

# Metabolic Syndrome-X

**A COMPLEX OF COMMON DISEASES—DIABETES, HYPERTENSION, HEART DISEASE, DYSLIPIDEMIA  
AND OBESITY—MARKED BY INSULIN RESISTANCE AND LOW MAGNESIUM/HIGH CALCIUM**

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Syndrome X is a term that is often applied to the disorders that exist together in many persons with different types of cardiovascular disease (CVD), as well as diabetes, in association with insulin resistance, hyperinsulinemia and cellular ionic abnormality.<sup>1-12</sup> Cardiologists have used the same name for coronary symptoms occurring without angiographically demonstrable coronary disease, so to prevent confusion, that syndrome has sometimes been modified as “Cardiac Syndrome X.”<sup>13-16</sup> For greater precision in identifying the set of conditions more commonly termed Syndrome X, “Generalized Cardiovascular Metabolic Disease” has been suggested<sup>7,10</sup> and shortened versions such as “Cardiovascular Metabolic Syndrome”<sup>17</sup> and “Metabolic Syndrome”<sup>18-20</sup> have been referred to. “Metabolic Syndrome X” is most descriptive<sup>21-23</sup> and, thus, is the term used here.

Prominent among the conditions represented in Metabolic Syndrome X are hypertension, abnormal glucose metabolism (often culminating in diabetes), abnormal fat metabolism leading to high blood cholesterol and/or obesity (mostly upper body, also referred to as abdominal, visceral or central), and thrombus formation leading to heart attacks and strokes. With or without hypertension or diabetes, people who have any of these cardiovascular problems are often also insulin resistant.<sup>24,25</sup> These disorders are prevalent in the elderly, so aging is mentioned among the conditions seen in Metabolic Syndrome X.<sup>18,26-36</sup> When the existence of insulin resistance was detected, both in diabetes and in hypertension,<sup>4,5</sup> whether or not both conditions were present in the same person, the term “Insulin-Resistance Syndrome” was widely accepted as an alternative to Syndrome X for the same group of disorders. Less generally known is that low levels of magnesium (Mg) in cells, that also contain excess calcium (Ca), have been identified in all of these conditions. Diabetics have long been known to have low blood Mg levels.<sup>37</sup> Low cellular Mg in association with high cellular calcium (Ca) has been identified in hypertension, as well as in the other abnormalities of Metabolic Syndrome X.<sup>8-12</sup>

## Underlying Factors in Diseases of Metabolic Syndrome X

Two conditions exist in each of the disturbances observed in Metabolic Syndrome X and each affects the other. Mg deficiency causes insulin resistance and impaired response to insulin interferes with both cellular uptake of glucose and with transport of Mg into cells. Additionally, Mg deficiency interferes with insulin

secretion and with its normal activity, so it is strongly linked to the other underlying factor, insulin resistance. Both influence fat utilization. Mg administration, as a dietary supplement to persons of all ages with hypertension and/or with the insulin-resistant form of diabetes (Type II), has corrected their insulin resistance, their abnormal blood cholesterol (more accurately termed dyslipidemia [see below]), while lowering their blood pressure. Another condition encountered, although less often referred to in discussions of Metabolic Syndrome X, is impaired oxidative metabolism—that is contributed to by inadequacies both of Mg and/or antioxidant vitamins.

## Low Intracellular Magnesium/Calcium Ratio Underlying Factor in Metabolic Syndrome X

Low Mg levels have been implicated as an important factor in most of the disorders of Metabolic Syndrome X. It is an intrinsic part of their ionic abnormality: low Mg and high Ca content within cells. The portion of the cells in which the Ca/Mg ratio is too high is the cytoplasm. The intracellular cytoplasmic free Ca is elevated and the cytoplasmic free Mg is deficient in all of the conditions that make up this metabolic syndrome, that is characterized by insulin dysfunction, and also by abnormal activity of the parathyroid hormone, which controls Ca and also has direct effect on blood pressure.<sup>38,39</sup> Cellular ionic imbalance causes many malfunctions that are expressed by abnormalities that produce or are associated with metabolic diseases, particularly of the cardiovascular system.<sup>1-3,6-12</sup>

How does the ionic content of cells fit into this complex of disorders? There are low Mg levels in both forms of diabetes: Type I, in which insulin secretion is subnormal, and Type II, which is the first of the diseases recognized as having subnormal response to insulin. It is postulated that there is a cellular ionic basis for the clinical and epidemiologic linkage of Type II diabetes with high blood pressure, coronary artery disease, enlargement of the heart, and for the abnormal fat metabolism that leads to high blood cholesterol and obesity.<sup>8-12,31,35,40</sup> There is considerable evidence that Mg in the cells plays a key role in modulating insulin-mediated glucose uptake by the cells and in diminishing the arterial constriction that excessive Ca increases.<sup>41</sup> Low intracellular Mg concentration might be the missing link that helps to explain why both diabetics and excitable people are likely to develop hypertension. It was shown many years ago that Mg suppresses release of adrenalin and that Ca increases it<sup>42</sup> and that its injection<sup>43</sup> or secretion as a result of stress<sup>44</sup> lowers Mg levels and

elevates blood pressure. The lower cellular Mg levels of excitable persons (Type A) than of those who are more tranquil (Type B)<sup>45</sup> might well contribute to their being more subject to high blood pressure and its adverse consequences than are calmer people. The benefits derived from daily Mg supplementation in Type II diabetic and hypertensive patients, whether these conditions exist alone or together, and by epidemiological studies showing that high daily Mg intake protects against each disorder<sup>46</sup> support the underlying role of Mg inadequacy. There is growing evidence that several of these disorders occur less often in regions where diets and/or drinking water supplies are rich in Mg.<sup>47,48</sup>

### Insulin Resistance and Hyperinsulinemia

When high blood pressure is accompanied by insulin resistance, insulin-secreting pancreatic cells secrete more insulin (the body's response to the high glucose levels which normally enables the body to continue to utilize the glucose in the blood).<sup>4,5</sup> It has been proposed that the resultant hyperinsulinemia results in hypertension by stimulating sympathetic nervous system activity and sodium and water reabsorption by the kidneys.<sup>4</sup> The early work, showing that low Mg and high Ca stimulate adrenalin secretion,<sup>42,44</sup> provides additional insight to the hypersecretion of sympathetic hormones in Metabolic Syndrome X. Both insulin resistance and hyperinsulinemia are seen in patients with high blood pressure in the absence of diabetes.<sup>3-9,49</sup> In both conditions, glucose intolerance and hyperinsulinemia are risk factors for coronary artery disease.<sup>4,10,12,40,49</sup> Their presence may help explain why the frequency of this disease was not reduced by the drugs prescribed for high blood pressure, that deleteriously affect glucose, insulin, and utilization of fat, that results in dyslipidemia—a condition in which harmful cholesterol are elevated and the beneficial cholesterol is depressed.<sup>5</sup> The loss of Mg caused by those drugs is contributory to their adverse effects that fit into Metabolic Syndrome X.<sup>50-56</sup> Insulin resistance impairs the ability of insulin to stimulate, not only glucose uptake by the cells, but cellular uptake of Mg as well.<sup>57,58</sup> Hyperinsulinemia, whether the insulin is injected or secreted, is a risk factor for heart disease, at least partially because it increases urinary loss of Mg,<sup>23</sup> as well as through the stimulating effect of low Mg levels on adrenalin release. Additionally, high cell cytosolic free Ca and low free Mg values are associated with hyperinsulinemia and insulin resistance, not only of hypertension and Type II diabetes, but of abnormal blood cholesterol,<sup>8-12,31,35,40,59,60</sup> obesity<sup>32,40</sup> thrombotic states,<sup>24,25,61,62</sup> and in the aged.<sup>31,35</sup>

