very short half-life of only a few seconds. Nitric oxide is involved in numerous biologic functions,50 but its cardiovascular effects include vasodilation, anti-atherosclerotic, anti-platelet, anti-growth and antioxidant effects.50

ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction occurs when the vascular endothelium undergoes a phenotypic modulation to a non-adaptive state characterized by the loss or dysregulation of critical homeostatic mechanisms that normally operate in healthy endothelial cells.44 The endothelial cell, VSMC and emigrated leukocytes (EML) are all oxidant stress sensors and the source of the biologic modification response.44

The two major paradigms of endothelial activation are biochemical and biomechanical and relate primarily to the critical balance of angiotensin II (A-II) and nitric oxide (NO) (Figure 9) (Table 5).44 Activation results in the release of numerous mediators with endocrine, paracrine, autocrine and intracrine actions. Endothelial activation and dysfunction is the key, initial event in vascular disease, present with only risk factors, but no atherosclerosis.39,41,42,44,44,45 Endothelial dysfunction precedes intimal thickening by a decade and clinical atherosclerosis by several decades. Endothelial dysfunction has a high correlation with future cardiovascular events such as MI, percutaneous transluminal angioplasty, coronary artery bypass graft and sudden death.51 ED begets numerous vascular consequences, setting up a vicious cycle of increasing ED.52 ED, therefore, leads to inappropriate vasoconstriction, reduced NO, PGI2, PGE, PGE3, increased platelet aggregation, thrombosis, vascular hypertrophy, proliferation, oxidative stress and vascular permeability that result in numerous vascular diseases such as atherosclerosis, hypertension, dyslipidemia, insulin resistance, hyperglycemia, metabolic syndrome, CHD and CVA.53,54,55,56,57,58,59

The action of insulin on peripheral glucose uptake is influenced by endothelial dysfunction (delayed transcapillary insulin transport) and by changes and/or redistribution of blood flow, supporting the link between vascular function and insulin sensitivity.60

INSULIN ACTIONS AND INSULIN RESISTANCE

The basic physiologic abnormality of the metabolic syndrome is insulin resistance and vascular endothelial dysfunction.61,62,63 Insulin mediated glucose disposal is primarily via skeletal muscle (80%) with the remainder via adipose tissue (10-15%) and other tissues (5-10%). Insulin is normally an anabolic hormone which induces lipogenesis, glycogenesis, glycolysis and protein synthesis.61,62,63
These metabolic effects occur in conjunction with specific mitogenic effects such as increases in insulin growth factor 1 (IGF-1) and vascular vasodilator actions. In the presence of normal insulin sensitivity, insulin is anti-inflammatory, anti-thrombotic, anti-platelet, profibrinolytic, anti-growth, antioxidant, vasodilatory, anti-hypertensive and anti-atherosclerotic; all effects which are mediated by numerous mechanisms (Table 6) (Figure 10).

Vascular endothelial dysfunction is, thus, one of the initial abnormalities that occurs in the MS. An excess angiotensin-II (Ang II) synthesis or action and a deficiency of nitric oxide (NO) bioavailability cause vasoconstriction, growth promotion and a pro-thrombotic, pro-inflammatory and pro-oxidant state. This constellation of events is directly related to insulin resistance and the frequent clinical association of hypertension, dyslipidemia and diabetes mellitus. The metabolic, mitogenic and vasodilatory-vascular functions of insulin occur in skeletal muscle and adipose tissue, as well as in the liver, brain, heart, blood vessels, pancreas and other tissues. Insulin binds and acts mainly through the insulin receptor and also via the insulin-like growth factor (IGF)-1 receptor. The beta subunit of the insulin receptor is a tyrosine kinase, which is activated when insulin binds to the alpha subunit (Figure 10). Insulin resistance results in an imbalance of the mitogen-activated protein kinase (MAPK) and the phosphoinositide 3-hydroxykinase (PI3K) pathways (Figures 11, 12 and 13). Since the PI3K pathway regulates insulin-mediated glucose uptake into heart muscle and insulin-dependent endothelial NO production, a defect in this pathway may be responsible for both IR and reduced NO production. This leads to cellular proliferation and migration; thrombosis; and inflammation, with increased cytokines and cell adhesion molecules, causing a reduction in both glucose transport and eNOS/NO bioactivity. Because the enhanced MAPK pathway is pro-atherogenic, it overrides the anti-atherogenic actions of the PI3K pathway. The role of the insulin receptor, mitochondrial function, pancreatic beta cell, inflammatory cytokines, radical oxygen species (ROS) and free fatty acids (FFA) are important in the clinical expression of insulin resistance and Type II diabetes. The combination of chronic insulin resistance followed by beta cell dysfunction and failure eventually produces Type II diabetes.

Vascular insulin resistance leads to vascular inflammation, endothelial dysfunction and atherothrombotic CVD characteristic of the MS (Figure 14). The mitochondria is intimately involved in insulin resistance and pancreatic beta cell function. Skeletal muscle is strongly dependent on oxidative phosphorylation for energy production via ATP. Insulin resistance in the MS and Type 2 DM involves dysregulation of both carbohydrate and lipid oxidation. Electron microscopy (EM) of skeletal muscle show that the mitochondria are smaller in Type 2 DM, obese and MS patients than from lean subjects. These EM findings suggest an impaired bioenergetic capacity of skeletal muscle mitochondria in Type 2 DM, obesity and the MS. In addition, IR in skeletal muscle, as evidenced by dysregulation of intramyocellular fatty acid metabolism due to an inherited defect in mitochondrial oxidative phosphorylation, has been demonstrated in the offspring of patients with Type 2 DM. These offspring have a 60% reduction in insulin-stimulated rate of glucose uptake by skeletal muscle (p < 0.001) and an 80% increase in the intramyocellular lipid content (p = 0.005) attributable to a 30% reduction in mitochondrial oxidative phosphorylation (p = 0.01) (Table 7). Hepatic lipid content is also increased.

Insulin resistance results in preferential metabolism of FFA reducing glucose utilization. FFA inhibit GLUT-4, enhance gluconeogenesis and stimulate adipose tissue release of specific cytokines such as TNF-alpha and IL-6, which exacerbate IR and increase FFA concentration. TNF-alpha induces IR in part by increasing lipolysis, which raises FFA. In addition, TNF-alpha directly induces IR by kinase inhibition and inhibits eNOS and NO production contributing to both IR and hypertension. IL-6 initiates lipolysis, increases FFA and IR, while it inhibits eNOS and NO. The chronic insulin resistance results in gradual pancreatic beta cell dysfunction and failure due to FFA increases in UCP-2, reduction in mitochondria ATP and insulin secretion (Figure 15). FFA also increase UCP-3, which uncouples mitochondrial respiration from oxidative phosphorylation and may serve as a FFA exporter (Figure 16).

Non-esterified fatty acids (NEFAs) may promote impaired fasting glucose and diabetes mellitus by one or more mechanisms. Potential processes include reducing hepatic insulin uptake, increasing hepatic gluconeogenesis, impairing pancreatic b-cell responses to glucose-stimulated insulin secretion, inducing apoptosis of pancreatic islet cells and decreasing both oxidative and non-oxidative glucose metabolism in skeletal muscle.

In cultured pancreatic b-cells, oleic acid increases basal insulin secretion, but inhibits glucose-stimulated insulin release. Insulin regulated the expression of 45 genes that participate in metabolism, cell growth, signal transduction, transcription and protein processing. The radical scavenger N-acetylcysteine essentially blocked the effects of oleic acid on cell growth and differentiation, but did not affect the other activities. In another study, cis-unsaturated but not saturated NEFA's induced phosphorylation of NDP kinase and the b subunit of heterotrimeric G-proteins, which are implicated in insulin secretion. The capacity of NEFAs to induce apoptosis of the pancreatic b-cells was mediated by increased expression of inducible nitric oxide synthase and de novo ceramide production. These experiments may elucidate at the cellular level the observation that some diabetic patients have enhanced basal

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INFLAMMATION, OBESITY AND INSULIN RESISTANCE

Adipose tissue is an active, intricate metabolic paracrine and endocrine organ that produces a variety of "adipokines," including inflammatory mediators and hormones that result in chronic inflammation and endocrine and metabolic dysfunction, manifesting as insulin resistance and the clinical diseases of hypertension, dyslipidemia, hyperglycemia, diabetes and CVD. Adipocytes are both a source and a target of pro-inflammatory signals, such as interleukin-6 and tumor necrosis factor alpha (TNF-alpha). The subsequent increase in high sensitive (hs)-CRP, which is both a risk marker and mediator of the inflammatory process is highly correlated with future cardiac events. The role of the peroxisome proliferator-activated receptor (PPAR) alpha and gamma receptors are important in insulin resistance, glucose and lipid metabolism as well as overall vascular function, inflammation, atherosclerosis and hypertension (Figure 18).

The infiltration of adipose tissue by inflammatory macrophages is a common feature of obesity. The adipocytes secrete numerous adipokines and also have surface cell receptors for inflammatory cytokines. Adipocyte mass as measured by weight, BMI or visceral obesity correlates quantitatively with genetic expression of macrophages that produce inflammatory mediators and markers. This adipose tissue macrophage accumulation may be as high as 40% in obese patients.

The adipocytes secrete resistin, acylation stimulating protein (ASP), various hormones, PAI-1, cytokines, leptin, FFA, adiponectin, complement and various chemotaxins. The relative balance of these secretory hormones and mediators result in insulin resistance, glucose intolerance, Type 2 DM, hypertension, dyslipidemia, thrombosis, inflammation and oxidative stress as well as other components of the MS. C-reactive protein (CRP) is one of the best composite inflammatory markers and mediators of CVD and predictors of MS (Table 8). The measurement of CRP should become routine in the assessment and efficacy of therapy of the MS as it relates to inflammation.

This adipose tissue, through its effective hormones and cytokines and CNS mechanisms, regulates food intake, energy homeostasis, whole body insulin action and insulin sensitivity, body adiposity, carbohydrate and lipid metabolism, blood pressure, inflammation, thrombosis and subsequent athero-thrombotic disease (Table 9) (Figure 21). The adipocyte and adipocytokine balance determines the biological and clinical risk of the MS and athero-thrombosis, although abnormalities in liver and skeletal muscle are clearly important (Figure 22). There exists a high frequency of genes encoding secretory proteins in adipose tissue; most are bioactive substances. For example, subcutaneous adipose tissue has 20% of such genes and the PAI-1 mRNA is normal. However, visceral adipose tissue has 30% of these genes and the PAI-1 mRNA is increased 10 fold along with endothelial growth factor (EGF). The actions of selected adipokines are shown in Table 10 and Figure 23.

Various etiologies for insulin resistance include genetics (polygenetic disorder), epigenetic contributions of nutritional insufficiency in utero or early postnatal (low birth weight infants), visceral obesity, BMI, caloric and carbohydrate intake, adult and childhood nutrition, free fatty acids, sedentary lifestyle, age, ethnicity, race, gender, postmenopausal status, lack of alcohol consumption, low income, biochemical pathway dysfunction and inflammation. The insulin resistance induces the biochemical, pathophysiologic and clinical sequelae of the metabolic syndrome (Figure 24).

THE METABOLIC SYNDROME COMPONENTS DETAILED

In this section, each of the components of the MS will be discussed in detail:

1. Glucose intolerance, Type 2 DM, insulin resistance
2. Visceral obesity
3. Hypertension
4. Dyslipidemia
5. Pro-thrombotic state
6. Microalbuminuria
7. Inflammation (HS-CRP)

1. GLUCOSE INTOLERANCE, TYPE 2 DM AND INSULIN RESISTANCE

Diabetes mellitus is the sixth leading cause of death in the U.S. The annual increase in prevalence is 3.5 to 7.0%,
having increased 61% from 1990 to 2001. In 2002, there were 17 million diabetics composing 9% of the U.S. population. The highest incidence of DM occurs in American Indians, Alaska natives, non-Hispanic blacks, Hispanic Americans and the elderly. Diabetes is the leading cause of end stage renal disease (ESRD) and results in a two to four-fold increase in CHD, MI, CHF and CVA. CVD is the leading cause of death in DM. Approximately 70% of Type 2 DM patients are hypertensive, especially in the presence of microalbuminuria. Numerous studies have demonstrated a continuum of risk with both FBG and 2-hour OGTT and the risk of CVD. In the Hamilton Study of 95,783 subjects over 12.4 years, the relative risk (RR) of CV mortality increased 33% from a FBG of 75 mg/dL to a FBG of 110 mg/dL (p = 0.056) and CV mortality increased 58% with a 2-hour OGTT from 110 mg/dL to 140 mg/dL (p = 0.00064). Thus, for each 1 mg/dL increase in FBG starting at 75 mg/dL, there is a 1% increase in CV events and for each 1 mg/dL increase in the 2-hour OGTT starting at 110 mg/dL, there is a 2% increase in CV events.

About 93% of all cases of DM are Type 2 DM, which is due to insulin resistance, poor nutritional and exercise habits, and obesity. There is an orderly transition from euglycemia to glucose intolerance (fasting and postprandial) and varying degrees of insulin resistance and deficiency that spans 10 to 20 years such that glucose intolerance progresses to DM at a rate of 10% per year (Figure 25). The biochemical consequences of chronic hyperglycemia are shown in Figures 26, 27, 28 and 29. Both the duration and magnitude of the hyperglycemia determines all the biochemical reactions and subsequent vascular and neurological complications. In muscle cells, insulin stimulation of vesicle bound transporters, such as GLUT-4, do not translocate to the plasma membrane, causing insulin resistance and reduced glucose uptake. In adipose cells, compromised translocation of GLUT-4 is minor, but pretranslational depletion of GLUT-4 mRNA is a major factor in insulin resistance. In the pancreatic beta cells, there is increased expression of uncoupling protein 2 (UCP-2), abnormal GLUT-2 function, reduced ATP/ADP ratio, increased FFA, increased UCP-3 and FA export.

Insulin resistance does not occur in all obese patients, but the metabolic abnormalities and increased CV risk in these patients are seen primarily in IR individuals. Accurate assessment of IR is difficult in clinical practice. The ATP III guidelines require a FBG of > 110 mg/dL as evidence of IR, but a TG/HDL ratio may be the most sensitive and specific predictor. The American Diabetes Association (ADA) defines impaired fasting glucose as > 100 mg/dL. In the West of Scotland Study, using FBG of > 99 mg/dL significantly improved the identification of those individuals who had MS. With > 4 components of MS, the hazard ratio of developing CHD was 3.65 and of developing diabetes was 24.4. In previous studies, the prediction of which individuals develop CHD and/or diabetes was significantly greater with elevated fasting plasma insulin levels or elevated 2-hour OGTT. While the diagnosis of IR is easily defined, the measurement of IR is cumbersome, especially when done by the insulin suppression test, which is the gold standard. To make the diagnosis of insulin resistance more practical, one study demonstrated that fasting plasma insulin levels of > 108 pmol/L, triglyceride levels of > 130 mg/dL, or a ratio of triglyceride to HDL of 1.8 SI units or TG/HDL ratio > 3.0 using mg/dL correlated with IR. Of the three surrogate markers, fasting plasma insulin levels and TG/HDL ratio correlated the best.

### 2. Visceral Obesity

Over 66% of the U.S. population is overweight (BMI > 25 kg/m2), with 31% considered obese (BMI > 30 kg/m2). The prevalence of a BMI > 30 kg/m2 has increased in all states in the U.S. dramatically from 1991 – 2001 (Figure 30). Visceral obesity is associated with a greater CV risk. Although both waist circumference (WC) as suggested by ATP III and BMI have been used to define the MS, neither are consistent independent markers for CVD risk in patients with the MS. The BMI, often used as a surrogate marker, has limitations in Asians who have an increased incidence of IR starting with BMI's above 21 kg/m2. In the U.S. population, there is a continuous rise with increasing BMI for the risk of unstable angina and MI. Beginning at a BMI of 22, which had an odds ratio of 1.2, the risk increases progressively to an odds ratio of 4.6 at a BMI of 40. In this analysis, BMI was independent of age, gender, BP, IR, leptin, fibrinogen, HS-CRP, CHD severity on angiography, smoking status and a history of MI or hypertension.

