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Metabolic Syndrome X – As Defined Through Hair Tissue Mineral Analysis (HTMA) Patterns

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Metabolic syndrome X (MSX) is a term that has been used to describe a cluster of symptoms that appear together, which may increase the risk for the development of diabetes and cardiovascular disease in an individual. MSX has been associated with a generalized metabolic disorder of insulin resistance and is often referred to as the insulin resistance syndrome (IRS). The syndrome is estimated to affect 20 to 25 percent of the adult population in the United States. Even though many of these risk factors have been known for over eighty years, there was not much interest in these findings until Dr. Reaven described Syndrome X in 1988. (George, 2005, Reaven 1988)

Even though the term MSX has gained a great deal of popularity since, there is much confusion, controversy and doubt about its application, particularly since there are no well-accepted criteria for determining the metabolic syndrome in individuals. An article appearing in USA Today by Sternberg discussed this controversy. (Sternberg 2005) To date, over six organizations including the World Health Organization (WHO), the American Heart Association (AHA) and National Heart, Lung, and Blood Institute (NHLBI) have their own versions of the definition and guidelines of MSX. The most current and widely used definition has lowered the guidelines of risk factors to near borderline levels and suggest that the presence of any three findings warrant diagnosis of MSX.

Central Obesity Increased fat deposition in the abdomen. (Waist circumference greater than 40 inches in males and 35 inches in females).

Dyslipidemia Elevated triglycerides (greater than 150 mg/dl), low HDL cholesterol (less than 40 mg/dl in men, less than 50 in females).

Insulin Resistance Hyperinsulinemia, hyperglycemia (fasting blood sugar greater than 110 mg/dl).

Elevated Blood Pressure (greater or equal to 130/85) Use of this definition would dramatically increase the number of people falling into this category and being classified as having MSX. Even Dr. Reaven, who coined the term Syndrome X stated "the AHA and NHLBI have marched beyond the borders of scientific fact. What the AHA did, with other groups, is to come up with a relatively capricious diagnostic category to focus on people who are at risk of coronary heart disease". The American Diabetes Association and

European Association for the Study of Diabetes asserted "too much critically important information is missing" to justify the use of the syndrome as a measure of cardiovascular and diabetes risk. Sternberg noted that the debate has left many questions such as when does a diagnosis genuinely describe an illness and when does it simply give pharmaceutical companies a bigger market?

Current Treatments For MSX

Current treatment of individuals with MSX include, weight management, exercise and drug therapies aimed at reducing specific metabolic risk factors. Drug therapies include anti-hypertensive medications for blood pressure control, statin drugs for abnormal lipoprotein profiles and drugs to help improve insulin sensitivity. Some of the drug therapies have limitations and potential high risks associated with their prolonged use. For example, statins and fibrates can prevent lowering of HDL cholesterol but may induce severe myopathy. Thiazides and B-blockers used for blood pressure control can exacerbate insulin resistance. Even though metformin and thiazolidinediones may improve insulin sensitivity it is unknown if they actually reduce cardiovascular disease risk while still contributing to toxic side effects. Even with treatment, in the long-term, the metabolic syndrome is often resistant to these therapies. (Shulman, et.al 2005) Improving risk prediction of cardiovascular heart disease, an initial goal for determining MSX has been disappointing to say the least. (Kohli, P, et al. 2006)

Factors Contributing to MSX

There are many underlying factors thought to be involved in the development of MSX including genetic and lifestyle factors, neuro-endocrine, metabolic and immunological imbalances as well as emotional status. There is evidence that nutrient imbalances are also involved yet little information is available on the nutritional status of individuals diagnosed with MSX. Since genetics, lifestyle, neuroendocrine and immunological factors contribute to nutritional and metabolic imbalances and which could be affected through nutritional therapy it would be reasonable to assume that MSX could be significantly impacted by individualized nutritional therapy.

Importance Of Nutrition

The need for nutritional assessment and counseling has never been more pressing than it is today due to the epidemic of chronic disease such as obesity, diabetes and hypertension. It is estimated that 300,000 to 800,000 deaths per year are the result of nutrition-related disease. National nutritional policies and recommendations are based largely on preventing short-term deficiencies conditions such as scurvy, beriberi, rickets, goiter etc. However, long-term nutritional deficiencies and imbalances lead to major chronic disease that may take years to manifest. Nutritional requirements needed to prevent inadequate long-term intake are much higher than required for short-term deficiencies and is most often overlooked. Heaney stated "recommendations based solely on preventing the index diseases are no longer biologically defensible." (Heaney, RP. 2003) However, most patients suffering from chronic disease and who also have long-term nutritional deficiency conditions receive little if any nutritional counseling. The estimated average time spent on nutritional counseling by doctors to their patients averaged less than one minute on the subject. A report by Simopoulos discusses the genetic variation and individuality of nutritional requirements and stated "The interaction of certain nutrients with genetically determined biochemical and metabolic factors suggest different requirements for individuals, which raises questions about the use of universal dietary recommendations for a population." (Simopoulos. 1995) It is well known that nutritional deficiencies as well as imbalances between nutrients develop long before signs and symptoms of nutrition-related disease manifest. Also, evidence from the above studies supports the view that nutritional needs should be based upon individual requirements rather than broad, nonspecific recommendations for a population as a whole. This is particularly true for recommendations being made for individuals with MSX as well as other disease conditions.