### Diseases Comprising the Metabolic Syndrome X Hypertension

The most prevalent risk factor for CVD, which is the leading cause of death in USA, is high blood pressure, as based on a 1980 survey that estimated the number of Americans with hypertension at over 30,000,000.<sup>63</sup> Termed a disease, hypertension is actually an important sign of disease usually accompanied by metabolic defects that are associated with low cellular Mg and high cellular

Ca<sup>1,12</sup> and with both insulin resistance and hyperinsulinemia.<sup>5,40,49,62</sup> The close, inverse relationship of free intracellular Mg with high blood pressure suggested to Resnick et al in 1984,<sup>1</sup> that this ionic metabolic abnormality might contribute to the pathophysiology of human essential hypertension. It applies also to how the Metabolic Syndrome X develops: 1) through the antagonistic direct effects of Mg and Ca on the production of adrenalin, high intracellular Ca/Mg increasing its secretion<sup>42,44</sup> and, 2) through the antagonistic effects of these ions on the contraction of the muscle of the arterial walls: Ca stimulating their contraction and Mg causing their dilatation, as demonstrated by Altura and colleagues.<sup>41</sup> Thus, both low Mg and high Ca in cells—the ionic abnormality of the Metabolic Syndrome X—raise blood pressure. Low intracellular Mg has also been shown to be related to decreased tissue insulin sensitivity, in essential hypertension alone or with diabetes.<sup>3</sup> In 1987, Reaven and Hoffman<sup>4</sup> proposed that abnormalities of glucose metabolism and insulin activity participate in both the etiology and clinical course of hypertension and coronary heart disease.

Emotional stress lowers intracellular free Mg as a result of release of the sympathetic hormones. This has been reported with thin and obese hypertensive patients, in hypertensive patients with or without diabetes, and in diabetics, regardless of blood pressure.<sup>9</sup> Among middle-aged patients with labile hypertension, only those with low total red blood cell Mg had a blood pressure-lowering response to three months of Mg supplements.<sup>64</sup> Workers in a high noise environment and students preparing for their final examination experienced a rise in blood pressure during the work or study period on diets providing about 5 mg/kg/day of Mg. Mg supplementation that increased daily Mg intake to 6-7 mg/kg/day prevented that emotional stress induced rise in blood pressure.<sup>65</sup>

Coexistence of hypertension with Type II diabetes has long been recognized and reported repeatedly.<sup>38,40,65</sup> It has been suggested that hyperglycemia might be a factor in the pathogenesis of both hypertension and atherosclerosis in diabetes by increasing intracellular free Ca and decreasing free Mg and that insulin resistance might mediate this association leading to the postulation that there is a cellular ionic basis for the clinical and epidemiologic linkage of high blood pressure, cardiac enlargement, obesity and diabetes. Even the long recognized role of excess dietary salt in raising blood pressure affects the intracellular Mg and Ca levels, with or without diabetes. It suppresses free Mg, while elevating cytosol free Ca, further supporting the likelihood that it is a generalized defect in cellular ion handling that underlies development of CVD and the other metabolic disorders with which it is associated.<sup>8,9,12</sup>

For example, Mg supplementation of patients with high blood pressure has raised their cellular Mg levels and corrected their dyslipidemia as well as their hypertension. In a double-blind, placebo-controlled study, 33 subjects were supplemented with oral Mg (411-548 mg Mg/d as the hydroxide) for four weeks or

given a placebo.<sup>66</sup> That study showed a statistically significant reduction of urinary noradrenalin excretion and blood pressure in the group given Mg, but not in those given placebo, and also provided insight into the mechanism by which the Mg corrected their dyslipidemia (see below). Providing Mg supplements to hypertensive patients has been useful, both in decreasing arterial blood pressure and in improving response to insulin.<sup>46</sup>

Hyperinsulinemia is an important factor in causing hypertension in diabetics. Several mechanisms mediated by hyperinsulinemia include: 1) sodium and water retention, 2) increased sympathetic nerve activity and reduced clearance of the sympathetic hormones: the catecholamines (adrenalin and noradrenalin), 3) increased intracellular Ca and reduced intracellular Mg, 4) increased coagulant activity and less fibrinolytic activity, 5) impaired endothelium-dependent nitric oxide synthesis and release, 6) increased vasculature responsiveness to vasoactive substrates, 7) increased proliferation of vascular smooth muscle by activation of protein kinase C or mediated by insulin and insulin-like growth factor action.<sup>67</sup>

Dietary Mg deficiency, as well as its abnormal metabolism, seems to be an important risk factor for hypertension, coronary artery disease from angina to infarction, and insulin resistance. Experimental, epidemiologic and clinical evidence provides evidence that the increase in extracellular Mg that results from increased Mg intake participates in divalent cation metabolism, release of intracellular Ca<sup>++</sup> and increase of free Mg in both vascular smooth muscle and endothelial cells. Ionized extracellular Mg is an important determinant of vascular tone, contractility and reactivity.<sup>41</sup>

In the four-week Mg supplementation study of 21 outpatients with uncomplicated essential hypertension given oral Mg supplementation (1 g/d of the oxide), they experienced significant lowering of their blood pressure, decreased cellular sodium content, with rise of cellular Mg and fall of their serum triglycerides.<sup>68</sup> After four weeks of oral Mg supplementation with 240 mg Mg/d, a significant increase in red blood cell Mg in borderline hypertensive patients was accompanied by both a decline in blood pressure and triglyceride levels.<sup>69</sup>

Pregnancy induced hypertension is a component of eclampsia, the convulsive toxemia of pregnancy. It is thus of interest that Mg has long been accepted as the preferable treatment of this condition,<sup>70</sup> that low Mg levels are often diagnosed in eclampsia,<sup>71,72</sup> and that insulin resistance has been detected in eclampsia.<sup>73</sup>

Low Mg in non-diabetic subjects is associated with relative insulin resistance, glucose intolerance, and hyperinsulinemia.<sup>74</sup> Variations in plasma Mg level have a relatively modest but significant effect on insulin-mediated glucose disposal in healthy subjects with lower plasma Mg concentrations associated with increased insulin resistance.