The BMI is associated with numerous co-morbidities proportional to the BMI, such as all cause mortality, CHF, CVA, arrhythmias, sudden death, thrombosis, diabetes, hypertension, hyperlipidemia and fair or poor health (Figure 31). The incidence of DM is directly proportional to the BMI and has increased in the U.S. during the 1991 – 2001 time period (Figure 32). In addition to WC and BMI, obesity is defined by body weight, waist hip ratio (WHR) and percent body fat. There exists a very definitive relationship between the BMI, percent body fat and prevalence of the MS in men, women, black and white subjects (Table 13 and Table 14) (Figure 33). In men with a BMI > 30 kg/m2 and 29% body fat, the prevalence of MS was 60.2%. In the BMI is > 35 and 36% body fat, the prevalence of MS was > 90%. In females, a BMI > 30 kg/m2 and 37% body fat had a 60.2%
prevalence of MS. If the BMI is > 35 with 43% body fat, the prevalence of MS is > 90%,107

Most studies indicate that the WC is a better predictor of the MS, CV risk factors and CV morbidity and mortality than BMI,5,14,15,16,18,19,20 but using a combination of WC with hypertriglyceridemia may predict MS better.16 The WC is a reliable indicator for the syndrome of visceral lipid accumulation as evidenced by the fasting triacylglycerol concentration. However, the WC loses its predictability with a BMI > 35 kg/m² (Class II obesity).16 Visceral adiposity is associated with enhanced FFA production, which is cleared entirely by the liver, but virtually every cell membrane of every tissue in the body has fatty acid binding proteins which shuttle fatty acids into the cytosol intact. This overproduction of inflammatory adipokines results in hypertriglyceridemia and increased HS-CRP.16 Visceral obesity has the highest correlation with hypertension.16,35

3. HYPERTENSION

Hypertension, defined as a systolic blood pressure (SBP) > 140 mm Hg and a diastolic blood pressure (DBP) > 90 mm Hg or > 130/80 mm Hg in subjects with the MS, is a significant, powerful, independent and modifiable CV risk factor. Hypertension increases the risk of atherosclerosis, peripheral arterial disease (PAD), cerebrovascular accidents (CVA), CHD, MI, congestive heart failure (CHF), chronic renal insufficiency (CRI), chronic renal failure (CRF) and end stage renal disease (ESRD), dementia and total CV mortality. The risk for hypertensive end organ disease doubles with every 20/10 mm Hg increase in blood pressure starting at 115/75 mm Hg.108 However, only approximately one-half of the risk of the doubling is due to hypertension alone with the other half due to concomitant increase in other risk factors based on a re-analysis of NHANES I follow-up data. Over 90% of people who have normal blood pressure at age 55 years will develop hypertension within their lifetimes.109

The NHANES IV survey demonstrated that hypertension prevalence is increasing in the U.S.110 Approximately 28.7% (58.4 million individuals) had hypertension in 1999 and 2000, an increase of 3.7% compared with 1988 – 1991. Non-Hispanic blacks had the highest prevalence of hypertension in 1991 – 1994 and 1999 – 2000. Mexican Americans had the lowest prevalence of hypertension during the same period of time. Non-Hispanic black women had the greatest increase in hypertension prevalence (7.2%) while the non-Hispanic white men had the smallest increase (1.0%). Hypertension prevalence in individuals aged 40 – 59 years and those aged 60 years and older was higher in the non-Hispanic blacks than in the non-Hispanic whites and Mexican Americans.110

Systolic hypertension (SBP > 160 mm Hg with DBP < 90 mm Hg) and increased pulse pressure may be better predictors of CV morbidity and mortality, especially in individuals over the age of 55 years.111 Stage 1 systolic hypertension (SBP > 140 mm Hg and DBP< 90 mm Hg) accounts for the majority of uncontrolled hypertension in the U.S.

Insulin resistance often precedes hypertension by 10–20 years (Figure 5).1,2,3,4,5,112 Although the mechanisms involved in IR-induced hypertension are complex, the primary pathophysiologic abnormalities include loss of eNOS and NO via the PI3K pathway (Figures 11, 12, 13, 14), inflammation in the vascular endothelium with endothelial dysfunction, decreased eNOS, reduced NO bioavailability, upregulation of the AT1R, arterial stiffness, collagen overproduction, increased SVR and BP via the MAPK pathway (Figures 11 and 12).37,62,112,113,114,115,116 The various mechanisms of IR-induced hypertension are shown in Table 15,37,62,113 Nitric oxide is very important in renal pressure natriuresis, which is ultimately the cause of any sustained BP elevation. Insulin stimulates glucose transport by NO/CGMP pathway in human vascular smooth muscle cells (VSMC’s) (Figure 34).114 However, in the presence of IR, the MAPK pathway dominates and becomes a hypertensive and pro-atherogenic pathway (Figures 11 and 12).61 In the absence of IR, the PI3-K pathway is anti-hypertensive and anti-atherogenic (Figures 11 and 12).61 The IR along with visceral obesity, endothelial dysfunction, inflammation and immunologic dysfunction contributes to the hypertension, atherosclerosis and thrombosis (Figure 35).112 Hypertension is at least, in part, an inflammatory disorder.112 Arterial stiffness increases with IR-induced glucose intolerance.115,116 There is loss of arterial compliance, distensibility and elastic modulus due to increased collagen and extracellular matrix with connective tissue-I and II. These arterial abnormalities precede clinical DM and hypertension by years. The mechanism of the arterial stiffness include hyperglycemia, advanced glycosylation end products (AGE’s), carbonyl and oxidative stress, chronic vascular inflammation and endothelial dysfunction.115,116 Arterial stiffness predicts future CV events.114,115,116 Coronary matrix remodeling related to IR and DM creates cardiac fibrosis, systolic and diastolic CHF, CAD and thrombosis (Figure 36).114

4. DYSLIPIDEMIA

The ATP III guidelines for the dyslipidemia of the MS are triglyceride (TG) levels > 150 mg/dL, HDL-C < 40 mg/dL in men and < 50 mg/dL in women.9 An atherogenic dyslipidemia is characteristic of the MS and has a specific phenotype that includes increased free fatty acids, elevated serum TG with large VLDL particle size and small remnant VLDL, decreased high density lipoprotein (HDL) cholesterol (small HDL particle size), normal to minimally increased low density lipoprotein (LDL) cholesterol and an increased number of small dense LDL particles.9,117,118,119,120,121 This lipid phenotype occurs due to
simultaneous overproduction of lipoprotein particles, impaired lipoprotein particle clearance and dynamic changes in core lipoprotein particle composition, and the variation in the amount of cholesterol carried per particle. Conventional lipid testing does not accurately measure the broad heterogeneity of lipoprotein particle number and size present in IR, MS and Type 2 diabetic patients. The large VLDL is prothrombotic and indirectly atherogenic via the increase in small dense LDL and reduction in total HDL with a shift to small HDL (Figure 37).

The small dense LDL-C is very atherogenic due to at least four mechanisms: 1. Small size increases rate of entry into subintimal space. 2. Enhanced susceptibility to oxidative modification. 3. Increased adherence to subintimal connective tissue. 4. Increased uptake by scavenger receptors into macrophages to foam cells.

Low HDL-C, with a shift to smaller size HDL, is common in MS and is due to TG enrichment of HDL (transfer of cholesterol from HDL to VLDL by cholesterol ester transfer protein [CETP]), increased HDL degradation by hepatic lipase and increased APOA1 catabolism (Figure 38). Studies utilizing nuclear magnetic resonance (NMR) spectroscopy provide more details of the lipoproteins in IR and MS. NMR lipoprotein measurement demonstrates the prevalence and characteristics of patients with a "disconnect" between conventional lipid profiles and directly measures the number of lipoprotein particles. The Framingham Offspring Study reported the prevalence and characteristics of discrepancies between LDL cholesterol and NMR measured LDL particle number. Subjects with LDL cholesterol below the 20th percentile (100 mg/dL) and above the 80th percentile (160 mg/dL) were compared to those with LDL particle concentrations below the 20th percentile (< 1100 mmol/L) and above the 80th percentile (> 1800 mmol/L). In those with LDL cholesterol values defined as "optimal" by current guidelines (< 100 mg/dL), 34% of subjects had increased numbers of LDL particles (> 1100 mmol/L). The increased triglycerides and decreased HDL cholesterol were significantly associated with the "disconnect" between normal LDL cholesterol and increased numbers of LDL particles.

Data regarding NMR LDL particle number associations with ATP III defined MS in the Framingham Offspring Study provides further insight into the magnitude of LDL particle excess in the MS. The mean LDL cholesterol levels were slightly higher in patients with MS (139 mg/dL vs. 129 mg/dL in patients without MS) with values showing little or no change as a function of the number of components of the MS present. Conversely, patients with MS showed disproportionately higher numbers of LDL particles (1,722 nmol/L vs. 1,375 nmol/L in patients without MS) overall. In contrast to LDL cholesterol, LDL particle concentration is a function of the number of components of the MS present. The disparity between LDL cholesterol and number of LDL particles was explained by abnormal LDL composition. Among MS patients, a 3-fold increase in small LDL particle number and corresponding decrease in large LDL particle number occurred with components of the MS ranging from zero to five. One consequence of abnormal LDL composition in MS subjects was that only 23% of subjects with "optimal" LDL-C levels of < 100 mg/dL (< 20th percentile) had correspondingly low LDL particle numbers (< 20th percentile). In terms of the magnitude of this disparity, 34% of individuals with LDL-C < 20th percentile had LDL particle number > 50th percentile. Advanced lipid testing using NMR spectroscopy not only makes it easier to evaluate CVD risk at the initiation of therapy, but is also predictive of subsequent risk while on therapy and is cost effective. Prediction of on-trial risk is not accurate by conventional lipid measurements.

In clinical practice, it is important to be able to rapidly and accurately diagnose the MS and IR with simple lipid markers. The ratio of TG/HDL has one of the highest combined sensitivities and specificities. The TG/HDL ratio > 3.0 has a sensitivity of 71% and specificity of 68% in defining IR (Table 16).

5. PROTHROMBOTIC STATE

The MS is a prothrombotic clinic state with alterations in coagulation and fibrinolytic pathways that include increased levels of PAI-1, thrombin, factors IX, X, prothrombin, fibrinogen, tissue factor, increased activation of Factor VII and enhanced platelet aggregation, which are related to IR, PI-3 kinase pathway, MAPK pathways and the RAAS, especially angiotensin II. These abnormalities increase the tendency for thromboembolic complications, development of CHD, MI and CVA.

The underlying atherogenic processes that culminate in these thrombotic events associated with the concept of a "vulnerable plaque" results in platelet activation and aggregation, thrombin generation and activation of inflammatory cytokines. Meade et al. showed the importance of fibrinogen as a CVD risk factor. Plasminogen activator inhibitor-1 (PAI-1) predicts the presence of clinical CVD. Platelet-dependent thrombosis is associated with glucose intolerance. Angiotensin receptor blockers reduce the prothrombotic state of hypertensive subjects and decrease the risk of atherothrombotic strokes.

6. MICROALBUMINURIA

Microalbuminuria (MAU) or albumin excretion rate (AER) is defined as > 30 mg per 24 hours, but < 300 mg/24 hours or > 20 micrograms/minute or an albumin creatinine ratio of > 30 mg/gram. MAU predicts the MS,
increased CV events (RR 1.83), all cause mortality (RR 2.09), CHF (RR 3.23) and ESRD at a rate of 5 – 10% per year.24,132 Once MAU starts, a predicted reduction in GFR at a rate of 1 – 24 cc/minute/year occurs (average reduction in GFR is 7 – 10 cc/minute/year).24,132 MAU appears to be a continuous risk factor for all CV events24,132,133,134,135 and reduction of MAU reduces CV events.134 The presence of MAU increases the mean arterial pressure (MAP) by 3 mm Hg/year.24,132 In the NHANES III, 34% of women and 42% of men with MAU had MS.24,132

7. INFLAMMATION AND HS-CRP

A number of inflammatory markers predict subsequent cardiovascular events such as TNF-alpha, IL-6 and HS-CRP.136 The HS-CRP is both a risk marker and probably a significant risk factor for CVD. However, definitive designation of HS-CRP as a risk factor will require demonstrating that interventions to selectively alter levels impact outcomes as has been done for hypertension, hyperlipidemia and diabetes mellitus. Guidelines for its use in clinical practice are published by the CDC and the AHA.136 Ridker et al.137 demonstrated in the Women’s Health Study that additional criteria for MS in women increased the cardiovascular risk proportional to the level of HS-CRP. In women who had four or five of the criteria for MS, the presence of a HS-CRP > 3 mg/dL further increased their cardiovascular risk during the eight year follow-up. Measurements of HS-CRP in patients with MS may be useful in determining which patients need the most aggressive therapy.

TREATMENT OF THE METABOLIC SYNDROME

In this section, we will review the prevention and treatment of the MS. The importance of appropriate assessment of IR and MS, global risk factor evaluation, continuity of risk in CVD, the nutrient-gene interaction concept, nutritional recommendations and clinical nutrition trials, the role of weight management, exercise, nutritional supplements such as vitamins, antioxidants, minerals, micronutrients and pharmaceutical drug intervention will be discussed.

ASSESSMENT OF IR, MS AND GLOBAL CV RISK

As discussed previously, some of the best clinical and laboratory indicators of IR include the BMI, weight, WC, WHR, BP level, percent body fat, FBG, 2-hour GGT, fasting pro-insulin, insulin and C-peptide levels, TG/HDL ratio, number and size of LDL-C particles, MAU, HS-CRP and measures of inflammation and thrombotic tendency. Evaluation of global CV risk using Framingham, Indiana, Procam/Munster risk scores is important to determine aggressiveness, timing and type of treatment.92,138,139,140,141,142,143,144,145,146,147 Only 10 – 15% of patients with CHD lack any of the five conventional CHD risk factors of hypertension, dyslipidemia, diabetes mellitus, smoking and obesity.149,150 Studies have clearly demonstrated a continuum of CV risk for hypertension starting at 115/75 mm Hg,151 LDL-C at 60 mg/dL,152,153,154 FBG at 75 mg/dL and homocysteine at 9 micromol/L.147

NUTRITION AND THE NUTRIENT GENE INTERACTION

Enormous research has been conducted on the nutrient-gene interaction in health and disease.155,156 Micronutrients and macronutrients have direct and indirect effects on gene transcription that may result in specific beneficial or detrimental outcomes on a variety of biochemical, physiologic and clinical outcomes. Dyslipidemia, hypertension, diabetes, insulin resistance, CVD, CVA and cancer are some of these clinical diseases (Figure 40).155,156

The various components of the MS are altered depending on the composition of dietary macronutrients such as carbohydrates, protein and fats as well as various micronutrients and total caloric intake.157,158,159,160,161,162,165,163,166,164 Nutritional interventions directed at reducing IR may improve many of the components of the MS and, thus, reduce CV events.155,156,157,158,159,160,161,162,163,164,165,166,167,168,169

LIFESTYLE CHANGES

The cornerstone for clinical management of adults with the metabolic syndrome is appropriate lifestyle changes. While drug therapy may be required, weight loss, exercise and appropriate nutrition and nutraceutical supplements are important to treat the MS. Moderate levels of weight loss, optimal nutrition and exercise reduce the risk for diabetes, improve components of the MS and reduce CV events.169 Approximately 50% of patients with Stage I hypertension may reach goal blood pressure with lifestyle modifications.169 A significant percentage of patients with the MS may achieve normalization of IR, fasting blood glucose, lipids and C-reactive protein (CRP) with lifestyle changes.169 Treatment of MS should always begin with lifestyle changes and continue in conjunction with any pharmacologic treatments.

Excessive dietary intake of refined carbohydrates with high glycemic index and high glycemic load in conjunction with an inappropriate low fat intake increases serum triglycerides, worsens IR, increases serum glucose and decreases HDL-C.157,158,159,160,161,162,163,164 Increased ingestion of fructose results in a 32% higher TG level than an equivalent intake of glucose due to fructose-induced hepatic TG synthesis.157 The ratio of simple or refined carbohydrate to complex carbohydrate should be about 40% to 60% to reduce IR, glucose intolerance, dyslipidemia and the MS.157

Many of the vascular abnormalities such as vascular inflammation and endothelial dysfunction are a consequence
prandial glucose and insulin, elevates serum TG, lowers HDL, increases dense LDL and LDL particle number, induces endothelial dysfunction, vascular inflammation, atherogenesis and CVD.169-186

A complete summary of evidenced-based dietary recommendations for patients with glucose intolerance and type 2 DM from the American Diabetes Association (ADA) is summarized in Table 18.187,188 The DASH I and DASH II diets reduce BP, lipids and homocysteine.189,190,191 Figure 43 summarizes many of the nutritional influences on the MS such as IR, BP and dyslipidemia.

WEIGHT LOSS AND THE MS

Weight reduction, decrease in total body and visceral fat improve all components of the MS.192,193,194,195,196,197,198,199,200 As little as 5-10% loss in weight improves BP, FBG, lipids, HS-CRP and IR. A one kg weight loss corresponds to a 1 mm Hg reduction in mean arterial pressure (MAP).169 The improved insulin sensitivity improves FBG, PPG, HgA1C, TG, LDL, VLDL, HDL and reduces inflammatory markers such as TNF-alpha, III-6 and HS-CRP.197

EXERCISE AND THE MS

Both endurance (aerobic) and resistance (anerobic) exercise have a significant impact on improvement of all components of the MS.169,172,192,193,199,201-213 Both types of exercise improve insulin sensitivity, reduce FBG and PPG immediately and these effects persist for 24 to 48 hours after cessation of exercise.208,211 However, the beneficial effects tend to subside within two weeks after detraining. Exercise also reduces BP and improves dyslipidemia (increases HDL, lowers TG, TC and LDL).169,211 In skeletal muscle, there is improved GLUT-4 transport, phosphorylation, disposal and oxidative capacity as well as improved muscle glycogen storage and increased FFA oxidation.203,208 Increase in lean muscle mass (LMM), which is responsible for 70-85% of insulin-stimulated glucose removal, occurs with chronic resistance training.207 60 minutes of daily physical activity that maintains the heart rate at 60% to 80% of 220 minus one’s age is recommended.169,202 Supervised low intensity resistance exercise for 30 minutes at least three to four times per week will improve LMM.202,207 The amount of exercise correlates inversely with the mortality in MS and DM.201,210,213

NUTRITIONAL SUPPLEMENTS IN THE TREATMENT OF THE METABOLIC SYNDROME

There exists a large scientific literature on the role of nutritional supplements such as vitamins, antioxidants, nutraceuticals and minerals in the treatment of the various components of the metabolic syndrome. In this section, we will review the clinical studies that support the use of these
supplements in the treatment of hypertension, dyslipidemia and hyperglycemia or DM.