Nutritional Assessment Through Hair Tissue Mineral Analysis (HTMA)

Mammalian hair contains minerals and other substances incorporated into the follicle during its development that is locked into the hair shaft as it grows from the scalp. Incorporation of minerals into the hair is influenced by several factors. These include diet, environmental exposures, metabolic activity, disease processes, drugs, neurological activity, endocrine activity, physiological needs, stress, immune function, genetics and even emotions. (Watts, 1989, 1990, 1991, 1993, 1994, 1999, 2005,). Any one or a combination of these influences will affect nutritional status that may be reflected in HTMA studies revealing patterns that can be readily recognized and associated with a number of metabolic events and health conditions. (Watts 1989, 1995, 2005) HTMA has become a significant research tool in numerous fields of study including, environmental, epidemiological, archeological, forensic, biochemical and nutritional fields. (Batzevich 1995, Lal, et al. 1987, Srikumar, et. al.1992, Pallholz, et al. 2005, Nowak, et.al. 1998)

For several decades, data from HTMA studies has been recognized as reliable by the Environmental Protection Agency (EPA) of the United States. Human hair is considered a meaningful and representative tissue when properly collected and analyzed for several nutritional elements and heavy metals. (EPA 1979)

HTMA is well accepted as a heavy metal screen but, its acceptance and utilization as a nutritional and metabolic screening tool

has been criticized. Criticism of HTMA as a viable nutritional screening tool is based upon a limited number of studies compared to the thousands of studies documenting its efficacy. To date there has been only a few published papers that criticize HTMA. These studies have been small, inadequate and flawed evaluations by individuals with little or no experience in the field and can only be considered as evaluations of inter-laboratory agreement. These criticisms have been addressed by several of the laboratories performing HTMA testing as well as myself. (Watts, 1999, 2000, 2001) Ultimately these studies simply show that there is some variation in measured results among laboratories performing HTMA. Variations can be expected with any test between laboratories using different procedures and analytical instrumentation.

Laboratories performing the HTMA test today have considerable experience and expertise in this industry. Most have been in existence for more than 20 years. They have invested considerable time and expense toward research, highly skilled professional support staff, and the latest laboratory instruments available for routine elemental analysis. Therefore, one can be assured that laboratory procedures are at their finest, providing accurate, reliable test results from hair specimens that have been properly collected according to established protocol. (Watts, 2000)

Understanding HTMA

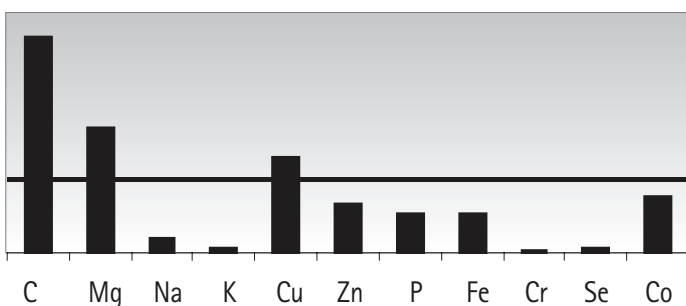
Mineral concentrations in hair are unique and understanding the results of HTMA is important for it to be useful in a clinical setting. Minerals are incorporated into the hair as a result of relatively long-term metabolic activity and are therefore, more stable compared to minerals circulating in the blood. Blood minerals although maintained within normal homeostatic ranges can rapidly change as a result of short-term metabolic activity. Mineral levels can also change in the blood over a short period of time by consumption of food, exertion and even by modifying breathing patterns. Also, since the blood is the mode of transport for minerals entering or exiting the body, and provides transportation of minerals that are being redistributed throughout the body, it is seldom that mineral concentrations found in the hair will match concentrations found in circulation, except in certain circumstances such as extreme deficiency or toxic states. Mineral concentrations found in various organs fluctuate due to many factors, therefore it would not be reasonable to expect hair mineral concentrations to match organ concentration. The same is true for blood minerals verses organ mineral concentrations. Mineral concentrations found in human hair reveal individual mineral levels providing an assessment of the interrelationship between nutrient minerals and heavy metals. HTMA also provides a view into the synergistic and antagonistic relationships between minerals. As an example, the minerals calcium and phosphorus are synergistic in that they work together in the proper balance for building normal bone. However, these two minerals are also antagonistic to each other and too much of one can cause a deficiency or increased requirement of the other. The ideal or optimum calcium/phosphorus ratio established by Trace Elements, Inc. (TEI) is 2.63:1. A marked elevation of calcium relative to phosphorus would indicate an increase in phosphorus requirements, even if the phosphorus level is within the normal range. If this ratio becomes too low a relative phosphorus excess would exist, thereby creating an increased requirement for calcium and calcium cofactors such as vitamin D.