## Diabetes

Diabetes is the seventh most common cause of death in the United States, is a major risk factor for strokes and coronary artery disease,<sup>75</sup> and is one of the two

diseases that has long been associated with Mg deficiency and with CVD,<sup>9,24,29,31,34,37,40,46,76,77</sup> the other being alcoholism.<sup>78,79</sup> Type I diabetes, the form in which there is insufficient insulin secreted, responds to insulin and is often referred to as insulin dependent diabetes mellitus (IDDM). The other, Type II, is insulin resistant, and is often named non-insulin-dependent diabetes mellitus (NIDDM). This is the late onset form of diabetes that is part of Syndrome X. In a recent analysis of 22 papers on NIDDM, frank hypomagnesemia was reported in half the patients and a third more had suboptimal levels.<sup>80</sup>

A 1952 study<sup>37</sup> found that insulin treatment temporarily further reduced already low blood serum Mg levels of diabetics because the injected insulin caused circulating Mg to enter cells. This early observation has been confirmed as a normal function of insulin, which increases intracellular Mg.<sup>41,81-83</sup> Insulin control of Type I diabetes results not only in lowered blood glucose, decreased urinary loss of Mg,<sup>84</sup> and raised the serum Mg levels—effects that were associated with correction of abnormal blood cholesterol.<sup>23,85</sup> Comparable results were achieved with Mg treatment of diabetics.<sup>41,86-88</sup>

On the basis of the American Diabetes Association (ADA) consensus panel findings of high prevalence and consequences of Mg deficiency in diabetics who have cardiovascular complications, a survey of a large series of diabetics, 70 percent of whom had concomitant CVD, was undertaken.<sup>77</sup> In 78 percent of 199 patients selected as likely to benefit, supplementation was initiated because of low serum Mg levels; in 21.7 percent, long term oral MgCl<sub>2</sub> supplementation was initiated empirically. In this study, although serum Mg levels did not correlate with control of glucose levels, supplementation was sustained to decrease cardiovascular complications. In other studies, Mg was found to be inversely related to insulin sensitivity in Type II diabetes and Mg repletion has improved insulin sensitivity as well as insulin secretion in diabetic patients.<sup>25,87-89</sup> Correcting Mg deficiency in diabetic patients is important because low Mg levels are a major factor in complications of diabetes.<sup>31,40,41,69,80,86,88-90</sup>

Additional to Type II diabetes, there are several diseases in which low intracellular Mg, insulin resistance and hyperinsulinemia exist that are associated with CVD. The insulin resistant conditions that predispose one to heart disease include high blood pressure, arteriosclerosis, and abnormal fat utilization that is manifested by high blood cholesterol (more accurately termed “dyslipidemia,” since there is elevation of triglycerides, but lowering of the high density lipoprotein cholesterol: (HDL-C), and obesity. Cardiac enlargement and congestive heart failure, coronary artery disease (ischemic heart disease), and arrhythmias are among the heart diseases of Metabolic Syndrome X. These conditions increase in prevalence in the elderly.

## Abnormal Fat Metabolism Leading to Obesity and Dyslipidemia

### Obesity

Being overweight—especially when the obesity is of the upper body or abdominal—increases the risk of developing the other manifestations of Metabolic

Syndrome X. This is the type of obesity more commonly seen in men; it is usually induced by excess calories in the presence of male sex hormones. It has been called “the deadly quartet” because it is usually seen in men whose vulnerability to potentially fatal CVD is associated with hypertension, diabetes, and hypertriglyceridemia, associated with hyperinsulinemia.<sup>91</sup> In obesity, high blood pressure, insulin resistance and hyperinsulinemia are closely related to high levels of cellular free  $\text{Ca}^{2+}$  and low cellular free-Mg<sup>2+</sup>.<sup>8,9</sup> A study of hypertensive and normotensive obese patients subjected to oral glucose tolerance tests to determine their insulin response showed a difference in effect on blood cell and plasma Mg.<sup>92</sup> Patients who were obese did not exhibit reduced plasma Mg or increased red blood cell and platelet Mg whether they had high blood pressure or not. These investigators commented that their impaired Mg homeostasis of obese patients could result from insulin resistance, hyperglycemia, and dysregulation of the adrenergic system.

### Dyslipidemia

Almost half a century ago, it was reported from South Africa<sup>93</sup> and New Zealand<sup>94</sup> that high levels of blood lipoproteins (the beta fraction, now called LDL-C) in patients with coronary artery disease were lowered with injections of Mg that relieved their chest pain (angina from coronary arterial constriction). Thirty years later, a pilot uncontrolled clinical study of response to oral Mg chloride of 16 patients who had very low levels of high-density lipoprotein cholesterol (HDL-C), high low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein (LDL-C) levels disclosed that their bad cholesterol (VLDL and LDL) decreased, while their good cholesterol (HDL) increased.<sup>95</sup> In these early demonstrations of the interrelation of Mg with dyslipidemia of heart disease, Mg was used as a medication.

Laboratory studies of experimental Mg deficiency showed changes in lipid metabolism in rats that bear resemblances to the those seen in Metabolic Syndrome X: dyslipidemia characterized by high triglyceride and low HDL-C, as well as decreased insulin response to a glucose challenge, and marked decrease of activity of the enzyme, lecithin-cholesterol acyltransferase (LCAT), that clears the triglycerides from the blood.<sup>96,97</sup> That this finding is relevant to the clinical situation has been demonstrated in the study of the effects of four weeks of Mg supplements (411-548 mg Mg as the hydroxide per day) in subjects seemingly normal but found to have marginally elevated blood pressure.<sup>98</sup> Those patients were clinically improved by reduction in blood pressure and with significant reduction in their LDL-C/HDL-C ratio during last two weeks of receiving supplemental Mg—changes that did not take place in comparable patients given placebo. Since increased LCAT activity was demonstrable, the investigators concluded that their patients’ improved serum lipids occurred through activation of LCAT, as well as through the suppression of adrenergic activity.<sup>98</sup> Now that measurement of ionized Mg in blood is an available procedure, the beneficial

effects of Mg on dyslipidemia are more readily demonstrable. In a study of children, it was found that the higher the ionized Mg level, the higher was the level of HDL-C, and greater the activity of LCAT.<sup>99</sup> Similarly, in a study of elderly men who were insulin resistant but not diabetic, atherogenic lipids: LDL-C and triglycerides were closely correlated with low intracellular free Mg ions, but not with levels of total blood Mg.<sup>32</sup> A statistically significant negative correlation having been found in the population as a whole between intracellular Mg and plasma triglycerides, it was suggested that triglyceride levels and possibly the metabolic syndrome may be characterized by low lymphocyte free Mg.<sup>60</sup>

Studies of the effect on abnormal lipids by correction of Type I diabetes with insulin suggests interrelation with the effect of Mg, since insulin increases cellular Mg uptake, and decompensated diabetes causes substantial Mg loss. In 1980, it was shown that such diabetic children's elevated triglycerides and LDL-C were correlated with their low red blood cell Mg levels and that when their diabetes was adequately managed, their HDL-C rose as did their Mg levels.<sup>85</sup> More recently, blood levels of the bad lipid, LDL, and triglycerides were lowered and levels of the good lipid, HDL, were raised when poorly controlled diabetes was adequately managed by insulin<sup>100</sup> or the Mg deficit was repaired.<sup>86</sup>

Cardiovascular risk factors were compared in 126 people with NIDDM with 530 non-diabetics (controls), in a random sample of middle-aged Singapore residents.<sup>19</sup> For both genders, people with NIDDM had higher waist-hip ratios and abdominal diameters, higher prevalence of hypertension, higher mean levels of fasting serum triglycerides, slightly lower mean levels of serum HDL-C, and higher mean levels of plasma clotting factors (plasminogen activator inhibitor-1 and tissue plasminogen activator (antigen). The effects on blood lipids of feeding a diet rich in Mg and potassium (K) for six weeks to 206 Asian Indian subjects versus a comparable group of 194 subjects whose customary diet was not changed disclosed significant falls in LDL-C and triglycerides only in those eating the Mg, K- rich diets.<sup>101</sup>