HYPERTENSION

New and future treatment guidelines for lower target blood pressure (BP) levels in the general hypertensive population as well as in specific populations of hypertensive patients will demand a combination of nonpharmacologic (lifestyle modification) and pharmacologic therapy. Hypertensive patients with metabolic syndrome, diabetes mellitus (DM), renal insufficiency (RI), proteinuria, congestive heart failure (CHF), coronary heart disease (CHD) and those with previous myocardial infarction (MI), cerebrovascular accidents (CVA) or transient ischemic attacks (TIA) often require three to four antihypertensive medications to reach a BP of 140/90 mm Hg or less. Lower recommended target BP goals of 130/80 mm Hg or perhaps 110/70 mm Hg cannot be attained without aggressive use of balanced drug and non-drug treatments. Nutrition, dietary supplements, nutraceuticals, achieving ideal body weight, exercise (aerobic and resistance training) and restriction of caffeine and alcohol are crucial ingredients of this combination approach if BP and subsequent target organ damage (TOD) are to be reduced.

HYPERTENSION, NUTRITION AND VASCULAR BIOLOGY

Hypertension (HTN) is a consequence of the interaction of our environment and genetics. Macronutrients and micronutrients are crucial in the regulation of BP. Subsequent TOD and atherosclerosis (AS). Nutrient-gene interactions, oxidative stress and subsequent gene expression have either positive or negative influences on vascular biology (VB) in humans. Endothelial dysfunction (ED) and vascular smooth muscle (VSM) dysfunction are the initiating and perpetuating factors in essential HTN. The correct combination of macronutrients and micronutrients will significantly influence prevention and treatment of HTN and subsequent vascular complications. Treatment directed at the blood vessel, as well as the BP, should include identification and optimal management of cardiovascular (CV) risk factors and oxidative stress in order to reduce AS and TOD. TOD reduction is dependent on both hypertensive and non-hypertensive mechanisms.

Nutritional needs have been imposed on the population during our evolution from a pre-agricultural, hunter-gatherer milieu to a highly technological agricultural industry that is dependent on mechanical processing for our food supply. The paleolithic diet consisted of low sodium, high potassium, high fiber, low fat, lean animal protein, low refined carbohydrate and low cholesterol intake composed of fruits, vegetables, berries, nuts, fish, fowl, wild game and other nutrient-dense foods. On the other hand, the modern diet of processed, chemically-altered, fast, fried and frozen food has resulted in an epidemic of nutritionally-related diseases such as HTN, hyperlipidemia (HLP), DM and obesity.

NUTRITION TRIALS AND HYPERTENSION

Reduction in BP as well as reductions in CV morbidity and mortality have been demonstrated in numerous short and long-term clinical HTN nutritional trials. Up to 50% of hypertensive patients in the appropriate stage and risk category may be initially treated with lifestyle modifications for six to twelve months based on JNC-7 guidelines. However, specific patients with existing CV, cerebrovascular, renal or other TOD, DM or multiple CV risk factors usually require immediate drug therapy in conjunction with lifestyle modifications. Combined nutrients present in food, especially fruits and vegetables, as well as single and combined nutraceutical and nutrient or dietary supplementation have been demonstrated to reduce BP (Table 19).

The combined low sodium Dash II diet reduced blood pressure 11.5/6.8 mm Hg within two weeks, maintained this BP for the duration of the two month study and improved quality of life. This level of BP reduction is equivalent to that achieved with pharmacologic monotherapy.

Sodium

A reduction in sodium intake to 2400 mg per day lowers BP an average of 4-6 mm Hg systolic and 2-3 mm Hg diastolic BP in salt-sensitive hypertensive patients. Reduced sodium intake also reduces renal dysfunction, proteinuria, CHF, CVA, vascular hypertrophy and left ventricular hypertrophy (LVH). Further reductions of BP can be achieved with progressive restriction from 150 mmol to 100 mmol to 50 mmol of dietary sodium per day in the DASH II diet.

Potassium

The magnitude of BP reduction with supplementation of 60 to 120 mEq per day of potassium is 4.4 mm Hg systolic and 2.5 mm Hg diastolic BP in hypertensive patients. In addition, potassium may reduce CV events and CVA independent of BP and reduce the risk of cardiac arrhythmias. The recommended dietary intake is a K+/Na+ ratio of 5:1.

Magnesium

Magnesium supplementation in the range of 500 to 1000 mg per day reduces systolic BP 2.7 mm Hg and diastolic BP 3.4 mm Hg. Magnesium lowers systemic vascular resistance (SVR) and reduces arrhythmias. The mechanism is blockade of calcium influx into VSM cells and increased levels of the vasodilating prostaglandin E1 (PGE1).

Calcium

A recent meta-analysis of the effect of calcium supplementation in hypertensive patients demonstrated a reduction in systolic BP of 4.3 mm Hg and diastolic BP of 1.5
mm Hg. Calcium is particularly effective in patients with a high sodium intake and when given in a natural form with potassium and magnesium. Blacks, elderly, diabetic, salt-sensitive, pregnant, postmenopausal women and low-renin hypertensives have the best response.

**Protein**

High intake of non-animal protein (1 mg/kg/day) (Intersalt Study, Intermap Study) is associated with a lower BP. Hydrolyzed whey protein, and bonito fish extract significantly lower BP in humans through an angiotensin converting enzyme inhibitor (ACEI) mechanism.

**Fats**

Consumption of omega-3 fatty acids (polyunsaturated fatty acids – PUFA) such as EPA (eicosapentaenoic acid) and DHA (docosahexanoic acid) significantly reduces mean BP in humans by 5.8 to 8.1 mm Hg. Consuming omega-3 fatty acids combined with omega-9 fatty acids (oleate oil) (monounsaturated oleic acid), low saturated fat, elimination of trans-fatty acids and increased GLA (gamma linolenic acid) may have dramatic effects on BP, VB and AS. The omega-3 to omega-6 fatty acid ratio should be 1:1 to 4:1 with consumption of cold water fish (cod, tuna, mackerel, salmon), flax seed/oil, fish oil (15 grams per day), cod liver oil supplements and EPA/DHA supplements (3-4 grams per day). The olive oil dose is 40 grams of extra-virgin olive oil per day (4 tablespoons).

**Garlic**

The prospective placebo-controlled studies utilizing the correct form (wild garlic is best) and dose of garlic demonstrate only minimal decreases in systolic BP of 5-8 mm Hg or mean BP of 2-3%. However, garlic may have numerous other beneficial vascular effects as it is a natural ACEI and calcium channel blocker (CCB).

**Seaweed**

Wakame seaweed in doses of 3.3 grams per day significantly lower BP in hypertensive humans within four weeks due to ACEI activity. The average reduction in BP was 14/5 mm Hg. Long-term use in Japan appears to be safe.

**Fiber**

Clinical trials with various types of fiber to reduce BP have been inconsistent. The average BP reduction in prospective studies using 60 grams per day of oatmeal fiber (3 grams of beta glucan per day, glucomannan or 7 grams of psyllium per day) is 7.5 mm Hg/5.5 mm Hg.

**Vitamin C**

Vitamin C at doses of 250 to 500 mg BID lowers BP, especially in hypertensive patients with initially low plasma ascorbate levels. Vitamin C improves ED, increases nitric oxide levels, is a potent antioxidant, decreases SVR and BP falls an average of 7/4 mm Hg. The greater the initial BP and the lower the plasma ascorbate level, the greater the response. Combinations with other antioxidants and vitamins may have synergistic antihypertensive effects.

**Vitamin B-6**

Supplemental vitamin B-6 at 5 mg/kg/day reduced BP 14/10 mm Hg over four weeks. Vitamin B-6 reduces central sympathetic nervous system activity, acts as a central alpha agonist (i.e. Clonidine), a CCB and a diuretic. Pyridoxine also improves insulin sensitivity and carbohydrate metabolism, which improves BP. Daily doses should probably not exceed 200 mg to avoid neuropathy.

**Lycopene**

Paran et al. evaluated 30 subjects with grade I hypertension given tomato lycopene extract for eight weeks. The BP fell 9/7 mm Hg within eight weeks. Lycopene is found in high concentrations in tomatoes, tomato products, guava, pink grapefruit, watermelon, papaya and apricots, although grapefruit should not be ingested when taking calcium channel blockers.

**Co-Enzyme Q-10**

Enzymatic assays show a deficiency of Co-Enzyme Q-10 (Co-Q-10) in 39% of essential hypertensive patients versus only a 6% deficiency in controls. Human studies demonstrate significant and consistent reductions in BP averaging 15/10 mm Hg in all reported prospective clinical trials. Doses of 100 to 225 mg per day (1-2 mg/kg/day) to achieve a therapeutic plasma level of over 2 mcg/ml are effective within four to eight weeks in reducing BP. The BP remains steady at this level and returns to baseline at two weeks following discontinuation of Co-Q-10. Co-Q-10 reduces SVR, catecholamine and aldosterone levels, improves insulin sensitivity, endothelial function and increases nitric oxide levels. No adverse effects have been noted at these doses with chronic use. Patients have been able to stop or reduce the number of antihypertensive drugs by one to three with chronic ingestion of Co-Enzyme Q-10. A reputable, certified absorbable form with excellent bioavailability and measurement plasma levels are important clinical considerations.

**L-Arginine**

L-arginine is the natural predominant precursor for vascular nitric oxide. Administration of 10 grams orally per day in food or as a supplement significantly reduces BP in human subjects by 6.2/6.8 mm Hg, improves ED and blood flow.

**Taurine**

Taurine, a sulfonic beta-amino acid, is significantly reduced in the urine of essential hypertensive patients. Administration of six grams of taurine per day lowers BP 9/4 mm Hg. Taurine induces a sodium-water diuresis, vasodilation, increases atrial natriuretic factor (ANF) and reduces sympathetic nervous system activity and aldosterone levels, improves insulin sensitivity and reduces homocysteine levels.
Celery

Celery has antihypertensive properties due to 3-N- butyl phthalide, apigenin and other substances that act like ACEI or CCB blockers. Four stalks per day or the equivalent in celery juice, oil or celery seed extract reduces BP in animals and humans.²⁵⁸,²⁵⁹,²⁶⁰,²⁶¹,²⁶²

Pycnogenol

Pycnogenol, a bark extract from the French maritime pine, at doses of 200 mg/day resulted in a significant reduction in systolic BP from 139.9 mm Hg to 132.7 mm Hg (p < 0.05) in eleven patients with mild hypertension over eight weeks. Diastolic BP fell from 93.8 mm Hg to 92.0 mm Hg (NS). Serum thromboxane concentrations were significantly reduced (p < 0.05).²⁶³

Phytonutrient Nutritional Concentrate Powder

Published studies suggest that the consumption of fruits, vegetables and fiber reduces systemic blood pressure (BP) and subsequent cardiovascular events. This encouraging data prompted a study that was completed in 2005 which evaluated the effect of a proprietary phytonutrient concentrate powder made from fruits, vegetables and berries (PNCP), on systolic and diastolic BP, and arterial compliance in a group of hypertensive and normotensive subjects. The Preliminary results from this study were presented in an abstract at the American Society of Hypertension meeting on May 15, 2005, in San Francisco, CA.

In this open label single treatment cohort, 24-month study, thirty-three (33) male and female normotensive and hypertensive subjects (on no antihypertensive medications or stable doses of antihypertensive medications) were given 4 capsules daily of PNCP. The results demonstrated that PNCP significantly lowered diastolic blood pressure (DBP) and improved large arterial compliance. There was a non-significant trend to reduce systolic BP. The group mean change from baseline for DBP was -5 mm Hg (p<0.002). This figure represents a -6% change in DBP from baseline for the study group of 33 participants. There was also a 27.9% improvement in large artery compliance (p<0.001).

The results of this study, which illustrate the health benefits of supplementing the diet with Phytonutrient Nutritional Concentrate Powder, as well as clinical data supporting the efficacy of consuming fruits, vegetables and fiber in the regular diets of hypertensive patients (DASH), confirm our contention that lifestyle changes (including dietary adjustments and supplements) are of paramount importance in the treatment of hypertension either as a singular disorder with myriad physiological effects, or as a component of the metabolic syndrome, the macrocosmic result of a combination of diseases and conditions.

Combinations

Combinations of various nutraceutical or dietary supplements, vitamins and antioxidants may further enhance BP reduction, reduce oxidative stress and improve vascular function and structure. Optimal doses and combinations are yet to be determined, but future research will provide important data.

Finally, the addition of lifestyle modification with low dose combination antihypertensive drugs provides additive or synergistic BP reduction to achieve these lower BP goals, improves risk factors, metabolic parameters, vascular structure and function, and allows for lower doses and number of drugs with reduced side effects to reduce TOD.

NATURAL ANTIHYPERTENSIVE COMPOUNDS CATEGORIZED BY ANTIHYPERTENSIVE CLASS

As has been discussed previously, many of the natural compounds such as food, nutraceutical and dietary supplements, vitamins, antioxidants or minerals function in a similar fashion to a specific class of antihypertensive drugs. Although the potency of these natural compounds may be less than or equal to the antihypertensive drug and the onset of action slower when used in combination, the antihypertensive effect is magnified. In addition, many of these natural compounds have varied, additive or synergistic mechanisms of action in lowering BP (Table 20).

Because of the potential for these synergistic effects, testing and correcting for deficiencies by adding supplements to the diet, with emphasis on those which have proven to be beneficial in regulating blood pressure, should be considered at the onset of treatment. As the transient serum levels of vitamins, minerals and antioxidants do not always accurately reflect the impact of absorption and utilization, an intracellular assay for micronutrients provides a better representation of the proper supplementation regimen for your patients. This functional assessment, as well as post treatment monitoring, is strongly recommended because the absorption and utilization of nutraceutical compounds and individual vitamins is key in the efficacy of treatment plans.

Further research is needed to better define the role of many of these nutraceuticals, vitamins, antioxidants and minerals in the prevention and treatment of hypertension and TOD.

DYSLIPIDEMIA TREATMENT

Although the definitions of the MS use hypertriglyceridemia and reduced HDL cholesterol, the therapeutic strategy should be to reduce LDL cholesterol to 60-70 mg/dL beginning with a combination of nutritional and statin therapies.¹⁵³,²⁶⁴,²⁶⁵,²⁶⁶,²⁶⁷ Treatment of patients with lipid abnormalities for LDL-cholesterol, HDL-cholesterol or triglycerides should be aimed to lower levels than those recommended in the recent ATP-III Report.¹⁵³,²⁶⁴,²⁶⁵,²⁶⁶,²⁶⁷ Ideally, HDL-cholesterol should be greater than 40 mg/dL.
in men and greater than 50 mg/dL in women. Triglyceride levels should be less than 150 mg/dL and optimally less than 75 mg/dL. Patients with the MS typically have hypertriglyceridemia, low HDL-cholesterol with small dense HDL3, an increased number of LDL particles (over 900) and a propensity to smaller dense LDL particles. Appropriate combinations of nutritional supplements and lipid lowering drugs may be needed in some patients to reach the recommended treatment goals in addition to diet, weight loss and exercise.

There are many foods, nutrients, nutraceutical supplements and herbs that have been demonstrated to favorably influence the serum lipid profile. Those that have the best scientific and clinical evaluation will be discussed in this section (Table 21).

Cardiovascular benefits in randomized clinical trials with hard clinical endpoints are unproven with most anti-lipid supplements with the exception of niacin and marine lipids. The mechanisms of anti-atherosclerotic and CV prevention of nutritional supplements include both lipid and non-lipid effects (Table 22). The lipid hypothesis and clinical trials on lipid reduction have suggested that lowering LDL-cholesterol is beneficial regardless of the treatment used. Therefore, it would be reasonable to assume that "natural" methods to improve dyslipidemia would also reduce CV events. Statin drugs have additional non-lipid pleiotropic effects that may contribute to the overall reduction in CV events.

The mammalian cell mevalonate cholesterol pathway and pyrophosphate pathway is shown in Figure 44. Selected nutritional supplements and statins are incorporated into this Figure to demonstrate the various mechanisms of action on this pathway. A brief discussion of selected nutritional supplements in the treatment of dyslipidemia follows.

**Niacin**

Niacin (nicotinic acid, Vitamin B3) lowers total cholesterol (TC), apolipoprotein B (APO-B), triglycerides (TG) VLDL, LDL-C and small dense LDL particles, lipoprotein a (Lp(a)) and increases HDL-C. The mechanisms of action include modulation of TG lipolysis in adipose tissue, modulation of TG synthesis resulting in increased intracellular APO-B degradation and reduction in the fractional catabolic rate of HDL-APO-AI without affecting synthetic rate, and by reducing hepatic HDL-APO-AI uptake. In addition, nicotinic acid induces fibrinolysis, inhibits platelet function, inhibits LDL-C oxidation, inhibits cytokines, inhibits cell adhesion molecules (CAM's) and is a potent antioxidant. Numerous clinical trials have demonstrated significant reductions in CV events in subjects treated with nicotinic acid (Table 23). Nicotinic acid provides a dose-related reduction in LDL-C of 10-25%, TG by 20-25% and increases in HDL-C of 15-35%. In the Coronary Drug Project, which enrolled men with previous myocardial infarction, nicotinic acid administration at 3 grams per day led to a 26% decrease in second nonfatal infarction and a 26% reduction in CVA over six years, and an 11% decrease in total mortality after 15 years follow-up (Table 23).