Hair Tissue Mineral Analysis (HTMA) Patterns as a Metabolic Indicator

Mineral interrelationships found in HTMA studies reveal recognizable patterns that can be associated with individual metabolic characteristics and various disease processes. (Watts, 1991) These patterns are derived from the calculated comparison between significant macro and micro-element findings. These calculations reveal significant mineral ratios that can be used to evaluate an individual's nutritional mineral status and metabolic characteristics.

TEI recognizes two major metabolic categories from HTMA patterns. These categories are termed Slow Metabolic Types (parasympathetic dominance) and Fast Metabolic Types (sympathetic dominance). A total of eight types are recognized and include Slow metabolic types 1-4 and Fast metabolic types 1-4.

Figure 1
Parasympathetic Mineral Pattern



In Figure 1 we can see the mineral characteristics of the Slow Metabolic Type 1. Calcium is elevated relative to phosphorus and calcium and magnesium are higher than sodium and potassium.

Figure 2
Sympathetic Mineral Pattern

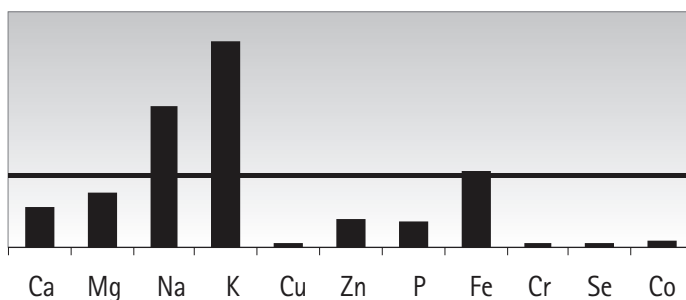


Figure 2 shows the Fast Metabolic Type 1 mineral pattern that is almost opposite of the Slow Metabolic mineral pattern. Phosphorus is higher than calcium while sodium and potassium are higher than calcium and magnesium.

HTMA tests results obtained from over 1 million individuals in the United States and other countries reveal the occurrence of the two major metabolic categories. The Slow Metabolic category is the predominant HTMA pattern type found in the general population. Figure 3 shows the percentage of occurrence of Slow and Fast Metabolic types in a number of different countries, including the U.S. The data includes individuals of all ages and both sexes. We can see that approximately 25 percent of the population fall within the Fast Metabolic category and approximately 75 percent fall within the Slow Metabolic type category for the United States. The other countries also display similar characteristics.

Figure 3
Metabolic Characteristics in Population Groups from various countries based upon HTMA studies

COUNTRY	FAST%	SLOW%
Argentina	11	89
Australia	32	68
Brazil	23	77
China	31	69
England	15	85
Italy	14	86
Indonesia	34	66
Korea	17	83
Norway	45	55
Poland	25	75
Sweden	30	70
United States	25	75

Diabetes Type I and Type II

The pathophysiology of diabetes is complex and poorly understood. However, it is known that the endocrine system including hormones from the hypothalamus, pituitary, adrenal, thyroid, parathyroid, gonads, vitamin D and endocrine function of fat cells are impaired, thereby contributing to the condition. (Alrefai, 2002)

Type I diabetes is characterized by severe insulin deficiency brought about by pancreatic beta-cell damage. Type I diabetes was previously termed juvenile-onset diabetes based upon the age of onset and accounts for five to ten percent of known cases of diabetes.

Type II diabetes, also known as adult or maturity onset diabetes is much more common and accounts for 90 to 95 percent of all cases. Type II diabetes is characterized by peripheral insulin resistance. Insulin resistance is defined as impaired sensitivity to the effects of insulin on whole body glucose utilization. (Williams 1994). Eventually progression of insulin resistance leads to a compensatory hyperinsulinism. (Bowman, Russell 2001). Insulin resistance can be acquired as a result of physiological needs, obesity, ageing, diseases and drugs that antagonize the action of insulin. The effect of insulin stimulating glucose disposal varies extensively among individuals who have diabetes as well as in those who do not have diabetes. (Reaven, 2005).

Our database reveals that diabetes occurs in both the Fast and Slow metabolic types. We calculated the incidence of individuals diagnosed with diabetes based upon metabolic type and found the incidence to be 65% with a Slow Metabolic pattern and 35% with a Fast Metabolic pattern. Since Type II diabetes is found in different metabolic types the mechanisms and therapeutic approach must also be unique.

Neuroendocrine Influence on Mineral Patterns, Body Types

The retention and excretion of nutrients by the body as well as adipose deposition is influenced greatly by the neuroendocrine system. Since mineral patterns can reflect neuroendocrine activity via sympathetic and parasympathetic neuroendocrine control HTMA may serve as a tool in recognizing the nutritional and endocrine abnormalities found in many disease conditions.