### Thromboembolic Diseases

Because of the linkages among high triglyceride, low HDL-C, reduced glucose tolerance, hyperinsulinemia, obesity, as well as increased coagulation and reduced fibrinolytic capacity, it has been suggested that a suitable name for this clustering of coronary risk factors might be athero-thrombogenic syndrome, thereby indicating that both atherosclerosis and thrombosis contribute to its development.<sup>102</sup>

Blood coagulation that takes place in blood vessels gives rise to thromboses and emboli that can result in heart attacks and strokes. Since it has long been known that Ca enhances the coagulation process while Mg inhibits it,<sup>103,104</sup> the high Ca/Mg ratio in the Metabolic Syndrome X is a likely factor in its thromboembolic complications. It was shown first in experimental Mg deficient animals that their platelets are more sensitive to aggregation caused by thrombin,<sup>96,97</sup> an effect that

## Magnesium Deficiency as a Metabolic Oxidative Stressor

was deemed important in initiating clinical vascular lesions and thrombotic complications. Whether low Mg levels were induced by diabetes or alcoholism, or in normal subjects on a low enough diet to cause hypomagnesemia, Mg infusions or oral Mg supplements at 400 mg/day inhibited increased platelet aggregation on exposure to various aggregating agents.<sup>24,25,62,79</sup> Mg also inhibited thrombin-induced Ca influx in platelets and stimulated synthesis of potent natural antiaggregating substances. Alcoholics' predilection to high blood pressure and atherosclerotic CVD has been attributed to their Mg loss.<sup>79</sup> Mg can inhibit platelet aggregation, an effect that is increased by insulin.<sup>62</sup> Decreased intracellular ionic platelet Mg has been suggested as a possible indicator for thrombosis and atherogenesis.<sup>105</sup>

### Aging

As we age, all of the manifestations of Metabolic Syndrome X are more frequently seen, but even elderly people without these problems tend to have increasing insulin resistance.<sup>18,26-29, 33,34,36</sup> Individuals with any of these conditions also have been found to have low Mg and high Ca levels in their tissues, whether or not they receive drugs that cause further Mg loss and low Mg levels. Elderly subjects who were otherwise healthy and not receiving antidiabetic medications have been found to have impaired insulin sensitivity. Atherogenic lipids have been found to be closely correlated with intracellular ionic Mg.<sup>32</sup> Aging cells may become more vulnerable to ion disturbances, leading to possible increased intracellular free Ca and concurrent Mg depletion. The "ionic hypothesis" of aging supposes that alteration in cellular mechanisms which maintain homeostasis of cellular Ca levels may play a key role in the aging process, with depletion of cell Mg providing the final common pathway for many aging-associated diseases including hypertension and NIDDM.<sup>35</sup>

Biologic changes associated with aging are caused by increased free radical formation with subsequent damage to cellular processes that include results of oxidation of unsaturated lipids in cell membranes, amino acids in proteins, and nucleic acids. Accumulation of unrepaired oxidative damage products may be a major factor in cell-aging.<sup>106</sup> Abnormal glucose and insulin metabolism are associated with lipid peroxidation, that is secondary to free radical formation, and that is an important factor in development of arteriosclerosis. Even in healthy centenarians, a rise in plasma free radicals has been attributed to hyperglycemia, elevated free fatty acids and hyperinsulinemia.<sup>36</sup>

### Magnesium and Other Nutrients that Protect against Oxidative Damage

Since the conditions that comprise Metabolic Syndrome X have evidence of free radical damage, which is counteracted by antioxidants it is important that magnesium deficiency is one of the conditions that releases free radicals, and that its supplementation not only corrects the low Mg/Ca ratio of such patients, but that it acts as an antioxidant.

Mg deficiency plays a definitive role in the oxidative aspect of the disorders of Metabolic Syndrome X acting as an oxidant directly leading to release of free radicals and lowering levels of antioxidants and activity of antioxidative enzymes in the body. The importance of Mg deficiency, as an oxidant, was first shown by the diminution of Mg deficiency-induced abnormalities by administration of other antioxidant nutrients. This was illustrated in Syrian hamsters over ten years ago by showing that the antioxidant vitamins E and C could diminish Mg deficiency-induced free radical damage to the heart.<sup>109,110</sup> High levels of oxidant-indicators in the tissues of young Mg deficient rats and their lipid peroxidation have been shown to be prevented by vitamin E.<sup>111-117</sup> Double deficiencies (of both Mg and vitamin E) were found to cause atherosclerosis-like changes.<sup>114</sup>

Weglicki and his group of investigators in the U.S.A., having shown that the free radicals released in the Mg-deficient hamster heart participated in its injury,<sup>109,110</sup> suggested that a mechanism through which free radicals caused the cardiac lesions involved a pro-inflammatory state that activated and injured vascular endothelial cells.<sup>118-121</sup> Many of the abnormalities caused by free radicals involve damage to the inner lining of blood vessels—the endothelium. Endothelial dysfunction results in hypercholesterolemia, thrombosis, increased adhesion of white blood cells to the lining of arteries (all of which play roles in atherosclerosis), and arterial constriction of hypertension as well as in other facets of Metabolic Syndrome X, including diabetes and aging.<sup>122</sup> Paradoxically, free radical-damaged endothelial cells generate additional free radicals.<sup>123,124</sup>

Rayssiguier and Durlach et al<sup>108</sup> in France observed that Mg deficient animals have increased susceptibility to oxidative stress with greater susceptibility of their tissues to peroxidation. They presented evidence that accumulation of oxidative damage products may be a major factor in aging of cells and that prime targets of reactive free radicals are unsaturated lipids in cell membranes, amino acids in proteins, and nucleic acids.<sup>108</sup> Oxidation of cellular proteins occur early in Mg deficiency and contributes to the tissue damage and loss of function observed in later stages of Mg deficiency—changes that contribute to aging.<sup>125,126</sup> A fairly recent study from Poland has demonstrated that as plasma levels of Mg dropped in mice fed a Mg deficient diet, so did heart and liver levels of the antioxidant enzymes.<sup>127</sup>

Prolonged oxidative stress on isolated cells has been shown to impair insulin-stimulated glucose metabolism<sup>128</sup> by disrupting the insulin receptor and by activating an enzyme (protein kinase)<sup>129,130</sup>—a situation that convinced the Israeli investigators that this oxidative mechanism contributes to insulin resistance. English and American investigators consider insulin resistance<sup>131</sup> and the vascular complications of diabetes to be due at least partly to activation of protein kinase,<sup>131-130</sup> an enzyme that also functions to increase calcium-induced arterial constriction,<sup>134</sup> especially in the presence of Mg

deficiency.<sup>135-138</sup> Amano et al<sup>139</sup> in Japan presented evidence that insulin controls the cardiac level of intracellular free Mg seemingly by activating protein kinase thereby preventing adrenergic-induced reduction of cardiac free Mg.