Nicotinic acid can be safely administered with other drugs to reduce CV events, favorably improve atherosclerosis in both native coronary vessels and bypass grafts and also in carotid and femoral arteries. Depending on the type of niacin administered, a safe efficacious dose is usually one to four grams per day in divided doses. The most frequent side effects include cutaneous flushing, pruritus, rash, hepatitis, hyperglycemia, hyperuricemia, hyperhomocysteinemia, gastritis and peptic ulcer disease, bruising, hyperpigmentation of the skin, supraventricular tachycardia and palpitations.

**Marine Lipids (Omega 3 Fatty Acids)**

Omega 3 fatty acids (FA) such as alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) produce a dose-response improvement in serum lipids with reductions in TC, LDL-C, APO-B, VLDL, TG, remnant lipoproteins and increases in HDL-C. The reductions in TG are dramatic with decreases ranging from 15 to 30%; HDL-2 is increased by DHA and LDL-C particle size increased. These lipid effects generally require three to five grams per day of combined EPA and DHA. Omega 3 FA ingestion significantly lowers heart rate and BP reduces the risk of incident atrial fibrillation and significantly reduces CV events (death, nonfatal MI and nonfatal CVA). The mechanisms of CV event reduction include decreased risk for arrhythmias and thrombosis, decreased lipids, especially TG and remnant lipoprotein levels, decreased rate of growth of atherosclerotic plaque, improved endothelial function, lower BP and reduced inflammatory responses.

**Policosanol**

Policosanol (saccharumofficinarum) is a sugar cane wax extract of eight aliphatic alcohols including octacosanol (60%), triacanatol, hexacosanol and five other minor aliphatic alcohols that has been demonstrated to have a significant effect on reducing serum lipids. Policosanol has several mechanisms of action that affect lipid metabolism and atherosclerotic risk. Cholesterol synthesis is impaired between the acetate and mevalonate production steps, but HMG-CoA reductase is probably not modulated. Policosanol promotes binding, uptake and degradation of LDL-C and reduces LDL lipid peroxidation and inhibits VSMH.
platelet aggregation,\textsuperscript{326,346,359,360} retards development of atherosclerotic plaques\textsuperscript{326} and improves PAD and claudication symptoms.\textsuperscript{326}

In over 60 clinical trials involving more than 3,000 patients, policosanol at a dose of 10 mg BID over four to twelve weeks reduced TC 14.7 to 21\% (p < 0.05), decreased LDL-C 17.9 to 29.2\% (p < 0.05), increased HDL-C 7.4 to 29.3\% (p < 0.05) and lowered TG 4.6 to 13.8\% (p < 0.05).\textsuperscript{326} There are minimal adverse effects, drug interactions or biochemical changes.\textsuperscript{326,327,329,333,334,336,339,355,357,358} Long term studies on clinical endpoints are unpublished to date.

**Chinese Red Yeast Rice (Monascus Purpureus)**

Monacolines are the active ingredients in Chinese red yeast rice, which inhibit cholesterol synthesis by competitive inhibition of HMG-CoA reductase and thus have the same mechanism as the "statin" drugs.\textsuperscript{362,363,364} Clinical studies have documented favorable effects on serum lipids in humans with reductions of TC of 17\%, LDL-C of 22\% and TG of 12\% with no change in HDL-C.\textsuperscript{362,363,364} The usual dose is 2.4 grams per day, which is equivalent to 5 mg of lovastatin. However, citrinin, a toxic fermentation by product consisting of a mycotoxin from penicillium and aspergillus, may induce renal failure and is mutagenic in animals.\textsuperscript{362,363,364}

**Plant Sterols**

Plant sterols are natural dietary components with serum cholesterol-lowering properties.\textsuperscript{365,366,367,368} The most common plant sterols are B-sitosterol, campesterol and stigmasteryl, which are classified as 4-desmethyl sterols of the cholestane series.\textsuperscript{365,366,367,368} Their structure is similar to that of cholesterol with an extra methyl or ethyl group and a double bond in the side chain. Saturated plant sterols are referred to as stanols.\textsuperscript{365,366,367,368}

The cholesterol-lowering effect is believed to be caused by an inhibition of cholesterol absorption resulting from the higher affinity of plant sterols than of cholesterol for micelles and by increasing bile acid excretion.\textsuperscript{365,366,367,368} Their effect is enhanced when consumed with a fatty meal.

The average serum lipid changes include reduction in TC by 8\%, LDL-C by 10\% with no change in TG or HDL-C.\textsuperscript{365,366,367,368} The most effective dose is 2 grams per day.

**Soy**

A meta-analysis of 38 clinical studies which evaluated soy protein at doses of 31 to 47 grams per day resulted in a significant improvement in dyslipidemia in humans.\textsuperscript{369} Total cholesterol decreased 9.3\%, LDL-C decreased 12.9\%, TG fell 10.5\%, but HDL-C did not change significantly.\textsuperscript{369} The changes in TC and LDL-C were directly related to the initial serum cholesterol concentration (p < 0.001). Other studies have shown soy protein significantly decreases LDL-C (p = 0.029) and the LDL/HDL ratio (p = 0.005) regardless of plasma lipid status when used with the NCEP Step I Diet in both normcholesterolemic and hypercholesterolemic men.\textsuperscript{370} Various mechanisms for soy protein effects on serum lipids include alteration in micellar lipid content and absorption and favorable effects of fiber, isoflavones and phytoestrogens.\textsuperscript{369,370}

**Green Tea (EGCG)**

Catechins, especially epigallocatechin gallate (EGCG), improves the lipid profile, reduce oxidation of LDL-C, decrease APO-B lipoprotein secretion from cells, interfere with micellar solubilization of cholesterol in the GI tract and reduce cholesterol absorption.\textsuperscript{371,372,373} In a rat study, doses of EGCG of 1.0\% reduced cholesterol absorption by 37\% (p < 0.05).\textsuperscript{371} To achieve these favorable effects in humans, the dose is about 800 ml of green tea per day.\textsuperscript{373}

**Flax**

Several studies have shown a significant reduction in CHD mortality and MS parameters and lipids with increased consumption of flax seed and alpha linolenic acid.\textsuperscript{374,375,376} The Seven Countries Study (SCS) conducted from 1961 to 1991 demonstrated reductions in CHD with alpha linolenic acid.\textsuperscript{374,375} The Lyon Diet Trial found a 50-70\% decrease in death and CHD at four years with a 1-2 grams flax seed oil per day containing 80\% alpha linolenic acid.\textsuperscript{376} The mechanisms may be related to anti-inflammatory effects, increased eNOS and NO, reduction in BP, reduction in vascular smooth muscle hypertrophy, fiber, lignans phytoestrogens or anti-lipid effects.\textsuperscript{377,378}

**Tocotrienols**

Tocotrienols are very effective in improving the serum lipids.\textsuperscript{379,380,381,382,383,384,385} Tocotrienols inhibit cholesterol synthesis by post-transcriptionally suppressing HMG-CoA reductase activity by two post-transcriptional actions.\textsuperscript{382} They increase the controlled degradation of reductase protein and decrease the efficiency of translation of HMG-CoA reductase mRNA.\textsuperscript{379,382} LDL receptor protein is also augmented. A 12-week study of the effects of adding a tocotrienol rich fraction of all tocotrienols to the diet, reduced TC 17\%, LDL 24\%, APO-B 15\% and Lp(a) 17\% (p < 0.05).\textsuperscript{379} In addition, platelet factor 4 fell 14\%, thromboxane B fell 31\% and fasting glucose was reduced. There was no significant change in APO-A-I or HDL.

The combination of a statin and tocotrienols may be additive in their lipid-lowering effects as their mechanism of action on HMG-CoA reductase is different and tocotrienols block the adaptive changes induced by statins.\textsuperscript{379,380,384} It should be noted that humans do not respond uniformly to the anti-lipid effects of tocotrienols, especially when cholesterol, fat and alcohol intakes are not controlled.\textsuperscript{379} Studies also indicate an attenuating effect of alpha-tocopherol\textsuperscript{379,380}

Epidemiologic studies indicate that diets high in cereal grains, vegetables and fruits that are high in tocotrienols pro-
vide protection against CV disease.\textsuperscript{379} The type of tocotrienol ingested determines the anti-lipid potency.\textsuperscript{379,383} The gamma and delta tocotrienols are 30 times more potent than the alpha and beta tocotrienols in reducing lipids.\textsuperscript{379,383} The desmethyl forms of tocotrienols are the most potent.\textsuperscript{379,383} Alpha tocopherol concentrations in the diet over 20% inhibit tocotrienol lipid lowering effects.\textsuperscript{380} Thus, the tocopherol intake should be less than 15 to 20% and consumed 12 hours from the tocotrienols if possible. There is a dose dependent cholesterol reduction with tocotrienols at about 100 mg per day, after which it plateaus.\textsuperscript{380} As the dose of tocotrienols increases, there is additional conversion to alpha tocopherol, which would limit their anti-lipid effects.\textsuperscript{380}

**Pantothenic Acid**

Pantothenic acid is a precursor to coenzyme A and lowers LDL-C 14%, TG 30% and increases HDL-C 10\%.\textsuperscript{386,387,388,389,390,391,392,393} Pantothenic acid inhibits cholesterol synthesis and accelerates fatty acid metabolism in mitochondria by inhibition of HMG-CoA reductase and inhibition of hepatic acetyl-CoA carboxylase. The usual effective dose is 300 mg TID.

**CONCLUSIONS**

The best clinical data for lipid lowering is niacin, omega 3 fatty acids, policosanol, gamma/delta tocotrienols, pantothenic acid, red yeast rice, plant sterols, soluble fibers, MUFA/PUFA/nuts and soy.

The best clinical data for CV event reduction is niacin, omega 3 fatty acids and ALA. The best clinical data for surrogate endpoint reductions are niacin, omega 3 fatty acids and ALA, policosanol, red yeast rice and plant sterols.

**HYPERGLYCEMIA TREATMENT**

Numerous vitamins, antioxidants, minerals, herbals and nutraceuticals have glucose lowering effects in humans (Table 25). Many of these agents, particularly those that have undergone the best scientific studies, will be reviewed in this section.

**Vitamin E Derivatives**

The various forms of vitamin E derivatives have been shown to improve insulin action and reduce insulin resistance.\textsuperscript{394} Improve glucose control and reduce glycosylation of proteins.\textsuperscript{395,396,397,398} Vitamin E tends to be lower in patients with DM and the risk of DM is reduced in patients with optimal serum levels of vitamin E.\textsuperscript{396,398} Optimal doses are unclear, but 200 to 400 IU of an appropriate mixture of tocopherols and tocotrienols is recommended.\textsuperscript{399}

**Alpha Lipoic Acid**

Alpha lipoic acid and its reduced derivatives, dihydrolipoic acid (DHLA), are potent universal antioxidants, effective in lipophilic and aqueous environments.\textsuperscript{400} Alpha lipoic acid has been demonstrated to improve insulin sensitivity and glucose tolerance in type 2 DM, reduce AGE products, improve diabetic neuropathy, improve mitochondrial function, reduce BP, improve vascular endothelial dysfunction, inhibit inflammatory, proliferative and growth mediators and reduce oxidative stress.\textsuperscript{400-434}

As a co-factor for certain mitochondrial dehydrogenases, lipoic acid can potentially influence the rate of glucose oxidation. It was observed in 1970 that lipoic acid increases insulin-stimulated as well as basal glucose uptake by isolated rat diaphragm.\textsuperscript{401} More recently, administration of lipoic acid also raised basal and insulin-stimulated glucose uptake by skeletal muscles of insulin resistant, glucose intolerant and non-insulin dependent diabetic animals.\textsuperscript{402,403,404} Treatment with lipoic acid also increases glucose uptake in erythrocytes\textsuperscript{405} as well as cardiac and skeletal muscle of streptozotocin diabetic rats and reduced the extent of hyperglycemia.\textsuperscript{406,407}

Studies in cultured muscle cells and cultured adipocytes have also noted that lipoic acid can increase glucose uptake.\textsuperscript{408,409} The mechanism involves increased translocation of GLUT1 and GLUT4 glucose transporters into the plasma membrane. This increased translocation appears to be mediated via increased kinase activity of the insulin receptor, insulin receptor substrate-1, phosphatidylinositol 3-kinase and protein kinase B, suggesting that lipoic acid can influence early signaling steps in the insulin action pathways. Whether lipoic acid can increase glucose uptake in part through an increase in glucose oxidation is not actually established.

Preliminary clinical studies in type 2 diabetic patients noted an acute enhancement of insulin-stimulated glucose disposal after administration of lipoic acid (600 or 1000 mg iv).\textsuperscript{410} Another study noted that treatment of 20 type 2 patients with lipoic acid (500 mg/day, iv) for 10 days increased insulin-stimulated glucose disposal by about 30% during a euglycemic hyperinsulinemic clamp.\textsuperscript{411} However, fasting glucose and insulin concentrations were not significantly altered, leaving unanswered the question of whether lipoic acid could serve as a therapeutic agent to provide a significant improvement of glycemic control in the treatment of patients with type 2 diabetes. Doses used in both diabetic glucose control and treatment of diabetic neuropathy range from 600 to 1800 mg per day without observed adverse effects.\textsuperscript{400}

**Chromium and Glucose Tolerance Factor (GTF)**

Chromium is an essential micronutrient that functions as a cofactor in many insulin regulatory steps.\textsuperscript{435,436} Glucose tolerance factor (GTF) is composed of chromium, nicotinic acid and glutathione (brewer’s yeast).\textsuperscript{435,436} Chromium reduces fasting glucose, postprandial glucose, hemoglobin A1C, C-peptide, fasting insulin, insulin resistance and serum lipids in selected type 2 diabetic patients.
who have abnormal chromium status. Chromium increases insulin binding to cells, increases insulin receptor number, activates the insulin receptor, tyrosine kinase and insulin growth factor-I receptor (IGF-1) by phosphorylation and inhibits phosphotyrosine phosphatase (PTP). The recommended dose is 8 micrograms/kg/day. The detailed mechanism of action is shown in Figure 45. Small doses of niacin, niacinamide and glutathione, NAC and lipoic acid will enhance GTF effects.

Green Tea and Epigallocatechin Gallate (EGCG)

Green tea, epigallocatechin gallate (EGCG), catechins, polyphenols and flavonoids reduce fasting and postprandial glucose, fructosamine, hemoglobin A1C and improve insulin resistance. EGCG protects against cytokine induced beta-cell destruction by inhibition of the inducible NOS (iNOS) gene expression and nuclear factor K-B (NFKB) inhibition. Green tea and EGCG reduce body weight, visceral fat, hepatic fat, leptin and hyperinsulinemia. The antioxidant effects result in increases in Superoxide Dismutase (SOD) and GSH, inhibit lipid peroxidation and promote scavenging of hydroxyl and superoxide ions. The effects on glucose metabolism are mediated by reduction in hepatic glucose production (gluconeogenesis) and increased tyrosine phosphorylation of insulin receptor substrate 1,2 (IRS-1,2), which improves insulin sensitivity. EGCG standardized to 500 mg BID is a recommended dose.

Vanadate

Vanadate is a protein-tyrosine phosphatase inhibitor that reduces glucose, inhibits lipolysis, increases glucose transport and uptake, improves insulin sensitivity, prolongs insulin action, increases intracellular magnesium, stimulates magnesium dependent ATP kinases distal to the insulin receptor kinase, and reduces BP and ED. Vanadate should be administered at oral doses to achieve a serum level of 40 to 80 microgram/L.

Magnesium

Magnesium is a cofactor in all ATP kinase transfer reactions (phosphorylation) and activates tyrosine protein kinases, which increases the phosphorylation of numerous insulin mediated substrates. Low levels of serum and dietary magnesium increase the risk for type 2 DM. Administration of magnesium reduces glucose, improves insulin sensitivity and insulin secretion. Oral doses of magnesium 500 mg BID with 50 to 100 mg of vitamin B6 is the usual recommended dose in patients without renal impairment. Magnesium and magnesium are often used interchangeably in many biochemical reactions.

Co-Enzyme Q-10 (Co-Q-10)

Co-enzyme Q10, a potent antioxidant and cofactor in the mitochondrial electron transport chain involved in ATP production, reduces fasting and postprandial glucose, hemoglobin A1C, insulin levels, BP, ED, microcirculation and improves insulin sensitivity in type 2 DM. At doses of 100 mg BID to achieve a serum level of Co-Q-10 of 3 micrograms/mL, hemoglobin A1C was reduced 0.37 + .17% (p < 0.03).

Vitamin C

Patients with type 2 DM have low intracellular levels of vitamin C. Vitamin C reduces glycosylation of proteins, blocks aldose reductase, reduces sorbitol accumulation, improves ED, but has no direct effect on glucose. A dose of 500 mg to 1000 mg BID is recommended.