As early as 1945 Melvin Page described various body types based upon anthropometric body measurements in conjunction with

blood and hormone tests which he termed andric and gynec patterns. Later Vague discussed masculine and feminine fat distribution and the relationship to risk of developing diabetes and atherosclerosis. (Vague, 1956) Both researchers were referring to peripheral (gynec, feminine) and central (andric, masculine) body fat distribution. Their findings received little attention until now since it is becoming increasingly obvious that fat distribution patterns can be an indicator of potential health problems. The findings of these researchers correlate closely with HTMA patterns.

Diabetes Type II and the Slow Metabolic Mineral Pattern (Insulin resistance)

From observations of HTMA patterns it would appear that Type II diabetes occurs largely in individuals who show a Slow Metabolic mineral pattern and who have reduced insulin sensitivity. Slow Metabolic Types tend to have a pear-shaped body structure due to peripheral adipose deposition (hips and thighs). Peripheral fat distribution or increased fat deposition in the lower extremities produces the pear shaped body structure. This is related to Page and Vague's description of being a gynec or female characteristic, although this pattern can be present in both males and females. Adipose distribution in these regions of the body is influenced by insulin, parathyroid hormone (PTH), and estrogen. PTH also promotes weight gain via the blunting of catecholamines on lipolysis (McCarty, et.al. 2003) This neuroendocrine pattern tends to reduce the metabolic rate due to the above endocrines opposing or blunting the thyroid and adrenal response. Insulin is known to suppress thyroid activity and reduce thermogenesis. (Piolono, 1990, Litaka 2000) Adipose tissue is a key target organ of insulin which inhibits lipolysis thereby, contributing to obesity due to an enlargement of fat depots. (Norman, Litwack 1997) This mineral pattern is associated with hyperinsulinism due to a likely defect in the number of receptors in target cells limiting the normal effects of insulin and may eventually contribute to adult onset diabetes.

Elevation of HTMA calcium and magnesium in conjunction with the increased calcium/magnesium ratio would indicate increased parathyroid (PTH) activity. (Watts, 1989) This pattern would also indicate increased vitamin D activity as influenced by PTH which are known to enhance insulin secretion. The mineral calcium is necessary for insulin secretion as well. This increase in potential insulin secretion is most likely a compensatory effect due to a decrease in tissue sensitivity. Hyperparathyroidism is associated with insulin resistance. Diabetic individuals with PTH tumors require significantly less insulin following PTH surgery and exhibit normalization of glucose control. (Gerl, et al. 1998, Richards, et al. 1999) Typically chromium, a metallo-enzyme involved in insulin receptors sites is usually found low, again increasing the requirement for insulin. Copper is known to be affected by estrogen. Estrogen and copper are considered diabetogenic when in excess. An increase in tissue copper in this pattern suggests further insulin stimulation.

Estrogen PTH and vitamin D all share in the synthesis and enhancement of insulin secretion by contributing to the rise in tissue calcium concentrations. Estrogen, PTH and vitamin D along with growth hormone are considered anabolic and lipogenic hormones that enhance fat storage. Their individual and most likely combined effects are responsible for increased peripheral fat deposition and reduced lipolysis. Reduced tissue insulin sensitiv-

ity enhances these hormonal responses in an attempt to compensate by increasing insulin production which increases fat deposition further reducing insulin's effect on tissues. An increase in circulating insulin and glucose depletes receptor sites due to increases in chromium loss. Eventually when compensation can no longer be achieved through this cycle, diabetes ensues and the higher insulin requirements must be met externally. A reduction in the metabolic rate also develops due to the antagonistic effect of PTH, estrogen, insulin, vitamin D and growth hormone on the thyroid and adrenal activity and/or by their effect of reducing the tissue sensitivity to the metabolic effects of adrenal and thyroid hormones. Rather than obesity causing diabetes we can see by this mechanism that this hormonal cascade actually contributes to obesity rather than obesity itself being responsible for the development of Type II diabetes.

A reduction in thyroid expression is related to increased blood cholesterol and triglyceride levels. However, individuals with this peripheral fat distribution characteristic, have an increased ability to rapidly clear or dispose of excess free fatty acids (FFA), an insulin antagonist, from the circulation. (Koutsari, 2006) Efficient disposal of circulating FFA's would greatly reduce progression of atherosclerosis.

The body's immune system may also be involved in the development of diabetes. Over activity of the cellular immune response can contribute to an autoimmune reaction. This can result in the production of antibodies to insulin and thyroid hormones. A cellular immune response can be triggered by many factors, but the most common triggers are from viruses and hormones particularly estrogen.