### Antioxidant Nutrients and Benefit of Antioxidant Supplements for Diseases of Metabolic Syndrome X

Nutrients that have antioxidant activity protect against oxidative influence (caused by their deficiency, as in the case of magnesium) or oxidation that originates endogenously from normal metabolic reactions. Nutrients that activate processes that release free radicals (such as excess non-bound iron or copper), drugs, pollutants, and irradiation are not considered here except to mention that antioxidants also protect against such oxidants. Antioxidants also protect against conditions that either increase activity of oxidant enzymes (like protein kinase) or lower tissue levels of antioxidants or of the enzymes that enhance antioxidant activity. Defenses against free radical damage are provided by alpha tocopherol (vitamin E), ascorbic acid (vitamin C), beta-carotene and other carotenoids, reduced glutathione (GSH), which is an endogenous antioxidant, and antioxidant enzymes that include GSH-peroxidase, catalase, and superoxide dismutase.<sup>140</sup> Tissue damage (such as can lead to components of Metabolic Syndrome X) results from imbalance between free radicals generated and antioxidant protective defense system. Most studies have been with individual antioxidant vitamins or other nutrients, but several indicate that combinations of antioxidants exert the best effects.

### Antioxidants in Diseases of Metabolic Syndrome X

Oxidative stress, which releases free radicals in the body, has been implicated in the conditions that comprise Metabolic X Syndrome: insulin resistance, hyperinsulinemia, dyslipidemia, diabetes, hypertension and other aspects of cardiovascular disease, aging, as well as Mg deficiency.<sup>21,28,30,36,106-108</sup> Experimental studies with rodents on Mg deficient diets in 1990 through 1995 in the United States and continental Europe have provided insight into another factor that increases the risk of Metabolic Syndrome X—release of free radicals that occurs with oxidative reactions that can be mitigated by antioxidants.<sup>109-113</sup> This is a serious problem that is intensified when there are inadequate levels of antioxidants in the body to protect against damage caused by free radicals. It is thus important to consider the nutritional imbalances that can induce oxidative stress actually functioning as oxidants—releasing free radicals and lowering levels of antioxidants. When antioxidant vitamins and other nutrients, including Mg, are deficient, their intracellular levels fall and oxidative stress with free radical release predominates. Dietary deficiencies of the antioxidants, by depleting the body stores, also result in loss of the ability to detoxify oxidants. The antioxidant nutrients vitamin E (alpha tocopherol), vitamin C (ascorbic acid), vitamin B<sub>6</sub> (pyridoxine), alpha-lipoic acid (ALA), and coenzyme Q<sub>10</sub>, as well as Mg,

all protect against free radical damage that are contributory to Metabolic Syndrome X.

### Efficacy of Combinations of Antioxidants Against Cardiovascular Disease

In 1981, Harman, who had long supported the concept that oxidant/free radicals participate in the aging process, summarized many of the abnormalities they cause and cited vitamins E, C, beta-carotene, and selenium-activated GSH-peroxidase, as well as superoxide dismutase as protective antioxidants.<sup>141</sup> Singh and his colleagues in India have reported on the difference in intakes of dietary antioxidants and plasma levels of vitamins E, C and beta-carotene in diabetics, in patients with heart disease, in obese, and in elderly subjects.<sup>142-145</sup> Their observations led them to suggest supplementation of such subjects with combined vitamin antioxidants with Mg, potassium, and zinc.<sup>144,145</sup> Sinatra and DeMarco, in the U.S.A.,<sup>146</sup> cited clinical research that documented the role of free radical damage in cardiovascular disease, secondary to lipid peroxidation, in their justification of use of antioxidant vitamins C, E, and beta-carotene, as well as Selenium (Se), coenzyme Q<sub>10</sub> and phytonutrients such as the natural flavonoids and carotenoids that are found in fresh fruits and vegetables. To prevent hyperhomocysteinemia, another major cardiovascular risk factor, they suggest vitamin B complex, particularly folic acid, and vitamins B<sub>12</sub>, and B<sub>6</sub>. Combination of a healthy diet with antioxidant supplements and phytonutrients is their prescription for promotion of optimum cardiovascular health. Emphasis on how antioxidants inhibit atherogenesis led Frei et al<sup>147-149</sup> to emphasize the importance of both vitamin E and vitamin C, not only to protect low-density lipoproteins against oxidation, but to protect against vascular cell dysfunction and necrosis, and particularly vitamin E to inhibit thrombosis. In their 2000 paper, they attributed these benefits more to vitamin C than to vitamin E because of its abilities to effectively scavenge a wide range of reactive oxygen and nitrogen species and to regenerate vitamin E.<sup>149</sup> They suggest that vitamin E may be effective only in combination with vitamin C.

The premise that multiple antioxygenic nutrients provide increased protection against lipid peroxidative damage was tested by Chen and Tappe<sup>150</sup> in rats fed diets deficient in both vitamin E and selenium. They concluded that protection by multiple antioxidants against lipid peroxidation may translate to prevention of peroxidative damage to human tissue, a factor in human disease.

Jean Durlach, in France, best known for his pioneer work on Mg deficiency, has (with his son and daughter), reevaluated epidemiologic data on the high prevalence of heart disease, especially in north Finland<sup>151</sup> in which low Mg/Ca intakes have reported to be contributory.<sup>47,152</sup> They suggest that the low cardiovascular disease rates in the sub-population of Laplanders might be due to their diet that is rich, not only in Mg from fish, but also in reindeer meat (lean, and like fish, rich in essential fatty acids) and in selenium. A fairly recent German study showed that a combination of vitamin E, coenzyme Q<sub>10</sub> and alpha-lipoic acid was most effective in preventing peroxidation of low-density lipoproteins.<sup>153</sup>

## Efficacy of Combinations of Antioxidants in Diabetes

Since free radical production has been reported to be increased in diabetic patients and it has been suggested that hyperglycemia may directly contribute to generation of oxidative stress, the effect of an oral glucose tolerance test on plasma antioxidants was explored.<sup>154</sup> Levels of protein-bound SH groups and vitamins C and E fell significantly in both normal subjects and NIDDM subjects, which supports the hypothesis that hyperglycemia can induce oxidative stress. Another study showed that vitamins C (2 grams) and E (800 IU) prevented the interference with normal arterial endothelial function expressed by endothelium-dependent dilatation that was caused by oral glucose loading (75 g) in a randomized, double-blind, placebo-controlled, crossover study of ten healthy volunteers.<sup>155</sup> A study of effects of high intakes of both Mg and vitamin E in genetically obese rats that had hyperglycemia and hyperinsulinemia showed reduction of their elevated plasma levels of insulin and correction of their dyslipidemia.<sup>156</sup>

### Individual Antioxidants

#### Magnesium

Discussed above is some of the evidence that Mg levels are low in patients with hypertension and other cardiovascular diseases, in diabetics, and in obese subjects, and that Mg repletion favorably affects their responses to hyperglycemia and hyperinsulinemia. As regards the antioxidant effects of Mg, it is important to note that low cellular Mg levels are associated with depressed levels of GSH, and of vitamins C and E, each of which protects against elevated levels of oxidants and free radical damage in both normal and hypertensive subjects.<sup>34, 46, 106-117</sup>