Vitamin B6

Vitamin B6 serves as a coenzyme (pyridoxal phosphate) in carbohydrate metabolism, homocysteine metabolism and transamination of amino acids. Deficiencies of B6 will impair gluconeogenesis, induce abnormal glucose intolerance and abnormal amino acid metabolism. Vitamin B6 prevents diabetic neuropathy, improves symptoms and inhibits glycosylation. Many diabetics have reduced serum B6 levels, especially those with diabetic neuropathy. Administration of thiamine and B6 improved symptomatic peripheral neuropathy within four weeks with reduced pain in 88.9%, reduced numbness in 82.5% and reduced paresthesias in 89.7%. Clinical signs of peripheral neuropathy decreased in 48.9% of patients. Vitamin B6 should be administered at 50 to 100 mg BID.

Manganese

Manganese is an important cofactor for numerous glycolytic enzymes. Manganese deficiency can lead to glucose intolerance. Manganese will improve insulin synthesis, insulin sensitivity and serve as an "insulin mimic." Manganese is also part of superoxide dismutase (SOD), which will reduce oxidative stress. The insulin receptor is a hormone-dependent kinase, which is stimulated by manganese and reduces the Km for magnesium ATPase. A functioning intact pancreatic beta cell is necessary for the action of manganese. Manganese has a peripheral effect on glucose entry into cells. The optimal dose is 5 to 10 mg per day.

Selenium

Patients with DM are frequently selenium deficient as noted by reduced selenium concentrations in erythrocytes compared to controls. Selenium is an important antioxidant enzyme for glutathione peroxidase (GPX) that detoxifies free radicals to reduce cellular oxidative stress, serves as an "insulin mimic," reduces FBG, protects against diabetic retinopathy, reduces ROS and lowers the risk of CVD, hypertension and other complications.

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CHD, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489. The recommended daily dose is 200 micrograms per day.

Biotin

Biotin mediates the phosphorylation of glucose (increases glucokinase activity) and may improve glucose tolerance and insulin sensitivity.\textsuperscript{490,491,492,493,494,495,496,497} Administration of 16 mg of biotin per day in type 2 DM reduced FBG by 50\% over seven days.\textsuperscript{490} Biotin may also improve symptoms of diabetic neuropathy.\textsuperscript{496} Other studies using smaller doses of biotin, 6 mg/day, did not demonstrate significant changes in glucose or lipids.\textsuperscript{498}

Folate and Vitamin B12

Folate and vitamin B12 do not appear to have any direct effects on glucose metabolism, but both improve symptoms of diabetic peripheral neuropathy.\textsuperscript{499}

Potassium

Hypokalemia resulting from any cause induces insulin resistance, hyperglycemia and hypertension.\textsuperscript{500,501,502,503,504} Administration of oral or intravenous potassium improves insulin secretion, insulin sensitivity and glucose intolerance.\textsuperscript{500,502,504}

Zinc

Zinc improves insulin binding, insulin sensitivity, increases insulin synthesis, secretion, serum levels and utilization, protects beta cells, reduces glucose and provides potent antioxidant effects via zinc SOD.\textsuperscript{505,506,507} Zinc may also improve diabetic retinopathy.\textsuperscript{508} Oral doses of 30 to 50 mg per day are recommended. Patients with diabetes excrete excessive amounts of zinc and are often zinc deficient.\textsuperscript{506}

Flavonoids

Bioflavonoids may enhance insulin secretion, improve insulin sensitivity, reduce serum glucose and inhibit sorbitol accumulation in the lens of the eye and in nerves in diabetic patients.\textsuperscript{509,510,511,512,513,514,515} Bioflavonoids also increase intracellular vitamin C, which has beneficial effects as previously discussed.\textsuperscript{510}

Omega 3 Fatty Acids

Omega 3 fatty acids activate PPAR gamma and alpha, which improves insulin sensitivity and reduces serum glucose.\textsuperscript{516,517,518,519,520,521} Insulin secretion increases, TG falls, HDL increases, ED improves and BP falls.\textsuperscript{169,516,517,518,519,520,521} The recommended dose is 900 mg of EPA and 600 mg of DHA, but the total daily dose of EPA plus DHA should be below 3 grams.

Gamma Linolenic Acid (GLA)

GLA improves glucose tolerance and insulin resistance, and protects against and improves diabetic neuropathy.\textsuperscript{522,523,524,525,526} In patients with diabetes, there is reduced conversion of LA to GLA due to delta-6-desaturase deficiency. Doses of GLA of 500 to 1000 mg per day are recommended.

Monounsaturated Fats (MUFA)

MUFA activates PPAR gamma, improves glycemic control, inhibits oxidation of LDL, improves the lipid profile and reduces BP.\textsuperscript{169,516} Extra virgin olive oil, four tablespoons per day, or whole olives, 12-16 per day, are recommended.

Carnitine

Carnitine is often depleted in patients with diabetes and its replacement will improve glucose and lipid metabolism, increase glucose disposal and favorably modulate insulin growth factor and insulin growth factor binding proteins (IGF/IGF-BP).\textsuperscript{527,528,529} Doses of one to two grams BID are recommended.

Inositol

Myo-inositol is required for normal nerve function and is often depleted in diabetes mellitus. Administration of oral inositol may improve diabetic neuropathy.\textsuperscript{530}

Niacinamide

Although niacinamide may improve insulin action or sulfonylurea action in type 1 diabetes, there is little long term evidence in RCCT that niacinamide alone improves glucose tolerance in doses considered safe (less than 3 grams/day) in type 2 diabetes or patients with the metabolic syndrome.\textsuperscript{531,532,533,534}

Taurine

Taurine improves glucose tolerance, insulin sensitivity, reduces glycosylation of proteins and hemoglobin, lowers fructosamine levels and decreases the accumulation of AGE’s and improves symptoms of diabetic neuropathy.\textsuperscript{535,536,537,538,539,540} Taurine should be administered at 1.5 to 3 grams BID.

Glutathione

Glutathione is the most potent intracellular antioxidant and decreased levels of reduced glutathione result in insulin resistance, glucose intolerance and increased oxidative stress.\textsuperscript{541,542,543,544,545,546,547,548,549} Alterations in glutathione peroxidase activity may result in similar carbohydrate intolerance, oxidative stress and increase risk of CVD.\textsuperscript{541,542,545} Glutathione administration or increasing glutathione indirectly with lipoic acid (ALA), N-acetyl cysteine (NAC), whey protein, selenium, vitamin C and E will improve insulin sensitivity and glucose metabolism.\textsuperscript{541,542,543,544,545,546,547,548,549}

Pycnogenol

Pycnogenol has been found to lower plasma glucose, HbA1C, improve glutathione levels, reduce oxidative stress, improve ED, and inhibit catalase and xanthine oxidase at doses of 100 mg per day.\textsuperscript{550,551,552,553,554,555}

N-Acetyl Cysteine (NAC)

NAC increases intracellular glutathione, neutralizes aldehydes (which induce insulin resistance and hyperten-
sion), has antioxidant, anti-inflammatory and anti-proliferative effects, improves insulin secretion, reduces insulin resistance, lowers serum glucose, reduces body fat, decreases AGE products and prevents diabetic related cataracts. Doses of NAC at 2 grams per day are recommended.

Copper
Copper deficiency may impair glucose metabolism, increase serum glucose and increase insulin resistance. However, too much copper may induce insulin resistance. The content of fructose relative to copper in the diet may influence insulin resistance and glucose intolerance.

Herbs and Botanicals
Numerous herbs and botanicals have been reported to have a favorable influence on glucose in diabetic subjects (Table 25). The reader is referred to numerous references on this subject, which are beyond the scope of this paper. Only cinnamon will be discussed in detail in this section, as it shows great promise in regulating glucose metabolism.

Cinnamon
Cinnamon has a favorable effect on serum glucose. The mechanisms include activation of glycogen synthase, increased glucose uptake (GLUT-4), inhibition of glycogen synthase kinase, activation of insulin receptor kinase, inhibition of the desphosphorylation of the insulin receptor and its antioxidant effects. In a study of 60 patients with type 2 DM, cinnamon at 1, 3 and 6 grams per day for 40 days reduced FBG 18 to 29%, TG 23 to 30%, LDL-C 7 to 27% and TC 12 to 26%. Various polyphenol type A polymers in cinnamon have insulin-like biological activity.

SUMMARY OF TREATMENT MECHANISMS AND HYPERGLYCEMIA WITH NUTRITIONAL SUPPLEMENTS AND BOTANICALS
The myriad of mechanisms that improve insulin sensitivity and glucose tolerance related to nutritional supplements and botanicals is summarized in Table 26. Combinations of these compounds with different mechanisms of action may have additive or synergistic effects on glucose intolerance in patients with metabolic syndrome or diabetes.

CONCLUSION
The metabolic syndrome is epidemic in the United States. Increasing rates of obesity in children and adults will result in more insulin resistance and all of the associated atherogenic components of the metabolic syndrome such as glucose intolerance, diabetes mellitus, dyslipidemia, hypertension, vascular inflammation, oxidative stress and prothrombotic risk. Complications such as coronary heart disease, myocardial infarction, congestive heart failure, stroke and renal disease will increase in proportion to the incidence, duration and severity of the metabolic syndrome.

Prevention and treatment of the MS with lifestyle modifications, weight reduction, exercise, optimal nutrition, nutraceutical supplements, vitamins, minerals, antioxidants, designer foods and selected herbs and botanicals is recommended. These modalities, supported by an enormous body of scientifically proven studies, can reduce many of the cardiovascular, cerebral and renal complications of the metabolic syndrome, thereby improving the quality of life and potentially increasing the lifespans of MS patients willing to put them into practice. In order to achieve this result, however, medical practitioners must make this body of scientific information available to their patients. As a team, which includes both physician and patient, decisions can then be made as to the feasibility of implementing as many of these treatment options as deemed necessary in order to control and treat the MS, case by case. Once patients are informed and decisions made for treatment, the crucial component of patient compliance will be more readily achieved when he/she is allowed to continue feeling part of a health promoting, health enhancing and health affirming doctor/patient alliance. Following these essential guidelines, which incorporate both mind and body in the healing process, will hopefully one day reduce the metabolic syndrome from an epidemic to an anomaly.
### TABLE 1
Published Criteria for the Diagnosis of the Metabolic Syndrome (Coron Artery Dis 2003; 14:338)

<table>
<thead>
<tr>
<th>Risk Factor Components</th>
<th>WHO</th>
<th>NCEP-ATP III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Current antihypertensive therapy and/or BP &gt; 140 / 90 mm Hg</td>
<td>Current antihypertensive therapy or BP &gt; 130 / 85 mm Hg</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Plasma triglyceride level &gt; 1.7 mmol/L (150 mg/dL and/or HDL-C level &lt; 0.9 mmol/L (35 mg/dL in men, &lt; 1.0 mmol/L (40 mg/dL) in women</td>
<td>Plasma triglyceride level &gt; 150 mg/dL, HDL-C level &lt; 40 mg/dL in men, HDL-C level &lt; 50 mg/dL in women</td>
</tr>
<tr>
<td>Obesity</td>
<td>BMI &gt; 30 kg/m² and/or waist/hip ratio &gt; 0.90 in men, &gt; 0.85 in women</td>
<td>Waist circumference &gt; 40 inches in men and &gt; 35 inches in women</td>
</tr>
<tr>
<td>Glucose</td>
<td>Type II diabetes or IGT</td>
<td>Fasting blood glucose level &gt; 110 mg/dL</td>
</tr>
<tr>
<td>Other</td>
<td>Microalbuminuria (overnight urinary albumin excretion rate &gt; 20 µg/min [30 mg/g Cr])</td>
<td>Any three of the above disorders</td>
</tr>
<tr>
<td>Requirements for Diagnosis</td>
<td>Confirmed type II diabetes, or IGT and any two of the above criteria. If normal glucose tolerance, must demonstrate three of the above criteria</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 2
AACE Clinical Criteria for Diagnosis of the Insulin Resistance Syndrome

<table>
<thead>
<tr>
<th>Risk Factor Components</th>
<th>Cutpoints for Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight / Obesity</td>
<td>BMI ≥ 25 kg / m²</td>
</tr>
<tr>
<td>Elevated Triglycerides</td>
<td>≥ 150 mg / dL (1.69 mmol / L)</td>
</tr>
<tr>
<td>Low HDL Cholesterol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt; 40 mg / dL (1.04 mmol / L)</td>
</tr>
<tr>
<td>Women</td>
<td>&lt; 50 mg / dL (1.29 mmol / L)</td>
</tr>
<tr>
<td>Elevated Blood Pressure</td>
<td>≥ 130 / 85 mm Hg</td>
</tr>
<tr>
<td>2-Hour Postglucose Challenge</td>
<td>&gt; 140 mg / dL</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>Between 110 and 126 mg / dL</td>
</tr>
<tr>
<td>Other Risk Factors</td>
<td>Family history of type II diabetes, hypertension or CVD</td>
</tr>
<tr>
<td></td>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td></td>
<td>Sedentary lifestyle</td>
</tr>
<tr>
<td></td>
<td>Advancing age</td>
</tr>
<tr>
<td></td>
<td>Ethnic groups having high risk for type II diabetes or CVD</td>
</tr>
</tbody>
</table>

No defined number of risk factors is specified; diagnosis is left to clinical judgement.
TABLE 3
EXPANDED DEFINITION - METABOLIC SYNDROME

Major Criteria
1. Fasting glucose over 110 mg% or hemoglobin A1C over 6.5, 2 hour PPG > 140 mg%, elevated fasting C-peptide
2. Abdominal obesity (visceral)
   - Men over 40 inches (102 cm) waist circumference (WC)
   - Women over 35 inches (88 cm) waist circumference (WC)
   - Waist Hip Ratio (WHR) over 0.85 in women
   - Waist Hip Ratio (WHR) over 0.90 in men
   - BMI over 30 kg/m²
   - Body fat over 29% in men (normal is < 16%)
   - Body fat over 37% in women (normal is < 22%)
3. Dyslipidemia (atherogenic)
   - TG over 150 mg% (large VLDL) (optimal is < 75 mg%)
   - HDL less than 40 mg% in men and 50 mg% in women (small HDL) (optimal is ≥ 85 mg%)
   - TG/HDL ratio > 3.0
   - Small dense type B LDL with increased LDL particle number exceeding 1100 (Nuclear Magnetic Resonance [NMR] analysis)
   - Elevated Lipoprotein(a) [LP(a)]
4. Hypertension: with BP over 135/85 mm Hg (24 hour ambulatory blood pressure monitor [ABM] with BP load, mean, circadian cycle and nocturnal dipping) (optimal BP 110/70 mm Hg)
5. Microalbuminuria over 30 mg in 24 hours or over 20 ug/minute or albumin creatinine ratio (ACR) over 30 mg/gram
6. Prothrombotic state (plasminogen activator inhibitor [PAI-1], increased platelet activation and aggregation, elevated fibrinogen, von Willebrand factor, Factor VII, thrombin)
7. Insulin resistance and hyperinsulinemia (fasting insulin [FI], proinsulin, C-peptide, OGTT, 2 hour PPG)
8. Pro-inflammatory state (HS-CRP, fibrinogen, interleukin-6 [IL-6], interleukin-1B [IL-1B], tumor necrosis factor-alpha [TNF-alpha], leukocytosis)

Minor Criteria
1. Endothelial dysfunction (indirect assessment by computerized arterial pulse wave analysis (CAPWA)
2. Abnormal arterial compliance: especially small resistance arteries, low C2 compliance and increased PWV (pulse wave velocity) (assessed by CAPWA)
3. Left ventricular hypertrophy (LVH) and diastolic dysfunction (2D-echo)
4. Hyperuricemia
5. Increased vascular oxidative stress (urinary isoprostanes, etc.)
6. Homocysteine over 9 ug/L (ideal is < 5 ug/L)
7. Objective evidence of accelerated atherogenesis for aged matched gender, ethnicity and age (EBT, carotid IMT ultrasound, CVA, TIA, CAD, PAD, ABI, etc.)

This is a continuum of risk starting at BP of 115/75 mm Hg, FBS of 75 mg%, LDL of 60 mg%, TG of 75 mg%, declining HDL from 85 mg% and homocysteine of 5 ug/L.