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Diabetes and the Fast Metabolic Mineral Pattern (Insulin antagonism)

Individuals who have fat distribution largely in the abdominal region termed central obesity, have been referred to as having an apple shaped body structure. This pattern of central fat deposition is largely a male characteristic. This is most common in individuals with the Fast Metabolic Type I mineral pattern and is influenced by dominance of anterior pituitary, adrenal cortex as well as the thyroid. Dominance of these stimulatory endocrine glands suppresses or blunts the expression of PTH, and estrogen and contributes to an increase in the metabolic rate. The basal metabolic rate is found to be increased in individuals with this body characteristic. (Tataranni, 1994) It should be noted that fat distribution in this region of the body is not influenced by insulin. Bujaiska and colleagues suggested that central obesity can be described as "Cushing's disease of the omentum". (Buja iska 1997) Omental fat cells can generate active cortisol due to constant exposure of those cells to glucocorticoid hormones generated by the adrenals. A similar metabolic situation is seen in patients with Cushing's syndrome, a metabolic condition related to the development of central obesity.

We can see in Figure 2 that the Sympathetic type mineral pattern reveals an elevation of the minerals sodium (Na) and Potassium (K) above the mean. Since these minerals are a reflection of the adrenal response, increased adrenal cortical activity may be indicated. The relationship or balance between Na and K can give an

indication of the dominant adrenal steroid influence. Specifically, a low Na/K ratio would indicate increased glucocorticoid (GC) dominance as GC increases K retention. GC also known as glyco-corticoid influences glycogen deposition or storage in the liver, acts as an anti-inflammatory hormone and is catabolic in nature.

Individuals with the Fast Metabolic Type 1 mineral pattern could be described as having sub-clinical "Cushing's Syndrome" and is the most likely pattern associated with insulin antagonism rather than reduced insulin sensitivity. The thyroid and adrenals are dominant in this pattern contributing to a loss of calcium and magnesium. Since insulin release is calcium dependent a low calcium/phosphorus, calcium/sodium, and calcium/potassium ratios would indicate reduced insulin release and/or insulin antagonism and is associated with a reduction in PTH. PTH through the action of PTH related protein (PTHrP) enhances beta cell function in the pancreas and inhibits beta cell death. (Sawads, et.al. 2001, Cerbian, A, et al.2002) It is therefore, not only important but imperative to restore PTH activity in diabetic patients with a Fast Metabolic Type mineral pattern.

Diabetes in Individuals With MSX - Better Described as Diabetes Type III

Since diabetes occurs in both metabolic types the mechanisms and progression of diabetes must be different as well. Insulin resistance and insulin antagonism or deficiency occurs along a very fine metabolic line and therefore, use of the term diabetes Type II may not be appropriate. I suggest that a better term would be a new classification of diabetes to include diabetes Type III based on insulin antagonism or insulin deficiency rather than insulin resistance or reduced insulin sensitivity. Mechanisms for this hypothesis are discussed below based upon HTMA analysis.

Insulin Antagonism Due To Endocrine Abnormalities in Diabetes Type III

Obesity is known to be related to endocrine abnormalities involving increased adrenal cortical activity (Cushing's Syndrome), insulinoma, polycystic ovarian syndrome (PCOS), hypothyroidism, testosterone and growth hormone deficiency. Treatment of the underlying endocrine abnormalities can lead to a reversal of obesity. (Kokkoris P, et al 2003) By the same token since diabetes is associated with co-existing endocrine abnormalities involving the hypothalamus, pituitary, adrenal, thyroid, parathyroid, gonads and adipose endocrine function (Alrefaih, et al. 2002), it is therefore, reasonable to assume that treatment of the endocrine abnormalities can lead to control and even amelioration of diabetes.

Diabetes Type III is associated with insulin antagonism rather than insulin resistance. Insulin antagonism can be caused by any one or combination of endocrine abnormalities listed above. Individuals with Cushing's syndrome, Grave's disease and acromegaly usually have impaired glucose tolerance and high levels of circulating insulin. Hyperthyroidism can antagonize the effect of insulin in hepatic and extrahepatic tissues. Excessive adrenal glucocorticoids also have an insulin antagonism effect (Iitaka, M, et al. 2000) and responds to a reduction in adrenal activity. (Ogura, M, et al. 2003).

Excessive Free Fatty Acids and Insulin Antagonism

Increased adrenal and thyroid activity contribute to an increase in lipolysis, thus contributing to increased circulating levels of free fatty acids (FFA). An increase in GC provides a ready supply of cortisol to the adrenal medullas and enhances the rate of norepinephrine to epinephrine conversion. (Hormones 2nd ed. 1997). Hormones from the adrenal medulla and cortex activate fat cell lipase which in turn causes hydrolysis of tryglycerides, releasing large quantities of FFA and glycerol into circulation. (Guyton and Hall, Physiology 1996), and enhances gluconeogenesis.