That Mg deficiency lowers levels of antioxidants in many tissues, including the heart and aorta of experimental animals, was shown in Germany by Guenther and his groups of investigators<sup>111-113</sup> as well as by Weglicki's group in the United States.<sup>123, 124</sup> Antioxidant activity in the body has also been identified by determining the activity of certain enzymes. Important antioxidant enzymes (glutathione peroxidase and superoxide dismutase) in the hearts and livers of Mg-deficient mice were found to fall on the tenth and 20th day of the deficiency.<sup>124</sup> The alterations of cardiac antioxidant enzyme activities were indicative of the adverse effects of oxidative stress, which can be responsible for the arterial and cardiac lesions associated initially with endothelial damage caused by Mg deficiency. (*Considered above: Magnesium Deficiency as a Metabolic Oxidative Stressor*). Shechter and his colleagues have provided important clinical data on the mechanisms by which Mg treatment benefits patients with coronary artery disease and acute heart attacks, which include its favorable effects on such abnormalities as hypertension, vasospasm, hypercoagulability, and dyslipidemia.<sup>157-160</sup> They have recently demonstrated that Mg supplementation of patients with coronary disease improves their endothelial function enhancing endothelial-dependent vasodilatation.<sup>160</sup> Since endothelial

dysfunction underlies additional disorders that are seen in Metabolic Syndrome X, including hypertension, blood lipid disorders and thrombosis, this further documents the direct benefit of Mg supplements in this syndrome.

#### Vitamin C

That low intake of vitamin C, even in healthy subjects, lowers endogenous defense against oxidants was shown in 1991.<sup>161, 162</sup> Ten years earlier, it was reported that diabetic patients have very low plasma vitamin C levels.<sup>163</sup> Two years later, in both normal and NIDDM patients, hyperglycemia was shown to decrease mononuclear white blood cell vitamin C levels, but the vitamin C levels were lower in diabetic than in normal subjects.<sup>164</sup> More recently, it was found that hyperglycemia leads to sorbitol production through the action of aldose reductase. Since intracellular sorbitol accumulation contributes to progression of chronic diabetic complications, the inhibiting effect of vitamin C supplements on this enzyme and its lowering of cell sorbitol levels is of important clinical significance, an observation made in 1994 both in the U.S.A.<sup>165</sup> and China.<sup>166</sup> High, but physiologic, concentrations of vitamin C have more recently been shown to inhibit red blood cell aldose reductase, which provides a rationale for its use as an oral supplement in diabetic patients.<sup>167</sup>

The impaired glucose tolerance, insulin resistance and hyperglycemia of patients with coronary disease that was associated with arterial spastic angina and endothelial dysfunction responded to intravenous vitamin C infusion by improvement both in endothelial function and in insulin sensitivity.<sup>168</sup> In patients with essential hypertension, vitamin C infusion improved their endothelial function, as determined by increased endothelium-dependent vasodilatation and blood flow, but did not improve insulin-mediated glucose uptake.<sup>169</sup> It has been proposed that because hyperglycemia induces deficiency of vitamin C in diabetic patients, its administration might slow atherogenesis by improving endothelium-dependent vasodilation.<sup>170</sup> Since, even in healthy people, hyperglycemia attenuates endothelium-dependent vasodilation, the effect of vitamin C on the reduced arterial blood flow in the arms of non-diabetic volunteers was determined.<sup>171</sup> Giving vitamin C restored endothelium-dependent vasodilation that had been impaired by acute hyperglycemia.

#### Vitamin E

A 1962 review of the data on the functions of vitamin E reported that it is the major lipid antioxidant of nature, reacting with free radical intermediates of lipid peroxidation and preventing oxidative damage to cell membranes.<sup>172</sup> The experiments that showed that Mg deficiency exerted oxidant effects employed vitamin E as an antioxidant to protect against the free radical cardiac damage caused by the Mg deficiency. (*See above: Magnesium Deficiency as a Metabolic Oxidative Stressor*). A 1995 survey of epidemiologic and controlled clinical studies found that all three large epidemiologic cohort studies of high level vitamin E supplementation, lasting at least 2 years, reported that it was associated with a significant cardiovascular disease reduction as

measured by fatal and non-fatal cardiovascular end points.<sup>173</sup> The clinical studies of vitamin E supplements (at sub-optimal doses) were less protective. The other vitamins (C or beta-carotene) were less effective in both epidemiologic and clinical studies. This observation conforms to the earlier findings of the effects of vitamins C and E on subcellular membranes that were made vitamin E deficient.<sup>174</sup> Vitamin C was not protective against lipid peroxidation unless there was adequate vitamin E in the membranes. In an evaluation of how the antioxidant vitamins C and E protect against coronary risk factors such as hypercholesterolemia, hyperhomocysteinemia, essential hypertension, atherogenesis, diabetes mellitus, smoking, and aging, their pivotal roles in regulation of vascular tone via stimulation of vascular smooth muscle cell relaxation and concomitant vasodilation were considered key to improving management of coronary artery disease.<sup>175</sup>

### Alpha Lipoic Acid

Treatment of diabetic polyneuropathy, a distressing complication of one of the manifestations of Metabolic Syndrome X, with alpha-lipoic acid (ALA) began to be explored in Germany when ALA was shown to prevent nerve dysfunction in experimental diabetes.<sup>176</sup> American investigators<sup>177</sup> attributed some of the nerve damage to nerve lipid peroxidation. Because ALA can prevent deficits in nerve blood flow, oxidative stress, and distal sensory conduction, they compared the efficacy of the R and S components of ALA in reducing oxidants in rat brain and sciatic nerve and found each to yield dose-dependent and statistically significant reduction in lipid peroxidation in both tissues. The initial clinical studies of ALA treatment of this condition were with intravenous infusions of 600 and 1200 mg, which were effective in reducing the foot pain, burning, paresthesia and numbness.<sup>178</sup> At the 600 mg intravenously administered dose, there was significant improvement of the microcirculatory function.<sup>179</sup> Oral use of ALA, in a daily dosage of 800 mg, in a four month, randomized, controlled, multicenter treatment trial involving NIDDM patients with cardiac autonomic neuropathy assessed by heart rate variability, produced some improvement.<sup>180</sup> A larger dose (1200 mg/day orally) was shown, in a pilot study of fewer diabetic patients, to increase significantly capillary blood flow, which supports their assumption that ALA might exert its beneficial effects on nerves at least partially by improving their microcirculatory blood supply.<sup>181</sup>

Since ALA enhances glucose utilization in experimental models of NIDDM, its effects (1000 mg/500 ml NaCl, intravenously administered) on insulin mediated glucose disposal in NIDDM patients was investigated in a pilot study also in Germany.<sup>182</sup> The encouraging significant increase of insulin-stimulated glucose uptake was followed by demonstration that four weeks of oral ALA (600 mg once, twice or three times daily) improves insulin sensitivity with no significant difference at the different doses.<sup>183</sup> A study in Canada showed that ALA improves insulin-responsive glucose utilization (uptake and transport) in rat muscle preparations and during insulin clamp studies performed in diabetic individuals.<sup>184</sup> Further clinical studies have verified the antioxidant

effects of ALA, even in diabetic patients with poor glycemic control and renal damage.<sup>185</sup>