Definition for Confirmed Diagnosis
1. Three major criteria  OR
2. Two major criteria plus two minor criteria
### TABLE 4
**METABOLIC SYNDROME: A PROGRESSIVE DISORDER**

<table>
<thead>
<tr>
<th>Insulin Resistance</th>
<th>childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>15 – 35 years of age</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35 – 50 years of age</td>
</tr>
<tr>
<td>Impaired Fasting Glucose</td>
<td>40 – 55 years of age</td>
</tr>
<tr>
<td>Diabetes</td>
<td>&gt; 55 years of age</td>
</tr>
</tbody>
</table>

### TABLE 5
**MAJOR CRITICAL MEDIATORS OF ENDOTHELIAL BALANCE**

**NITRIC OXIDE**
- Anti-hypertensive
- Anti-inflammatory
- Anti-growth
- Anti-thrombotic
- Anti-oxidant
- Anti-atherosclerotic

**ANGIOTENSIN II**
- Hypertensive
- Inflammatory
- Growth Promotion (TGF-B)
- Thrombogenic
- Oxidative (NADPH oxidase)
- Atherosclerotic
TABLE 6

INSULIN IS ANTI-INFLAMMATORY AND ANTI-ATHEROSCLEROTIC HORMONE

Mechanisms of Action for these Effects
1. Suppress NFkB binding
2. Increases inhibitor KB (IKB)
3. Suppress ICAM-1 in endothelial cells
4. Suppress MCP-1 in endothelial cells
5. Suppress ROS generation
6. Suppress p47 phox subunit of NADPH oxidase (O₂⁻)
7. Suppress AP-1
8. Suppress early growth response-1 (EGR-1)
9. Reduce MMP’s
10. Reduce TF
11. Reduce PAI-1
12. Suppress TNF-alpha
13. Suppress MIF (adipocytes)
14. Induce eNOS/NO
15. Anti-platelet via NO-cGMP pathway
16. Anti-apoptotic in acute MI reduces myocardial necrosis
17. Reduces HS-CRP
18. Reduces serum amyloid A
19. Suppress macrophage cholesterol synthesis and content
20. Reduce macrophage lipid peroxide content and ROS generation

TABLE 7

IMPAIRED MITOCHONDRIAL ACTIVITY IN THE INSULIN-RESISTANT OFFSPRING OF PATIENTS WITH TYPE II DIABETES

- 80% increase in intramyocellular lipid content of skeletal muscle in IR subjects (also in liver)
- 30% reduction in mitochondrial ATP production in IR subjects (and smaller and fewer mitochondria)
- Low ratio Type I/Type II fibers (Type I = oxidative; Type II = glycolytic)
- Reduced number of mitochondria and reduced mitochondrial oxidative phosphorylation
- Mitochondria are smaller (55% of their normal size)
### Table 8

**CRP Is an Atherosclerotic/Inflammatory Biomarker and Mediator**

*(Circulation 2003; 108:1917)*

- Reduces eNOS transcription, destabilizes eNOS mRNA in EC with reduced basal and stimulated NO with ED
- Stimulates ET-1 release
- Stimulates IL-6 release
- Upregulates CAM’s (ICAM, VCAMS) and leukocyte adhesion
- Upregulates selectins
- Stimulates MCP-1 with increased transmigration
- Increase macrophage LDL uptake via scavenger receptors (SR-A, CD36, LOX-1)
- Increase EC apoptosis
- Inhibits angiogenesis
- Upregulates nuclear factor KB and transcription factors for pro-atherosclerotic genes
- Inhibits BM derived EPC’s survival and differentiation
- Upregulates AT1R
- Stimulates VSMC migration, proliferation and neointimal formation
- Stimulates ROS production
- Increased restenosis rate
- Increase plaque rupture and increase MMP’s
- Increase PAI-1 → thrombosis
- Complement activation

### Table 9

**Adipose Tissue (AT) and Insulin Resistance**

- **Hormones and mediators of “AT”:**
  - TNF-α, MCP-1, MIP-1α, C3, CRP, PGE-2, CSF-1
  - IL-6, IL-1B
  - PAI-1, Tissue Factor and Factor VII
  - A-II
  - Leptin
  - Acylation Stimulating Protein (ASP)
  - Adiponectin
  - Resistin (inhibited by PPAR agonists)
  - Angiotensinogen and Angiotensin (→ A-I → A-II) (HBP)
  - FFA
  - iNOS
  - CAM’s
**TABLE 10**
*(Current Opinion in Lipidology 2002; 13:51-59)*

**Leptin**
- CNS action inhibits food intake and activates thermogenesis (in conjunction with insulin) (Phosphatidylinositol 3-kinase)
- Levels proportional to body adiposity and recent energy uptake
- Glycogenolysis, TCA cycle, etc. increases insulin and leptin secretion
- Reduction of leptin my macronutrients in order of effect:
  - Fat: 40 - 60%
  - Fructose: 30%
  - Glucose: < 5%
- Increase in leptin
  - Weight loss (variable and anorexia)
  - Improve IRS (increase insulin sensitivity)
  - Improve dyslipidemia
  - Insulin
- Reduce leptin
  - Catecholamines
  - TZD’s
- Obese patients = leptin resistance with hyperleptinemia

**Adiponectin**
- Decrease in obesity (visceral > SC), Type 2 diabetes mellitus, high insulin levels and insulin resistance and CHD
- Inhibit atherosclerosis (↓ CAMS, ↓ TNF stimulation NFκB, ↓ SRA macrophages, ↓ VSMH)
- Increase HDL, lower TG and FFA (FAOX)
- Promotes weight loss
- Lowers glucose (hepatic) (HGP)
- Increased by PPAR gamma agonists and calcium ionophoreses
- Improves insulin sensitivity
- Reduced by:
  - Catecholamines
  - Glucocorticoids
  - TNF-α
  - CAMP
  - β-agonists
  - Activators of adenylyl cyclase
- Down-regulates macrophage SRA

**Acylating Stimulating Protein (ASP)**
- Produced by adipocytes after interaction with:
  - C3
  - Factor B
  - Adipin (Factor D)
- ASP: promotes storage of energy as fat
  - Efficient triacylglycerol synthesis (paracrine/autochone)
  - Stimulates adipocyte glucose uptake
  - Activate DGAT (diacylglycerol transferase)
  - Inhibit hormone sensitive lipase (HSL)
  - Increased after meals
  - Increased in obese humans
  - Increased after sulfonylureas
  - Increased by insulin
  - Increased by circulating lipids and chylomicrons, VLDL
  - Increased by nitric acid
TABLE 11
PATHOPHYSIOLOGY OF TYPE 2 DIABETES
INSULIN RESISTANCE

- Insulin receptor (IR) defect with reduced insulin binding to IR
- Signal transduction defect
- Post-receptor defect
- Inadequate glucose transport into skeletal muscle and adipose tissue
- Mitochondrial dysfunction (PGC-1 polymorphism), abnormal oxidative phosphorylation, et al.
- Oxidation of FA
- Inadequate suppression of hepatic gluconeogenesis
- Variable phenotypes (visceral obesity)
- Tissue dependent with variable signaling pathway
- Role of PPAR’s

TABLE 12
PATHOPHYSIOLOGY OF TYPE 2 DIABETES
PANCREATIC BETA CELL DYSFUNCTION

- Loss of glucose sensing
- Impaired glucose stimulated insulin secretion (GSIS)
- Increased basal insulin secretion
- Decreased islet insulin content
- Altered gene transcription
- Changes in intracellular signaling intermediates
- Loss of beta cell mass
- Activation of UCP-2-mediated mitochondrial proton leak with reduction of ATP from glucose
  (superoxide anion [O2•−], hyperglycemia, Hyperlipidemia activate UCP-2) (Also in thymus cells)
- Mitochondrial dysfunction (PGC-1)
- Oxidative stress/ROS: FFA ↑ ROS in beta cells

TABLE 13
RISK OF METABOLIC SYNDROME,
BMI AND BODY FAT

*(Arch Intern Med 2003; 163:427)*
*(Am J Clin Nutr 2003; 78:228)*

<table>
<thead>
<tr>
<th>% Body Fat</th>
<th>Prevalence of Metabolic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5 – 24.9</td>
<td>4.8%</td>
</tr>
<tr>
<td>25 – 29.9</td>
<td>22.8%</td>
</tr>
<tr>
<td>30 – 34.9</td>
<td>60.2%</td>
</tr>
<tr>
<td>&gt; 35</td>
<td>&gt; 90%</td>
</tr>
</tbody>
</table>
### TABLE 14
Thresholds of Percentage Body Fat (% BF) Corresponding to Established BMI Cutoffs

<table>
<thead>
<tr>
<th>% BF and Corresponding Percentiles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td><strong>Women</strong></td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td><strong>BMI cutoffs (kg/m^2)</strong></td>
</tr>
<tr>
<td>Cutoff</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>18.5</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>35</td>
</tr>
</tbody>
</table>

### TABLE 15
MECHANISMS OF INSULIN RESISTANCE, OBESITY AND HYPERTENSION

1. Impaired insulin-mediated vasodilation
2. Abnormal endothelial signaling via NO dependent pathways
3. Increase SNS activity by insulin → ↑SVR
4. Sodium retention (renal tubules) → ↑IV volume
5. Increased growth factors production and activation leading to vascular SM proliferation
6. Increased rates of intimal expansion
7. Reduced arterial compliance and elasticity (PDGF)
8. Oxidative stress (↑ROS)
9. Stimulation of AT1R and ET receptors
10. Activation RAAS with increased A-II and aldosterone
11. Intra-renal compression by adipose tissue (mechanical)
12. Sleep apnea (OSA)
13. Reduced eNOS and NO
14. Altered vascular wall sodium/potassium ratio → ↑SVR
15. Hyperglycemia → AGE's → RAGE + AT1R + ET1R
16. LDL → dense oxLDL → AT1R
17. Adipokines and inflammatory mediators
18. Hyperleptinemia → ↑SVR
19. Generalized ED
20. Impaired baroreflexes
**TABLE 16**

**METABOLIC MARKERS OF METABOLIC SYNDROME**
**TG/HDL RATIO AND INSULIN RESISTANCE**
*(Ann Intern Med 2003; 139:802)*

<table>
<thead>
<tr>
<th>Metabolic Marker</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG ≥ 130 mg/dl</td>
<td>67%</td>
<td>64%</td>
</tr>
<tr>
<td>TG/HDL ratio ≥ 3.0</td>
<td>71%</td>
<td>68%</td>
</tr>
<tr>
<td>Fasting insulin ≥ 109 pmol/L</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>ATP III Criteria</td>
<td>52%</td>
<td>85%</td>
</tr>
</tbody>
</table>

---

**TABLE 17**

**Randomized Clinical Trials with Lifestyle Interventions to Prevent Type II Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th># Subjects</th>
<th>Mean duration of follow up (yrs)</th>
<th>Incidence of Diabetes (per 100 person-years)</th>
<th>Relative Risk Reduction</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finnish Diabetes Prevention Study (DPS)</td>
<td>Intensive Lifestyle Modification</td>
<td>265</td>
<td>3.2</td>
<td>3.2</td>
<td>-58%</td>
<td>22 over 1 year 5 over 5 years</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>257</td>
<td>7.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Prevention Program (DPP)</td>
<td>Lifestyle Modifications</td>
<td>1079</td>
<td>4.8</td>
<td></td>
<td>-58%</td>
<td>16 over 1 year 7 over 3 years</td>
</tr>
<tr>
<td></td>
<td>Metformin 850mg BID</td>
<td>1073</td>
<td>2.8</td>
<td>7.8</td>
<td>-31%</td>
<td>31 over 1 year 14 over 3 years</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1082</td>
<td>11</td>
<td></td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>TRIPOD</td>
<td>Troglitazone</td>
<td>133</td>
<td>2.6</td>
<td></td>
<td>-50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>133</td>
<td>2.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

50% Compliance in all studies with all suggested lifestyle modalities
**TABLE 18**

**NUTRITIONAL AND DIETARY INTERVENTIONS FOR HYPERGLYCEMIA, HYPERTENSION, METABOLIC SYNDROME, DIABETES MELLITUS AND IR**

- **Fat (30%)**
  - Total fat not important, but type of fat is
  - MUFA increase
  - PUFA increase
  - Omega 3 FA increase
  - SFA decrease
  - TFA decrease
  - Cholesterol decrease
  - Nuts and peanut butter: increase

- **Carbohydrates (40%)**
  - Low GI and GL (50 grams/d)
  - Fiber: soluble and insoluble (50 grams/d) (guar gum, pectin, oat bran)
  - Complex CHO: increase
  - Refined CHO: decrease (↓ BS, lipids, weight)
  - Whole grains: increase
  - 8 – 10 servings fruits and vegetables per day

- **Protein (30%) (0.8 – 1.8 gm/kg/d)**
  - HBV – lean with low SFA
  - Fish, wild game
  - Vegetable (soy)
  - Whey
  - Less conversion of AA to glucose vs. CHO ingestion

- **Total Calories**: Reduce and adjust to total energy expenditure to decrease weight, BMI, WC, % fat, WHR and increase LMM (maintain weight – wt [lb] x 10 = calories)

- **Low Glycemic Index (GI) and Glycemic Load (GL) Foods**: Reduce “glucose toxicity” to pancreatic beta cells, preserve and improve beta cell function, ↓ PPG, improve insulin sensitivity, lipids, fibrinolysis, oxidative stress

- Combined protein and fat to CHO foods reduces rapid glucose absorption and postprandial hyperglycemia

- Reduce glucose ratio to lactose, sucrose, fructose

- Increase soluble and nonsoluble fiber (gastric emptying delayed, ↑ satiety, ↓ rate of absorption and digestion of glucose, ↓ lipids)

- Avoid soft, overcooked, highly processed or over-ripened food textures (rapid digestion, ↓ structural integrity)
### TABLE 19\textsuperscript{169}

**LIFESTYLE CHANGES AND SBP META-ANALYSIS OF CLINICAL DIET TRIALS**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Reduction in SBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \uparrow \text{Mg}^{++} )</td>
<td>0-1</td>
</tr>
<tr>
<td>( \downarrow \text{Mg}^{++} )</td>
<td>2</td>
</tr>
<tr>
<td>( \downarrow \text{K}^{+} )</td>
<td>4</td>
</tr>
<tr>
<td>( \downarrow \text{ETOH} )</td>
<td>4</td>
</tr>
<tr>
<td>Fish Oil</td>
<td>6</td>
</tr>
<tr>
<td>( \downarrow \text{Na}^{+} )</td>
<td>6</td>
</tr>
<tr>
<td>( \downarrow \text{Weight} )</td>
<td>8</td>
</tr>
<tr>
<td>Exercise</td>
<td>10</td>
</tr>
<tr>
<td>DASH Diet</td>
<td>12</td>
</tr>
</tbody>
</table>

### TABLE 20\textsuperscript{169}

**NATURAL ANTIHYPERTENSIVE COMPOUNDS CATEGORIZED BY ANTIHYPERTENSIVE CLASS**

**Diuretics**
1. Hawthorne Berry
2. Vitamin B-6 (Pyridoxine)
3. Taurine
4. Celery
5. GLA
6. Vitamin C (Ascorbic Acid)
7. \( K^{+} \)
8. \( Mg^{++} \)
9. \( Ca^{++} \)
10. Protein
11. Fiber
12. Coenzyme Q-10

**Central Alpha Agonists (CCA)**
1. Taurine
2. \( K^{+} \)
3. Zinc
4. \( Na^{+} \) Restriction
5. Protein
6. Fiber
7. Vitamin C
8. Vitamin B-6
9. Coenzyme Q-10
10. Celery
11. GLA/DGLA
12. Garlic

**Direct Vasodilators**
1. Omega-3 FA
2. MUFA (Omega-9 FA)
3. \( K^{+} \)
4. \( Mg^{++} \)
5. \( Ca^{++} \)
6. Soy
7. Fiber
8. Garlic
9. Flavonoids
10. Vitamin C
11. Vitamin E
12. Coenzyme Q-10
13. L-Arginine
14. Taurine
15. Celery
16. ALA
### Calcium Channel Blockers (CCB)
1. Alpha Lipoic Acid (ALA)
2. Vitamin C (Ascorbic Acid)
3. Vitamin B-6 (Pyridoxine)
4. Magnesium (Mg++)
5. N-Acetyl Cysteine (NAC)
6. Vitamin E
7. Hawthorne Berry
8. Celery
9. Omega-3 Fatty Acids (EPA and DHA)
10. Calcium

### Angiotensin Converting Enzyme Inhibitors (ACEI)
1. Garlic
2. Seaweed – various (Wakame, etc.)
3. Tuna protein/muscle
4. Sardine protein/muscle
5. Hawthorne Berry
6. Bonito Fish (dried)
7. Pycnogenol
8. Casein
9. Hydrolyzed Whey Protein
10. Sour Milk
11. Geletin
12. Sake
13. Essential Fatty Acids (Omega-3 FA)
14. Chicken Egg Yolks
15. Zein
16. Dried Salted Fish
17. Fish Sauce
18. Zinc
19. Hydrolyzed Wheat Germ Isolate

### Angiotensin Receptor Blockers (ARB’s)
1. Potassium (K+)
2. Fiber
3. Garlic
4. Vitamin C
5. Vitamin B-6 (Pyridoxine)
6. Co-Enzyme Q-10
7. Celery
8. Gamma Linolenic Acid (GLA) and DGLA
### TABLE 21

**FOODS, NUTRIENTS, NUTRACEUTICAL SUPPLEMENTS AND HERBALS THAT HAVE BEEN DEMONSTRATED TO FAVORABLY INFLUENCE SERUM LIPID PROFILE**

#### Nutrition: Foods and “Designer Foods”
- Policosanol (*Saccharum Officinarum*)
- Red Yeast Rice (*Monascus Purpureus*)
- Plant Sterols
- Soluble Fibers: Psyllium, Guar Gum, B-Glucan
- Soy
- Omega 3 Fatty Acids (PUFA)
- Flax
- Green Tea (EGCG)
- Nuts: Walnuts, Almonds, Macadamia, Peanuts
- Grape Products
- Wine and Alcohol
- Citrus: Orange, Grapefruit, Pomegranate
- Barley
- Blueberries
- Coriander Seeds
- Blue Green Algae
- Corn Husk Oil
- Esterin Alfalfa
- MUFA

#### Nutraceuticals, Vitamins, Antioxidants, Minerals
- Tocotrienols: Gamma and Delta
- Niacin and Inositol Hexanicotinate (IHN)
- Pantethine (Pantothenic Acid)
- Vitamin C
- Co-Enzyme Q-10
- Chromium
- Probiotics and Prebiotics
- Isoflavonoids and Flavonoids
- Carotenoids