The thyroid has a synergistic relationship to the adrenal hormones. Typically when the adrenals are dominant the thyroid is also dominant. An increase in thyroid secretion also enhances the secretion of other endocrine glands. In its relationship with the adrenals, thyroid hormone increases the rate of GC inactivation by the liver. This causes a feedback mechanism of increasing adrenocorticotrophic hormone production by the anterior pituitary that in turn increases the rate of glucocorticoid production by the adrenals. (Hormones 2nd ed. 1997). This vicious circle results in their combined effects of increasing central adipose deposition, antagonizing insulin, further contributing to lipolysis and excessive FFA in circulation. Normal metabolic levels of FFA do not adversely affect insulin, but high levels may antagonize insulin, and contribute to lipotoxicity. (Bergman, 2000, Feldstein et al 2004, Reaven, 1988, Koutsari 2006) Excessive FFA produces ectopic redistribution of fat into the liver, musculature and even the pancreas. This process is associated with carbohydrate sparing effect, increased glucose production and decreased glucose uptake through changes in the activity and ratios between leptin, resistin, tumor necrosis factor-alpha and adiponectin. (Harris, et al. 2004)

Inflammation and Insulin Antagonism

Inflammation has also been associated with diabetes and cardiovascular disease risk. Inflammation apparently produces a defect in insulin-stimulated muscle glucose transport involving activation of the serine kinase cascade. This can lead to an increase in intramuscular cellular lipid content similar to defects in mitochondrial fatty acid oxidation. (Perseghin, et al. 2003) Elevated sympathetic activity leads to increased cortisol, which increases levels of interleukin-6 and C-reactive protein that is an indicator of inflammation. (Hjemdahl, 2002)

Elevated Homocysteine and Insulin Antagonism

Hyperhomocysteinemia is a contributor to increased vascular risks. Animal models have shown that elevated homocysteine levels were associated with a significant increase in triglycerides and blood pressure. (Oron-Herman, et al 2003) The sympathetic dominant mineral pattern particularly the elevated Na and K and low Na/K ratio indicate an increased need for Co and B12. B12 requirements may also be increased when the K/Co ratio is elevated above 450.

Neurohumoral Response to Stress and Insulin Antagonism

The release of corticotrophin, epinephrine, norepinephrine and glucocorticoids are increased during periods of stress and are mediated by sympathetic stimulation. (Guyton, 1996). Excessive stress or more importantly when adaptation to stress is lacking the ensuing endocrine and metabolic cascade discussed previously will become prolonged and contribute to Type III diabetes due to exacerbation of insulin antagonism. (Hjemdahl, 2002, Bjorntorp, 1999). Stress or maladaptation has a major influence on disease progression particularly cardiovascular disease and diabetes. Perceived stressors initiate the hypothalamic-pituitary-adrenocortical axis, thereby enhancing glucocorticoid release. Faulty glucocorticoid receptors (GR) leads not only to insulin antagonism but, also to altered Na-K ATPase activity. (Hjemdahl, 2002, Bjorntorp, 1999, Kurup, 2003). Another neuronal pathway exists between the liver and adipose tissues via the afferent vagus nerve from the liver to the hypothalamus and eventually the sympathetic neurological effects upon adipose tissues. Normally as excess energy builds up within the liver information is sent to the hypothalamus via the afferent vagus nerve which then activates the sympathetic response to increase energy expenditure and lipolysis. (Uno, K, et.al. 2006). When this homeostatic control mechanism is disrupted another vicious cycle develops. Increased lipolysis results in an increase in FFA's further contributing to liver lipotoxicity which activates the afferent vagus-hypothalamic-sympathetic response increasing lipolysis and further release of excessive FFA's.

Nutritional Imbalances and MSX

The Fast Metabolic type has nutritional imbalances that can further contribute to and/or exacerbate MSX, diabetes and the associated cardiovascular predisposition, progression and complications. HTMA studies can readily reveal these imbalances and provide a specific targeted approach to therapy.

Calcium and Vitamin D Deficit

An increase in the need for calcium and calcium cofactors (vitamin D), are usually present in the Fast Metabolic Type. This is related to the neuroendocrine factors such as increased adrenal and thyroid activity as well as a reduction in PTH expression. As mentioned previously PTHrP enhances beta cell function in the pancreas and inhibits beta cell death. (Sawads, et.al. 2001, Cerbian, et al. 2002). This neuroendocrine pattern leads to diminished absorption and an increase in the loss of calcium from the body. This would result in a decrease in normal insulin release from the pancreas since insulin requires adequate amounts of extra cellular calcium concentration for its release. (Nordin, 1988).

Since insulin release is calcium dependent low calcium/phosphorus calcium/sodium, and calcium/potassium ratios would indicate reduced insulin release and /or insulin antagonism and is associated with a reduction in PTH. This neuroendocrine pattern also results in the retention of the minerals phosphorus, sodium and potassium that are also antagonistic to calcium and calcium cofactors. Increased retention of these elements would further reduce insulin release.