There are two recent publications on the properties and clinical potential of ALA. Packer et al, in the U.S.A., points out that this powerful antioxidant scavenges oxidants produced by metabolic processes and disease (as in diabetes) and increases glucose uptake through recruitment of the glucose transporter-4 to plasma membranes, a mechanism that is shared with insulin-stimulated glucose uptake.<sup>186</sup> Powell et al, in North Ireland, after reviewing how hyperglycemia-induced oxidative stress plays a key role in the pathogenesis of diabetic vascular disease, reports that under high glucose conditions, incubation of vascular smooth muscle cells with ALA restores normal antioxidant (GSH) levels that had been lowered by a pharmacologic oxidant.<sup>187</sup>

### Coenzyme Q<sub>10</sub>

A component of the mitochondrial respiratory chain that is involved in energy-producing oxidative respiration and other metabolic pathways, coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) occurs in all cellular membranes as well as in blood serum and in serum lipoproteins. It efficiently protects membrane phospholipids, thereby stabilizing them and protects serum low-density lipoprotein from lipid peroxidation.<sup>188-190</sup> Low levels of an enzyme involved in maintaining CoQ<sub>10</sub> levels, having been demonstrated in patients with hypertension by Folkers and his colleagues in Japan in the 1970s, and to correct their abnormal bioenergetics, it was suggested that there might be an advantage to improve treatment of those with low levels by adding CoQ<sub>10</sub> to antihypertensive drugs.<sup>191-193</sup> In 1994, Langsjoen and coworkers, together with Folkers, found that high dosage CoQ<sub>10</sub> (225 mg/day), added to 109 symptomatic hypertensive patients' drug therapy for at least six months, lowered their systolic and diastolic blood pressures as well as their drug requirements. Fifty-one percent of the patients came completely off between one to three anti-hypertensive medications at an average of 4.4 months after starting CoQ<sub>10</sub>.<sup>194</sup> After a shorter treatment period (10 weeks) in 26 hypertensive patients given 50 mg twice daily, reported by Diegesi et al from Italy the same year, CoQ<sub>10</sub> was reported to lower blood pressures from 165 mm systolic and 98 mm diastolic to 146 mm systolic and 86 mm diastolic.<sup>195</sup> Singh and his colleagues in India, in a randomized, double-blind trial of 30 hypertensive patients receiving anti-hypertensive medication who had 60 mg CoQ<sub>10</sub> added to their regimens twice daily for eight weeks, compared their responses to those of 29 comparably treated hypertensives, but who had vitamin B complex added. Patients provided the vitamin B complex with their drug therapy had no changes other than increases of vitamin C and beta carotene levels. Those given CoQ<sub>10</sub> exhibited higher levels of antioxidant vitamins A, C, E, beta carotene as well as of the good lipid (HDL-C). More importantly, their blood pressures fell as did their lipid peroxides, triglycerides, and oxidant indicators, as well as their elevated insulin levels suggesting that their insulin resistance had diminished.<sup>196</sup>

Among the additional cardiovascular conditions for which CoQ<sub>10</sub> has been tried, studies of its use in

congestive heart failure have provided the most promising findings. In an evaluation of results over an eight-year period (1985-1993), the Langsjoen group treated 424 patients with various forms of cardiovascular disease by adding oral CoQ<sub>10</sub> to their medical regimens, in doses from 75 to 600 mg/day (average 242 mg).<sup>197</sup> Patients who had ischemic cardiomyopathy, dilated cardiomyopathy with cardiac failure, diastolic dysfunction, hypertension, mitral valve prolapse, and valvular heart disease were followed for an average of close to 18 months. According to the New York Heart Association (NYHA) functional scale, there was significant improvement: 58 percent improved by one NYHA class, 28 percent by two classes, and 1.2 percent by three classes, with significant improvement in myocardial function. Before CoQ<sub>10</sub> addition, most patients were taking up to five cardiac medications. During the study, medication requirements dropped considerably: 43 percent stopped one to three drugs. Also from the U.S.A., Sinatra<sup>198</sup> termed CoQ<sub>10</sub> a vital nutrient with particular value for congestive heart failure because of its multiple activities as an antioxidant, in energy-producing metabolic pathways, in inhibition of lipid peroxidation in cell membranes and serum, and its membrane-stabilizing activity, as well as its bioenergetic activity in mitochondria, where it is an essential component of electron transport involving enzyme systems in energy metabolism.

From Sweden, a double-blind, crossover, placebo-controlled study of 79 patients with three month treatment periods, comparing 100 mg dose of oral CoQ<sub>10</sub> with placebo added to conventional therapy, indicated significant betterment of quality of life during CoQ<sub>10</sub> period, but only slight improvement in maximal exercise capacity. A study comprising 17 patients in the U.S.A. explored some of the claims made for CoQ<sub>10</sub> in congestive heart failure.<sup>200</sup> The results of this study showed that functional class improved 20 percent after four months of CoQ<sub>10</sub> addition, and there was 27 percent improvement in mean congestive heart failure score, as well as a mean 25.4 percent increase in exercise duration and 14.3 percent increase in workload. The conclusion by Sacher et al was that CoQ<sub>10</sub> produced significant functional, clinical, and hemodynamic improvements.

With addition of 100 mg of CoQ<sub>10</sub> twice daily for 12 weeks, Munkholm et al from Denmark undertook a cardiac catheterization randomized double-blind study of 22 heart failure patients that included a three minute exercise test to confirm results obtained with non-invasive tests.<sup>201</sup> They reported that stroke index at rest and work improved significantly, pulmonary artery pressure at rest and work decreased (significantly at rest), and pulmonary capillary wedge pressure at rest and work decreased (significantly at 1 minute work). These results suggest improvement in left ventricular performance, which supports the contention that patients with congestive heart failure may benefit from adjunctive treatment with CoQ<sub>10</sub>. In the U.S.A., at the same daily dosage of CoQ<sub>10</sub> of 200 mg, 46 patients completed a study in which they were randomly assigned to CoQ<sub>10</sub>

(200 mg/d or placebo) and had their left ventricular ejection fraction and peak O<sub>2</sub> consumption and exercise duration monitored.<sup>202</sup> Although mean serum concentration of CoQ<sub>10</sub> increased about two-fold in patients who received active treatment, ejection fraction, peak O<sub>2</sub> consumption, and exercise duration remained unchanged in both CoQ<sub>10</sub> and placebo groups.