#### Herbals
- Choleretics
  - Silymarin (Milk Thistle) ⊕
  - Globe Artichoke ⊕ (↓ TC 18.5%)
  - Dandelion Root, Black Radish Root, Beet Leaf Tops
- Garlic ⊕
- Ginkgo Biloba ⊙
- Fenujseek ⊙
- Ginseng ⊙
- Yam Extract ⊕ (↑ HDL)
- Guggulipid ⊕
TABLE 22
ANTI-ATHEROSCLEROTIC MECHANISMS OF ACTION OF NUTRITIONAL SUPPLEMENTS

Anti-Lipid Effects
- Reduce TG, LDL, VLDL, TC, Lp(a)
- Increase HDL
- Alter particle size (LDL, VLDL, HDL)
- Alter particle number (LDL0
- Alter apolipoprotein concentration
- Reduce oxLDL

Non-Lipid: Pleiotrophic Effects
- Reduce inflammatory markers: HS CRP, ICAM, VCAM
- Reduce inflammatory cytokines: TNF-α, IL
- Increase eNOS/NO
- Improve ED, FMD
- Anti-thrombotic
- Anti-proliferative/growth
- Anti-oxidant
- Anti-hypertensive

TABLE 23
EARLY PLACEBO-CONTROLLED SECONDARY PREVENTION TRIALS WITH NIACIN

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy</th>
<th>Lipid Changes</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Drug Project (CDP)</td>
<td></td>
<td>Total Cholesterol (TC)</td>
<td>27% ↓ in recurrent nonfatal myocardial infarction</td>
</tr>
<tr>
<td>6 year duration</td>
<td></td>
<td>Triglycerides (TG)</td>
<td>13% ↓ in coronary disease mortality</td>
</tr>
<tr>
<td>Postmyocardial Infarction Men</td>
<td>Daily Dose</td>
<td>10% ↓ TC</td>
<td>26% ↓ in cerebrovascular events</td>
</tr>
<tr>
<td></td>
<td>Niacin 1g TID</td>
<td>25% ↓ TG</td>
<td>10.6% ↓ in all cause mortality relative risk ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stockholm Ischemic Heart Disease Study</td>
<td>Niacin 1 g TID</td>
<td>13% ↓ TC</td>
<td>36% reduction in coronary disease mortality</td>
</tr>
<tr>
<td>5 year duration</td>
<td>Clofibrate 1 g BID</td>
<td>19% ↓ TG</td>
<td>26% reduction in all cause mortality (p &lt; 0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol-Lowering Atherosclerosis</td>
<td>Niacin 3 – 12 g</td>
<td>43% ↓ LDL-C</td>
<td>25% reduction within 2 years</td>
</tr>
<tr>
<td>Study Class I (2 years)</td>
<td>Colestipol 30 g</td>
<td>37% ↑ HDL-C</td>
<td>42% reduction within 4 years in cardiovascular events slowed progress</td>
</tr>
<tr>
<td>Non-smoking post coronary bypass men</td>
<td></td>
<td></td>
<td>and detectable atheroma regression in native coronary arteries and bypass grafts by angiography</td>
</tr>
</tbody>
</table>
TABLE 24

CLINICAL TRIALS WITH Omega-3 POLYUNSATURATED FATTY ACIDS*

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>End Points</th>
<th>IER, %</th>
<th>CER, %</th>
<th>ARR, %</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet and Reinfarction Trial</td>
<td>Randomized controlled,</td>
<td>Fish meal twice weekly or fish oil</td>
<td>Total mortality</td>
<td>9.3</td>
<td>12.8</td>
<td>3.5</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>2,033 men after MI, 24-month</td>
<td>(1500 mg/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lyon Diet Heart Study</td>
<td>Randomized controlled,</td>
<td>ALA-enriched spread</td>
<td>CHD death and nonfatal MI</td>
<td>1.32</td>
<td>5.5</td>
<td>4.3</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>605 patients after MI, 27-month follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indian Experiment of Infarct Survival</td>
<td>Randomized controlled,</td>
<td>Fish oil (EPA, 1 g/d) or mustard seed oil (ALA, 2.9 g/d)</td>
<td>CHD death and nonfatal MI</td>
<td>24.5</td>
<td>34.7</td>
<td>10.2</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td>360 patients after MI, 12-month follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GISSI-Prevenzione Trial</td>
<td>Randomized controlled,</td>
<td>Fish oil (EPA + DHA, 850 mg/d)</td>
<td>CHD death and nonfatal MI</td>
<td>6.9</td>
<td>9.2</td>
<td>2.3</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>11,324 patients after MI, 42-month follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*IER indicates intervention event rate; CER, control event rate; ARR, absolute risk reduction; NNT, number needed to treat to prevent 1 cardiovascular event; MI, myocardial infarction; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CHD, coronary heart disease; and ALA, alpha-linolenic acid.

TABLE 25

HYPERGLYCEMIA TREATMENT SUMMARY

Nutritional Supplements
- Vitamin E derivatives
- Alpha Lipoic Acid
- Chromium and GTF
- Green Tea (EGCG)
- Vanadate
- Magnesium
- Co-Enzyme Q-10
- Vitamin C
- Vitamin B6
- Manganese
- Selenium
- Biotin
- Folate and Vitamin B12
- Potassium
- Zinc
TABLE 25 CONTINUED

- Flavonoids
- Omega 3-FA
- GLA
- MUFA (Oleic Acid)
- Carnitine
- Inositol
- Niacin and Niacinamide
- Taurine
- Glutathione
- Pycnogenol
- NAC
- Copper

**Herbals**
- Onion (Allium Cepa)
- Garlic (Allium Sativum)
- Bitter Melon (Momordica Charantia) (Balsam Pear)
- Gymnema Sylvestre
- Fenugreek (Trigonella Foenumgraecum)
- Salt Bush (Atriplex Halimu)
- Bilberry (Vaccinium Myrtillus)
- Ginkgo Biloba
- Ginseng
- Aloe Vera
- Goat’s Rue (Galega Officinalis)
- Madagascar Periwinkle (Catharanthus Roseus)
- Jambol (Syzygium Jambolanum)
- Reishi Mushrooms (Ganoderma Lucidum)
- Maitake Mushrooms (Grifola Frondosa)
- Cordyceps (Cordyceps Sinensis)
- Nopal Cactus (Opuntia Fuliginosa)
- Spices: Nutmeg – Allspice – Cloves - Bay Leaf - Cinnamon (Methylhydroxychalone Polymer) - Turmeric
- Aegle Marmelos Fruit (Bael Tree)
- Proteinase Inhibitor Extract of Potatoes – P12 (CCK)
- Agrimony Eupatoria (Agrimony)
- Avocado (Persea Americana)
- Other
TABLE 26
SUMMARY OF TREATMENT MECHANISMS
AND HYPERGLYCEMIA WITH NUTRITIONAL SUPPLEMENTS AND BOTANICALS

1. Improves insulin sensitivity
   • Alpha Lipoic Acid
   • Chromium (GTF)
   • Green Tea (EGCG)
   • Vanadate
   • Magnesium
   • Niacinamide
   • Biotin
   • Vitamin E
   • Potassium
   • Manganese
   • Omega 3-FA
   • Ginseng
   • Zinc
   • Taurine
   • NAC
   • Cinnamon

2. Increases insulin production or protects beta cell
   • Green Tea (EGCG)
   • Niacinamide
   • Potassium
   • Zinc
   • Flavonoids
   • Omega 3-FA
   • Onion and Garlic (increase free insulin)
   • Bitter Melon (mimetic also)
   • Gymnema Sylvestre
   • Ginseng
   • Selenium
   • Magnesium
   • Manganese
   • Various Spices

Improves glucose utilization and metabolism
   • Alpha Lipoic Acid
   • Green Tea (EGCG)
   • Vanadate
   • Biotin
   • Magnesium
   • Manganese
   • Cinnamon

3. Antioxidant, reduces oxidative stress and ROS
   • Alpha Lipoic Acid
   • Tocopherols (Alpha)
   • Green Tea (EGCG)
   • Niacinamide
   • Vitamin C
TABLE 26 CONTINUED

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4.</td>
<td>Reduces glycosylation (AGE’s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Alpha Lipoic Acid</td>
<td>• Tocopherols</td>
<td>• Vitamin C</td>
<td>• Vitamin B6</td>
</tr>
<tr>
<td></td>
<td>• Taurine</td>
<td>• Gymnema Sylvestre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Inhibits inflammatory vascular disease, ED and AS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Vitamin E</td>
<td>• Flavonoids</td>
<td>• Niacinamide</td>
<td>• Vitamin C</td>
</tr>
<tr>
<td></td>
<td>• Omega 3-FA</td>
<td>• Lipoic Acid</td>
<td>• NAC</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Reduce sorbitol accumulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Vitamin C</td>
<td>• Flavonoids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Diabetic neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Vitamin B6</td>
<td>• Vitamin B12</td>
<td>• GLA</td>
<td>• Inositol</td>
</tr>
<tr>
<td></td>
<td>• Biotin</td>
<td>• Taurine</td>
<td>• Alpha Lipoic Acid</td>
<td>• Thiamine</td>
</tr>
<tr>
<td>8.</td>
<td>Diabetic retinopathy and eye disease, cataracts, MD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bilberry</td>
<td>• Ginkgo</td>
<td>• Vitamin C</td>
<td>• Pycnogenol</td>
</tr>
<tr>
<td>9.</td>
<td>Reduce carbohydrate absorption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Fiber</td>
<td>• Ginseng</td>
<td>• Fenugreek</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>Angiogenesis inhibitors (reduce adipocytes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Catechins in Green Tea</td>
<td>• Isoflavones on Soybeans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Activate PPAR’s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Omega 3-FA (PUFA): PPAR gamma and alpha</td>
<td>• MUFA (oleic): PPAR gamma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Inhibit NFkB and inflammatory, proliferative, growth mediators</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• NAC</td>
<td>• Alpha Lipoic Acid</td>
<td>• Omega 3-FA (PUFA)</td>
<td>• MUFA</td>
</tr>
</tbody>
</table>
FIGURE 1
Prevalence of Metabolic Syndrome
NHANES III Data Using NCEP ATP III Criteria

% of Population

- Age-Adjusted Prevalence
  - 60-69 yr
  - 70+ yr
  - Men
  - Women
  - Mexican Americans
  - Whites
  - African Americans
  - Other Ethnic Groups

22% (47 million) U.S. Adults have Metabolic Syndrome

JAMA 2002; 287:356

FIGURE 2
Metabolic Syndrome
Unadjusted Kaplan-Meier Hazard Curves for CHD Mortality

Coronary Heart Disease Mortality

RR (95% CI), 3.77 (1.74-8.17)

No. at risk

Metabolic Syndrome

Yes 866 852 834 292

No 288 279 234 100

JAMA 2002; 288:2714
FIGURE 3
Metabolic Syndrome
Unadjusted Kaplan-Meier Hazard Curves for CVD Mortality

Cardiovascular Disease Mortality

<table>
<thead>
<tr>
<th>Follow-up, years</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (95% CI)</td>
<td>3.55 (1.96-6.43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cumulative Hazard, %

JAMA 2002; 288: 2714

FIGURE 4
Metabolic Syndrome
Unadjusted Kaplan-Meier Hazard Curves for All-Cause Mortality

All-Cause Mortality

<table>
<thead>
<tr>
<th>Follow-up years</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (95% CI)</td>
<td>2.43 (1.64-3.61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cumulative Hazard, %

JAMA 2002; 288: 2714
FIGURE 5
Recognition and Assessment of Insulin Resistance and the Metabolic Syndrome

Insulin Sensitivity
Insulin Secretion
Associated risk factors
Hypertension
Dyslipidemia
Atherogenesis
Microvascular complications
Fasting blood glucose

Age (yrs)  Type 2 diabetes

euglycemia  impaired fasting glucose  diabetes

FIGURE 6
Vascular Endothelium: Strategic Anatomical Position

Modulates

CIRCULATING BLOOD
◆ Platelet Function
◆ Coagulation
◆ Monocyte and Leukocyte Adhesion
◆ Inflammation

Modulates

ENDOTHELIUM  Strategic Location
◆ Permeability
◆ Contractile State
◆ Proliferative Response (Growth)
◆ Migratory Response
◆ Redox State

VASCULAR SMOOTH MUSCLE CELLS (VSMC)

Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston, MD
FIGURE 7
The Endothelium Maintains Vascular Health

Dilatation
Growth Inhibition
Antithrombotic
Anti-inflammatory
Antioxidant

Constriction
Growth promotion
Prothrombotic
Proinflammatory
Pro-oxidant

FIGURE 8
Endothelium-Dependent Responses
(not present in all blood vessels)

Short term regulation
Long term regulation

Blood

ET ACh VP P 5-HT α T Bk

Blood

AT-II VP T

Endothelium

EDHF

EDHF

K+

EDHF

hyperpolarization

Relaxation

Smooth muscle cells

Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston, MD
FIGURE 9
Two Paradigms of Endothelial Activation: Biochemical and Biomechanical

Activation or dysfunction = Phenotypic Modulation of Structure and Function of Resting Endothelial Cell

The term endothelial activation is used to connote the modulation of endothelial functional phenotype, in response to physiologic and pathophysiologic stimuli, which can have both adaptive and nonadaptive consequences. By virtue of its position at the interface between flowing blood and tissues, endothelium is exposed to a vast array of both biochemical and biomechanical stimuli that can induce endothelial activation. The biochemical stimuli (hormones, growth factors, cytokines and bacterial products) can be delivered via the blood and also in an autocrine (acting on the cell of origin) or paracrine (acting on adjacent cells) manner. The biomechanical stimuli consist of wall shear stresses (tractive forces generated at the luminal endothelial interface by blood flow), pressures (hydrostatic forces that act perpendicular to the endothelial interface), and cyclic strains (circular stretching of endothelium and other cells within the vessel wall, as a consequence of pulsatile blood flow).

FIGURE 10
Insulin Signaling

Insulin Receptor → Insulin → Alpha subunits → IRS 1/2 → PI3-K → PI3, 4, 5P3 → Akt → GLUT 4

Autophosphorylation of IR
Tyrosine Residues
IR Kinase Activity
Phosphorylation of Insulin Receptor Substrates
GLUT 4 Translocation

IRS = Variable deficiencies in intracellular signaling pathways

IRS = Variable deficiencies in intracellular signaling pathways

IRs = Insulin receptor substrates
PI3-K = phosphoinositide-3-kinase
PK = Protein kinases
ERK = Extracellular signal-regulated kinases
GLUT 4 = Glucose transporter 4

J Nutr 2001; 131: 2782S-86S
FIGURE 11

INSULIN

In normal states
- Vasodilator
- Anti-atherogenic through increased NO synthesis / release
- Decreased stiffness of large arteries acutely

In the insulin resistance syndrome
- Attenuated vasodilation
- Increased vascular smooth muscle cell growth
- Associated with increased arterial thickness and stiffness in whites and Hispanics

FIGURE 12

Stimulation of the MAPK Pathway in Endothelial and VSM Cells$^{61}$

Insulin

Insulin Receptor

MAPK

- Cell Growth
- Cell Movement
- $\uparrow$ PAI -1
- $\uparrow$ ICAM -1
- $\uparrow$ MCP -1

P13-K

- Glucose Transport
- eNos Stimulation
- $\uparrow$ NO

Insulin Dependent Target Tissues
- Adipose tissue
- Skeletal muscle
- Heart

Angiotensin II

Proatherogenic pathway

Systemic defect in this Pathway defines IR

Anti-Atherogenic Pathway

Am J Cardiol 2003; 92: 10,F$^{1}$
FIGURE 13

Endothelial Dysfunction in Insulin Resistance

↓ PI3-K Pathway

↓ Insulin-Stimulated eNos

↓ HDL Cholesterol
↑ Blood Pressure
↑ sdLDL Cholesterol
↑ Uric Acid
↑ Angiotensin II Sensitivity
↑ Free Fatty Acids

↑ NAD(P)H

NO → O₂⁻ + ONOO⁻

eNos = endothelial nitric-oxide synthase;
HDL = high-density lipoprotein;
NAD(P)H = nicotinamide adenine dinucleotide phosphate (reduced form);
NO = nitric oxide;
PI3-K = phosphatidylinositol 3-kinase;
sdLDL = small, dense low-density lipoprotein.

FIGURE 14

Vascular Insulin Resistance

Inflammation

Endothelial Dysfunction

Atherothrombotic Cardiovascular Disease
The pancreatic beta cell is uniquely equipped to adapt insulin secretion to ambient glucose levels. The glucose transporter GLUT2 mediates the uptake of glucose by beta cells. Glucokinase, the first enzyme of the glycolytic pathway, serves as a glucose sensor. The metabolism of glucose by means of glycolysis and the citric acid cycle generates NADH and the reduced form of flavin adenine dinucleotide (FADH2), which donate electrons to the mitochondrial electron-transport chain. Protons are then pumped out by complexes I, III, and IV, creating a proton electrochemical gradient. When protons reenter the mitochondrial matrix through adenosine triphosphate (ATP) synthase, ATP is generated from adenosine diphosphate (ADP) and inorganic phosphate. Alternatively, if the reentry route used by the protons is uncoupling protein 2, energy is released as heat instead of in the form of ATP. ATP and ADP are exchanged between the cytosol and the mitochondrion by the adenine nucleotide carrier (ANC). An increase in the ratio of ATP to ADP inhibits ATP-sensitive potassium channels and provokes a decrease in the depolarization of the plasma membrane, which opens voltage-gated CA2+ channels. The increase in the intracellular calcium concentration and energy-dependent cellular events such as the activation of ATPases contributes to the exocytosis of insulin-containing granules.