Magnesium

A lack of magnesium or an increase in the requirement for magnesium exaggerates the stress response. As stated by Seelig, "When magnesium deficiency exists, stress paradoxically increases risk of cardiovascular damage including hypertension cerebrovascular and coronary constriction and occlusion, arrhythmias and sudden cardiac death" (Seelig, 1994) The adrenergic stimulation of lipolysis is intensified with magnesium deficiency and magnesium deficiency enhances adrenergic stimulation, increasing the release of catecholamines by the adrenals. This can be brought on by physical or psychological stress. Low intracellular magnesium is implicated as a significant component of MSX. (Seelig, 2002) and diabetes Type II. (Huerta, 2005, Hasebe, 2005, Mitka, 2004, Lal et al. 2003, Rodriguez-Moran et al 2003) Experimental magnesium deficiency has been shown to be related to an inflammatory syndrome and excessive free radical production. (Mazure, et.al. 2006)

Increased sodium retention antagonizes magnesium retention and of course a reduction in magnesium enhances sodium retention. This interrelationship leads to an elevation in blood pressure. This condition of excess sodium retention and increased magnesium loss are both associated with the inflammatory response.

Magnesium deficiency has also been associated with metabolic disturbances due to a mitochondrial defect. A mutation in a mitochondrial gene has been found to be associated with hypertension and hypercholesterolemia, in conjunction with lowered levels of magnesium. (Marx, J. 2004). It is interesting to note that Watson suggested that individuals who he classified as having a "Fast Oxidation" rate were experiencing a rapid glycolytic activity within the cell. (Watson, 1972). The first step of glucose metabolism in the glycolysis cycle involves the enzyme hexokinase which is magnesium dependent. Watson's description of the "Fast Oxidizer" tends to resemble our description of Fast Metabolic Types recognized through HTMA mineral patterns. Even though magnesium is deficient in the Fast Metabolic HTMA pattern, a rapid rate of cellular glycolytic activity may still exist due to increased levels of glucose-6-phosphatase (G-6-P), an enzyme that can inhibit hexokinase and can be hydrolyzed directly by glucose-6-phosphatase (G-6-Pase). G-6-Pase is present in the liver, kidneys and intestine and yields free glucose. Liver G-6-Pase activity requires and is enhanced by the presence of lipids. (Bondy, et al. 1980). Increased activity of this enzyme may account for the elevated glucose in patients with MSX.

Copper

Copper is essential in collagen synthesis and antioxidant enzyme systems and therefore, vascular integrity. A deficiency of copper is known to result in glucose intolerance, decreased insulin response and is associated with hypercholesterolemia, abnormal HDL/LDL ratios and enhanced glycation. Copper deficiency is known to be related to diabetes and cardiomyopathy. (Saari, et al. 1999, Prohaska, 1990, Medeiros, et al. 1993, Schuschke, 1997).

Copper/Iron Ratio

Since copper is necessary for the binding of iron to hemoglobin a deficiency of copper can result in an increase in hepatic and pancreatic iron accumulation. Excess iron relative to copper enhances lipid peroxide formation adversely affecting insulin

release and liver function. (Bureau, et.al. 1998, Watts, 1988,1989).

Zinc/Copper Ratio

Klevay has shown a positive relationship between a relative copper deficiency and heart disease. A deficiency of copper relative to zinc (elevated Zn/Cu ratio >14) is associated with a decrease in HDL and an increase in LDL. (Klevay, 1975). An elevated hair zinc/copper ratio has been found in individuals who were hospitalized for myocardial infarction (MI). The similar hair mineral imbalance was also found in the descendants of MI patients. This suggests that an elevated Zn/Cu ratio may be predictive in younger individuals to the susceptibility of MI. (Taneja, et.al. 2000). Statistical studies conducted at Trace Elements revealed that the HTMA Zn/Cu ratio was elevated in over seventy-five percent of a patient population who had suffered a stroke.

Nutritional Indications and Contraindications in MSX

Diet as well as dietary supplementation can play a significant role in the prevention or progression of syndromes related to MSX. High carbohydrate diets and trans fatty acids for example have been shown to adversely affect and even accentuate the metabolic abnormalities of MSX such as weight gain, atherosclerosis and insulin abnormalities. (Reaven, 1997. Odegaard, et al. 2006. Mozaffarian, et. al. 2004).

Excess fructose intake has also been related to increase blood pressure in animal studies. Fructose is known to antagonize copper (Fields, M, et al. 1984, O'Dell, 1990) and thus can exacerbate the imbalance between zinc-copper and iron-copper ratios. (Watts, 1989) These imbalances lead to increased free radical production and tissue damage.

Other factors such as excess intake of vitamin C, vitamin A, niacin, zinc, molybdenum and iron also are antagonistic to the mineral copper and can contribute to insulin abnormalities, cardiovascular disease as well as other components of MSX. It can be noted that these factors are unrelated to fat intake. (Bogden, et al. 2000). Copper is an essential element in reversing the tissue damage caused by free radical damage particularly those caused by excess of other elements, such as iron.

Vitamin A in small concentrations aids in the stimulation of insulin release from the pancreas but high concentrations can inhibit insulin release. (Mooradian, et al. 1987). A recent study found elevated levels of retinol-binding protein 4 (RBP4) in patients with central obesity and in patients with diabetes compared to individuals who did not exhibit obesity or diabetes. RBP4 is of course the principal transport protein for vitamin A or retinol, and is secreted by adipocytes. (Graham, et al. 2006). This would be expected since vitamin A is antagonistic to vitamin D and calcium. (Watts, 1991, 1990).