Whether CoQ<sub>10</sub> is efficacious in treating congestive heart failure resulting from different forms of cardiac disease has evoked disagreement. There have been several evaluations of the published reports, including a meta-analysis of eight controlled clinical trials.<sup>203</sup> A 1997 analysis disclosed significant improvement in several important cardiac parameters: ejection fraction, stroke volume, cardiac output, cardiac index and end diastolic volume index. The average patient in the CoQ<sub>10</sub> group had a higher score in stroke volume and cardiac output than patients in placebo group by 76 percent and 73 percent respectively. In 1998, an evaluation of 32 controlled trials and several open and long-term studies on the clinical effects of CoQ<sub>10</sub> in several cardiovascular diseases, including relevance to open heart surgery, indicated that attainment of higher blood levels of CoQ<sub>10</sub> (> 3.5 μgms/ml) with use of higher doses of CoQ<sub>10</sub> appears to be desirable to enhance both magnitude and rate of improvement.<sup>204</sup> A literature survey pertaining to safety and efficacy of CoQ<sub>10</sub>, specifically for cardiovascular indications that included clinical trials, articles, and reviews from 1974 to 2000, indicate that CoQ<sub>10</sub> appears to be safe and well tolerated in adults.<sup>205</sup> Favorable effects of CoQ<sub>10</sub> on ejection fraction, exercise tolerance, cardiac output, and stroke volume are demonstrated in the literature, so use of CoQ<sub>10</sub> as adjuvant therapy is supported for patients with heart failure.

The Langsjoens and Folkers<sup>206</sup> made an interesting observation that might pertain to Mg deficiency another manifestation of Metabolic Syndrome X. Among their 115 patients with congestive heart failure entered into a CoQ<sub>10</sub> intervention study, 60 had hypertension, 27 had mitral valve prolapse and 28 had chronic fatigue syndrome. CoQ<sub>10</sub> administration produced improvement in all; specifically, a reduction in hypertension of 80 percent, and a reduction in almost a third of those with mitral valve prolapse and chronic fatigue. It is of more than passing interest that Mg deficiency has been implicated in both mitral valve syndrome and in chronic fatigue syndrome.<sup>207</sup> Since CoQ<sub>10</sub> has been reported to exert its bioenergetic benefits partially as a result of its elevation of intracellular free Mg,<sup>208,209</sup> it is possible that the patients with heart failure in association with mitral valve prolapse and chronic fatigue might have benefitted more by addition of Mg to the CoQ<sub>10</sub>.

## Selenium

A trace mineral that has stimulated interest in its potential value as a protector against cardiovascular disease because of epidemiologic findings, selenium (Se) has been shown to activate antioxidant enzymes and several seleno-proteins.

## Concluding Observations

Two important observations made in the mid-1980's showed that many disorders that were found to exist together in patients with cardiovascular diseases were not coincident occurrences but were causally related. Reaven's 1986-1987 observation that insulin resistance existed, not only in late onset diabetes (Type 2, or NIDDM), but in hypertension,<sup>5</sup> led to the categorization of those linked disorders as the Insulin Resistance Syndrome, as more non-diabetic conditions were found to be insulin resistant. From 1984 to 1986, Resnick and his coworkers discovered that hypertensive patients had low cell Mg and high cell Ca levels as well as insulin resistance.<sup>1-3</sup> Low Mg/Ca levels, having been found in each of the disorders of the Metabolic Syndrome X, and low Mg intake from food and water, being prevalent in the United States and other countries of the developed world where recommendations of high Ca intake are common,<sup>47,48</sup> increasing Mg intake is important in coping with these problems. Among people amenable to altering their diet, the intake Mg-rich foods should be greater. Mg supplementation may be a practical alternative for those whose dietary habits and preferences are difficult to modify sufficiently to meet the high Mg need of those with vulnerability to or existence of Metabolic Syndrome X. There are nutrients that have activities that can amplify the protective effects of Mg, namely, the antioxidants. Experimental and clinical studies indicate the desirability of adding them to dietary supplement regimens, especially for individuals with a familial or personal history of presence of some of the manifestations of Metabolic Syndrome X.

Although not generally considered a contributory factor in the Metabolic Syndrome X, elevated plasma free radicals have been related to aging, diabetes, and atherosclerosis. Even in healthy subjects, a rise in plasma free radicals and reduction in antioxidant levels has been correlated with hyperglycemia, elevated free fatty acids, and hyperinsulinemia. Thus, antioxidants might potentially be useful in preventing or delaying development of atherosclerosis, diabetes, coronary heart disease and possibly other manifestations of the syndrome. Mg deficiency causes the release of free radicals and the resultant oxidative reactions. Thus, repairing Mg deficiency protects against the oxidative damage that is caused by the free radicals. Oxidative stress causes membrane damage of the myocardium, endothelium, and erythrocytes in which release of free radicals participates. That experimental cardiomyopathy of Mg deficiency, alone, also involves free radicals is indicated by the protective effects of the antioxidant vitamin E. This is pertinent to the observation that high intakes of antioxidant nutrients, as well as of Mg, were cardioprotective in a large series of Indian cardiac patients. Among additional nutrients with antioxidant activity that have been suggested for use are vitamins C and E, as well as alpha-lipoic acid, coenzyme Q<sub>10</sub>, and selenium.

Vitamin C has many functions that relate to Metabolic Syndrome X. Some of the attributes were demonstrated with the vitamin given intravenously, such as correction

of insulin resistance and endothelial dysfunction in cardiac and diabetic patients, but oral administration even in normal subjects has also been effective. An important effect of vitamin C has been more recently identified, that of inhibiting the enzyme that mediates high blood sugar to sorbitol a substance that is responsible of several serious diabetic complications. Vitamin C was not protective against lipid peroxidation unless there was adequate vitamin E in the membranes.

Vitamin E has long been known to be the major lipid antioxidant of nature, reacting with free radical intermediates of lipid peroxidation, preventing oxidative damage to cell membranes. The experiments that showed that Mg deficiency exerted oxidant effects employed vitamin E as an antioxidant to protect against the free radical cardiac damage caused by the Mg deficiency. (*See above: Magnesium Deficiency as a Metabolic Oxidative Stressor*). A 1995 survey of epidemiologic and controlled clinical studies found that all three large epidemiologic cohort studies of high level vitamin E supplementation, lasting at least 2 years, reported that it was associated with significant cardiovascular disease reduction as measured by fatal and non-fatal cardiovascular end points.

Alpha-lipoic acid (ALA) has improved insulin sensitivity in NIDDM patients and has maintained the antioxidant activity of coenzyme Q<sub>10</sub>. Additionally, because of its improvement of capillary blood flow to nerves and other tissues, it has decreased complications of diabetes.

Coenzyme Q<sub>10</sub> has long been known to play important roles in energy-producing oxidative respiration in all cell membranes. Intracellularly, it has direct antioxidant activity, functioning with the other antioxidants in protecting against oxidation of LDL. Its increase of intracellular Mg content may contribute to its usefulness in patients with heart failure associated with mitral valve prolapse and chronic fatigue which are complaints encountered in Mg deficient patients as well as to its antioxidant potency. There have been clinical studies showing efficacy of coenzyme Q<sub>10</sub> in hypertension and in congestive heart failure from a variety of cardiac disorders. Although several indicate impressive lowering of blood pressure, or improvement of cardiac function and quality of life, the current recommendation is that it should be used as adjunctive therapy, in combination with pharmacologic agents.

A trace mineral, selenium, has been reported to be an antioxidant, mostly because of its being a cofactor of antioxidant enzymes, thereby functioning to maintain endogenous antioxidants. It has been reported useful in cardiovascular disease.

This brings us to the likelihood that combinations of the antioxidant nutrients that protect against free radicals, in combination with the mineral that is likely to be deficient in the occidental diet, and deficiency of which releases free radicals—magnesium—are the most promising approaches to controlling the diseases that comprise the Metabolic Syndrome X.

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