An increase in uncoupling protein 2 levels may result from the increase in free fatty acid levels associated with obesity and the insulin-resistance syndrome. The increase in uncoupling protein 2 decreases mitochondrial coupling of ATP synthesis with oxygen consumption, which may decrease the production of reactive oxygen species (a benefit) or impair insulin secretion (a detriment).
The figure shows key proteins in the inner mitochondrial membrane involved in mitochondrial respiration, oxidative phosphorylation, uncoupling, and import of long-chain acyl-CoA molecules. Two potential roles for UCP3 function are illustrated (right-hand side) UCP3 functions as an uncoupler by acting as a channel for proton entry into the matrix, which dissipates the transmembrane potential generated by respiratory chain complexes I through IV. This reduces the motile force for proton entry via the F1F0-ATPase, which catalyzes ATP synthesis, and, in effect, uncouples respiration from oxidative phosphorylation. Substrate oxidation proceeds via transfer of electrons from donors (reductants) to acceptors (oxidants) along the respiratory chain to water, releasing energy as heat. Another consequence is a reduction in reactive oxygen species formation, since these species are generated under condition of high trans-membrane potential and electron flow. (left-hand side) In another scenario, UCP3 acts as an exporter of fatty acid anions (FA-). This could facilitate fatty acid oxidation and explain experimental observations linking regulation of UCP3 expression and genetic variation with effects on fat oxidation. Under conditions of high fatty acid flux into mitochondria via carnitine palmitoyltransferase 1 (CPT1), excessive accumulation of long chain acyl-CoA molecules would be harmful to membranes and sequester CoA, thereby impairing fat oxidation. To prevent these events, up-regulation of mitochondrial thioesterase cleaves the acyl-CoA allowing export of the fatty acid anion via UCP3. Reuptake of a neutral fatty acid could deliver the proton (plus fatty acid anion) back into the matrix resulting in uncoupling, however the fatty acid export function would not necessarily depend upon an uncoupling action for UCP3.

e, electron; I, Complex I or NADH-ubiquinone oxidoreductase; II, Complex II or succinate ubiquinone oxidoreductase; III, Complex III or ubiquinol-cytochrome c oxidoreductase; IV, Complex IV or cytochrome c oxidase; Q, coenzyme Q or ubiquinone; c, cytochrome c; UQ2, ubiquinone; O2, superoxide; ROS, reactive oxygen species; SOD superoxide dismutase; F1F0 is the hydrophobic transmembrane complex that together comprise the F1F0-ATPase
FIGURE 17
IMPAIRED MITOCHONDRIAL ACTIVITY IN THE INSULIN-RESISTANT OFFSPRING OF PATIENTS WITH TYPE II DIABETES MELLITUS

- Mechanism

- PGC-1 Polymorphism Abnormality
- ↑ Intramyocellular FA Metabolites
- Activate Serine Kinase Cascade
- Decrease Insulin-Stimulated Activity of IRS-1 Associated PI-3K
- Reduced Glucose Transport
  Reduced Glycogen Transport

FIGURE 18
Chronic Inflammation, Obesity and Insulin Resistance Overview

- Increased Adipose Mass (Visceral)
- Adipokines Proinflammatory Molecules
- Inflammatory Mediators
  Chronic inflammation
- Endocrine and Metabolic Dysfunction
- Hypertension
  Dyslipidemia
  Hyperglycemia
  Diabetes
  CVD
  Cancer
  Thrombosis
  Atherosclerosis
FIGURE 21
Clinical Consequences of Excessive Adipose Tissue

- Hypertension
- Insulin Resistance
- Glucose Intolerance
- Diabetes
- Dyslipidemia
- Inflammation
- Thrombosis

Atherosclerosis and Vascular Disease

FIGURE 22
ADIPOCYTE-ADIPOCYTOKINE BALANCE

(Arterioscler Thromb Vasc Biol 2004; 24:29-33)

<table>
<thead>
<tr>
<th>Adiponectin and Others</th>
<th>VS</th>
<th>Adipocytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-diabetic</td>
<td></td>
<td>Pro-diabetic</td>
</tr>
<tr>
<td>Anti-atherosclerotic</td>
<td></td>
<td>Pro-atherosclerotic</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td></td>
<td>Pro-inflammatory</td>
</tr>
<tr>
<td>Anti-lipid</td>
<td></td>
<td>Pro-lipid</td>
</tr>
<tr>
<td>Anti-hypertensive</td>
<td></td>
<td>Pro-hypertensive</td>
</tr>
<tr>
<td>Anti-obesity</td>
<td></td>
<td>Pro-obesity</td>
</tr>
</tbody>
</table>
FIGURE 23
Actions of Leptin, Acylation Stimulating Protein and Adiponectin

Leptin
- Increases food intake
- Decreases energy expenditure (CNS)
- Increases insulin sensitivity
- Many peripheral actions

Insulin (via glucose metabolism)
- Catecholamines
- TZD

Adiponectin
- Increases insulin sensitivity
- Liver
- Muscle
- FAO
- CNS

Adipocyte
- Food and Obesity
- Subcutaneous
- Retinoid Acid
- Inflammation
- Hypoglycemic

Targets
- Adipose tissue (Paracrine)
- Adipokines

ASP
- Glucose uptake
- DGAT
- HSL
- TG synthesis

FIGURE 24
Role of Insulin Resistance in the Metabolic Syndrome

Insulin Resistance
- T-Cell Stimulation
- Insulin Exhaustion
- Adipose Tissue
- FFA

Endothelial Dysfunction
- Blood Vessels
- Arterial Wall

Diabetes
- Arterial Compliance Reduced

Hypertension
- Atherogenesis

Liver
- Dyslipidemia
- Procoagulants

Adipokines

Insulin resistance and the resulting hyperinsulinemia and hyperglycemia precede and are thought to be responsible for all the negative consequences of the metabolic syndrome.
FIGURE 25
Pathogenesis of Type 2 Diabetes Mellitus

- Obesity (central)
- Diet
- Age
- Stress
- Peripheral Insulin Resistance
  - Hyperinsulinemia
    - ↑ Pancreatic Beta Cell Mass
      With Compensatory Insulin Production
    - Normoglycemia
      - Impaired First Phase Insulin Secretion
        - Postprandial Hyperglycemia
          - ↓ Pancreatic Beta Cell Mass (>50%)
            - Apoptosis
              - Hyperglycemia
                - Type 2 DM

FIGURE 2697,98
Diabetes Mellitus
Hyperglycemia: Biochemical Results

- Glucose
  - Polyol Pathway
    - Polyols (Sugar Alcohols)
      - ↑ Sorbitol
      - ↑ Fructose
      - ↓ NAD(P)H-REDOX Imbalance
      - Change in Signal Transduction
  - Glycolylation of Proteins
  - Hexosamine Pathway
    - Increased Mitochondrial
      Superoxide Anion (O₂⁻) Production
  - Advanced Glycation End Products (AGEs)
    - Non-Enzymatic Glycosylation
      - Hemoglobin
      - Albumin
      - All Proteins
  - Glycogen Accumulation
    (non-insulin dependent tissue)
  - PKC

All reactions are related to:
- Duration of Hyperglycemia
- Magnitude of Hyperglycemia
FIGURE 2797,98
Diabetes Mellitus: Non-Enzymatic Glycation Products

凝集反应
快速
可逆

Unstable Schiff Base Intermediates (Aldimine) (Pre $A_1 C$)

Amadori Rearrangement (Ketoamine) ($HbA_1 C$)
(Reflects previous 6-8 wks)

Stable Protein-Glucose Adducts

Advanced Glycation End Products (AGEs)

Glycated Albumin (GSA)
Amadori Albumin Adducts (AAA)

VSMC growth and migration

Atherosclerosis

RAGE

Oxidant Stress (ROS)

Intracellular Cytokines (p21 MAPK), Erk

NFKB + AP-1 Transcription Factor activation
FIGURE 30
Obesity in US Adults
1991-2001

Prevalence of BMI > 30 kg/m²
- <10%
- 10-14%
- 15-19%
- >15%

Mokdad et al. JAMA 2003;289:76-79.

FIGURE 31
Association of Comorbidities and BMI

Prevalence (%)

Mokdad et al. JAMA 2003;289:76-79.

FIGURE 32
Diabetes in US Adults
1991-2001

Prevalence of Diabetes
- <4%
- 4-6%
- 6-10%
- >10%

Mokdad et al. JAMA 2003;289:76-79.

FIGURE 33
Relationship of BMI and Percent Body Fat

Mokdad et al. JAMA 2003;289:76-79.

FIGURE 34
Prevalence of Diabetes
1991-1992
1993-1994
1995-1996
1997-1998
2001

Mokdad et al. JAMA 2003;289:76-79.
FIGURE 34
Insulin and Blood Pressure

Insulin stimulates glucose transport by NO/CGMP pathway in human vascular smooth muscle cells (VSMCs).

FIGURE 35
Hypertension is, in Part, an Inflammatory Disorder

Obesity, IRS, Vascular Endothelium, Immune System, Inflammatory Mediators, CRP, eNOS/NO, Upregulates AT, R, PAI - 1, Other.
FIGURE 36
Coronary Matrix Remodeling in IR Diabetes

- Insulin
  - AT₁R
  - TGF-β
  - ECM Expansion (Collagen Type I and III)
  - Thrombosis
  - ECM Expansion
  - Coronary Matrix Remodeling Abnormal
    Cardiac fibrosis: Systolic and Diastolic CHF
    Coronary Artery Disease/Thrombosis

- A-II
  - AGE
  - ET₁

- DM has
  - Decreased MMP-2 and 9
  - Increased TIMPS
  - ECM Accumulation
  - Increased PAI-1

Arterioscler Thromb Vasc Biol 2003; 23: 2021
FIGURE 37
Mechanism of Small, Dense LDL Production and LDL Particle Number

Insulin Increases HMG-CoA Reductase Activity

Small, dense LDL are formed due to enhanced transfer of triglycerides from VLDL in hypertriglyceridemic subjects. Hepatic lipase hydrolyzes the triglycerides in the LDL, which produces lipid-depleted small, dense LDL.

Insulin influences CETP and HMG CoA Reductase

FIGURE 38
Mechanism of Low HDL-C Levels in Insulin Resistance

1. Triglyceride enrichment of HDL

HDL-C levels are reduced due to enhanced exchange of triglycerides between VLDL and HDL, and the subsequent degradation of the triglycerides in HDL by hepatic lipase.

Insulin influences CETP

*CETP= cholesteryl ester transfer protein

*gef= cholesteryl ester transfer protein
DYSLIPIDEMIA OF INSULIN RESISTANCE
(Nutr Rev 2003; 61:363)\(^{122}\)

**Figure 1.** Increased flux of albumin-bound free fatty acids (FFA) is considered the underlying event leading to the high triglyceride (TG) level and low high-density lipoprotein cholesterol (HDL) level common in obesity and type 2 diabetes. Excess caloric intake perpetuates a vicious cycle, causing calories to be stored in visceral adipose tissue as TG. Increased FFA flux induces greater hepatic glucose output. It also induces insulin resistance in adipose tissue and muscle, which is reflected in an increased intracellular TG in muscle. Visceral adipose tissue, which is resistant to insulin inhibition of hormone-sensitive lipase, sends excess FFA directly to the liver. Excess TG from the diet contributes to FFA flux via lipoprotein lipase action on chylomicron TG, producing a chylomicron remnant, that still contains TG and cholesterol, which is then taken up by the liver, releasing apoA-I at the same time. Fatty acids and cholesterol, now within the hepatocyte, can serve as ligands for nuclear hormone receptors (peroxisomal proliferator-activated receptors [PPARs], liver X receptors [LXRs], and farnesoid X-activated receptors [FXRs], which regulate TG, cholesterol, and bile acid metabolism). The insulin-resistant liver releases more fatty acids as very low-density lipoprotein (VLDL)-TG and VLDL cholesterol ester (CE). Much of the CE fatty acid is oleate. CoA desaturase-1 produces oleate from stearate and has now been shown to be a key enzyme in determining VLDL-CE output in mice. The liver now secretes more VLDL, which accounts for the high TG. The liver also secretes apoA-I, in two forms: (1) as lipid-poor apoA-I, joining the pool from chylomicrons, and (2) as a larger nascent HDL particle, enriched in TG. Lipid-poor apoA-I can remove cholesterol and phospholipid from cell membranes via the ABCA-1 transporter (this process is not shown in the figure) to begin the process of forming mature HDL. The liver now secretes more apoA-I, in two forms: (1) as lipid-poor apoA-I, joining the pool from chylomicrons, and (2) as a larger nascent HDL particle, enriched in TG. Lipid-poor apoA-I can remove cholesterol and phospholipid from cell membranes via the ABCA-1 transporter (this process is not shown in the figure) to begin the process of forming mature HDL. In obesity and type 2 diabetes, HDL becomes TG rich through the action of CETP (cholesterol ester transfer protein), which exchanges CE for TG. Lecithin-cholesterol acyl transferase (LCAT), which is closely associated with HDL, is responsible for converting cholesterol to CE in HDL (this process is not shown in the figure). CETP can then exchange HDL-CE, as well as VLDL-CE, for TG, which accounts for the TG-rich HDL and CE-rich VLDL, which tends to have a slower fractional catabolic rate (FCR). Although obesity may increase the apoA-I production rate (PR), the main determinant of the low HDL is the increased FCR of TG-rich HDL.
**FIGURE 40**

Nutrient Regulation of Gene Expression

```
Nutrient
  "Interaction Action"  Not
  Parallel Action

Gene

Beneficial Outcome
- Lower Lipids
- Lower Glucose
- Lower BP
- Lower Cancer Risk
- Reduce Cardiovascular Risk

Detrimental Outcome
- Increase Lipids
- Increase Glucose
- Insulin Resistance
- Increase BP
- Increase Cancer Risk
- Increase Cardiovascular Risk
```

Current Opinion in Lipidology 2000; 11:3-7

**FIGURE 41**

Prevention of DM

```
Cumulative Incidence of Diabetes
According to Study Group (DPPRG)

At 3 years

- Placebo: 28.9% (P)
- Metformin: 21.7% (M)
- Lifestyle: 14.4% (C)

P<0.001 for each comparison

FBS ≤ 126mg% IGT with 75 gram OGTT

NEJM 2002; 346(6):393-403
```

JANA Vol. 8, No. 2, 2005
**FIGURE 42**

Tripod Study

- Placebo
- Troglitazone

Cumulative Incidence of Diabetes (%)

Months on Trial

P = 0.009

**FIGURE 43**

Nutrition, Insulin Resistance, Hypertension, Dyslipidemia

- **Diet**
  - Increase
  - ↑ CHO
  - ↑ SFA
  - ↑ TFA

- **Insulin Resistance**
  - ↑ SNS Activity

- **Hyperglycemia**
  - AGE
  - RAGE

- **Dyslipidemia**
  - oxLDL
  - LOX-1R

- **Adipocytes**
  - Cytokines
  - TNF-α
  - MMIF

- **Ang-II**
  - AT_1R
  - BP

- **ATP**
  - HLP
  - HBP
  - DM
  - HC

- **Atherosclerosis**
  - NO
  - PGI

- **Cytokines**
  - TNF-α
  - MMIF

- **EPA**
  - DHA
  - GLA
  - DGLA
  - AA

- **Δ-6 desaturase**
  - Δ-5 desaturase

- **PNS activity**
  - ↑ Ach

- **NO**
  - –

- **ROS**
  - +

Diabetes 2002; 51: 2796-2803

JANA Vol. 8, No. 2, 2005
**FIGURE 44**
The Mammalian Cell Mevalonate Cholesterol Pathway and PP (pyrophosphate)

```
Pantothenic acid → HMG-CoA Reductase
      ↓
HMG-CoA Reductase → Mevalonate
          ↓
Mevalonate → Mevalonate-PP
              ↓
Isopentenyl-PP → Dimethylallyl-PP
              ↓
Geranyl-PP → 2-cis Geranylgeranyl-PP
              ↓
All-trans Geranylgeranyl-PP → Ubiquinone

Prenylated Proteins
```

**FIGURE 45**
CHROMIUM / GTF

(continued)

Figure 1. Proposed mechanism for the activation of insulin receptor activity by low-molecular-weight chromium-binding substance (LMWCr) in response to insulin. The inactive form of insulin receptor (IR) is converted to the active form by binding insulin. This triggers a movement of chromium from the blood into insulin-dependent cells, which in turn results in apoLMWCr (triangle) binding chromium. Finally, the holoLMWCr (square) binds to insulin receptor, further activating the receptor kinase activity. ApoLMWCr is unable to bind to receptor and activate kinase activity. When the insulin concentration drops, holoLMWCr is released from the cell to relieve its effects.

*Nutr Rev 2000; 58(3):674*
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61. Haue WA, Quinones MJ. Role of endothelial dysfunction in insulin resistance. *Am J Cardiol* 2003; 92:10J-17J.


542. Cao HX, He LQ, Shen YJ. Changes of SOD, GSH and MDA levels on protein oxidation in cultured lens cells, and in crys-