Any dietary or other factors that would inhibit calcium could potentially worsen any of the syndromes associated with MSX. The Mediterranean-style diet is known to reduce the prevalence of MSX and associated risk factors.

However, there has been found an increase in hypertension in individuals who add cereal intake in conjunction with the diet. (Meydani, 2005). Cereals and grains contain phytate that inhibit calcium absorption and may reduce retention and increase excre-

tion of calcium, as well as other critical elements from the body.

The avoidance of refined carbohydrates, grains, cereals and fructose is extremely important for reducing the progression of MSX and related syndromes. Adequate protein intake is important for building lean muscle mass and weight loss. Magnesium has been proven to be important in individuals with MSX as well as anyone with cardiovascular disease, diabetes and related disorders. Magnesium along with calcium and vitamin D helps in preventing progression of MSX complications by aiding in the reduction of the stress reaction as well as helping reduce blood pressure and maintain glucose control. Chromium supplementation is found helpful in all types of diabetes and may play a significant role in preventing progression of cardiovascular disease.

Conclusion

The metabolic syndrome has no defined etiology that can be targeted by specific treatment and its' use in predicting risks for cardiovascular disease has proven disappointing as well. (Kohli, et al. 2006) Kahn, et al. stated that the new definitions of MSX has major flaws. (Kahn, R, et al. 2005) The definition of MSX is assumed to predict diabetes and cardiovascular disease (CVD), but in fact includes diabetes and CVD. The American Heart Association (AHA) and American Diabetes Association (ADA) have been at odds over the clinical relevance of the metabolic syndrome. The ADA feels that MSX is poorly defined and misleading and there is no consensus of agreement as to the utility of the grouping of risk factors associated with MSX. (Mitka, 2006).

It is obvious from the above discussion that the development of MSX is complex and multi-causal. The condition involves not only genetic, lifestyle, environmental and emotional factors, but development and progression is greatly influenced by neuroendocrine and nutritional imbalances.

HTMA may serve as a useful screening tool for assessing individuals with a predisposition toward MSX. Further research will undoubtedly show that HTMA patterns will provide not only an indication of MSX but, also reveal factors contributing to the underlying progression of the associated syndromes. HTMA will substantially aid in assessment of the collective factors, which is necessary for determining a specific targeted nutritional approach in treatment and prevention.

In reviewing this paper one should be cautious in drawing conclusions and making applications. There are not only biological differences contributing to diabetes and CVD, but also biological variability among each metabolic type. One should not assume that there exists a single mineral pattern and therefore, nutritional approach for all individuals who have MSX. There are several subtype mineral patterns associated with each metabolic type. Therefore, each person should be assessed and treated as an individual rather than being grouped under a broad category of disease or syndrome. With the recognition of biological individuality that can be assessed through HTMA and other methods, the concept of one diet or nutritional approach for diabetes, heart disease and other health conditions is obsolete and can no longer be justified. Quoting Ann Coulston, "Changes in philosophy, scientific recommendations, and terminology shift the nutrition management of diabetes from a mathematical to a cognitive process.." (Coulston, 1994). This statement is true for the treatment of most health conditions and provides the opportunity for increasing the effectiveness of nutritional therapy.

References available by request or at www.interclinical.com

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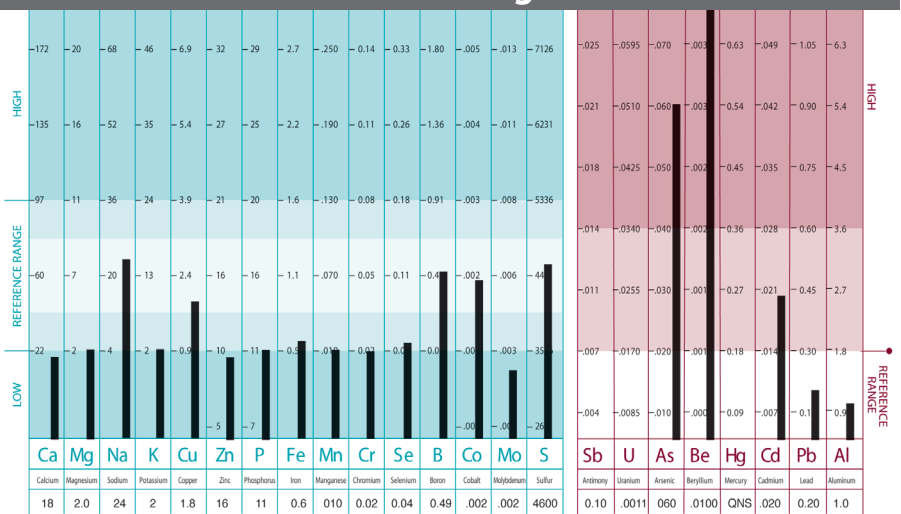
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