Women's Health Profile Guide

Vive la Différence

"For what is done or learned by one class of women becomes, by virtue of their common womanhood, the property of all women."
—Elizabeth Blackwell (The first woman in the U.S. to become a physician)

Information about women's health was originally gleaned from extrapolating data from studies of men. Women's health is of course distinct; women are not little men. However, women often still do not receive the same level of treatment as men. (Kim, Hofer, and Kerr, J., Gen Intern Med 18:854-863, 2003 (AHRQ grant HS11540). Therefore it is imperative that women take charge of their own health. One of the biggest contributors to understanding a woman's health is knowing and understanding her laboratory test values.

Endocrine

Insulin Sensitivity

Metabolic syndrome is a combination of different risk factors. Insulin resistance increases the risk for atherosclerotic cardiovascular disease by 2-fold, and raises the risk for type 2 diabetes by 5-fold. More than 50 million Americans have metabolic syndrome.[1] Women however have unique features of metabolic syndrome that include insulin resistance associated with both polycystic ovarian syndrome and increased abdominal fat.[2] Menopause also changes a woman's risk via a decline in circulating estrogen levels.[3] Furthermore, research has found women's health issues are less likely to be managed as aggressively as men's. In a study of adults with atherosclerosis and high cholesterol women were 23% less likely to receive intense cholesterol management than men.[4]

The National Cholesterol Education Program - Clinical Identification of the Metabolic Syndrome

Waist Circumference	>88 cm (>35 in)
Triglycerides	>150 mg/dl
HDL cholesterol	<50 mg/dl
Blood pressure	>130/>85 mmHg
Fasting glucose	>110 mg/dl

1. Insulin

Insulin is a hormone, secreted by the pancreas, which helps put glucose, or blood sugar, into cells. Cells use glucose as fuel. Glucose is therefore essential, but excess glucose can lead to significant health problems. Many people have a condition called insulin resistance or metabolic syndrome. Insulin resistance happens when the body does not respond correctly to insulin, so it continues to pump more and more insulin to help get glucose into the cells. Generally, though, the body cannot completely compensate and the person ends up with elevated glucose and insulin levels.[5] Many diabetes medications work by stimulating the pancreas to secrete more insulin.

2. Glucose

Blood glucose is a term used to refer to levels of sugar in the blood. Blood glucose is regulated by hormones, such as insulin. If the body is unable to regulate glucose levels appropriately, blood glucose levels will become elevated and have a negative effect on health. Diabetes or insulin resistance syndrome result in elevated glucose levels. Increased glucose levels can lead to micro vascular disease and increase the risk of cardiovascular disease, amputations, blindness, kidney disease and others. The American Diabetes Association defines a fasting plasma glucose level of < 100 mg/dl as normal, and a level of 100-126 mg/dl as impaired fasting glucose, for those without diabetes.[6]

3. HDL

HDL is also called the 'good cholesterol' because it takes cholesterol from the arteries and delivers it to the liver where it is excreted or processed, thus it takes cholesterol away from cells. An HDL over 60 mg/dl is considered to be protective, while below 40 mg/dl is a risk factor for cardiovascular diseases.[7] Low levels of HDL have been shown to be a stronger risk factor for women than for men.

4. LDL

LDL, also called the "bad cholesterol", transports cholesterol from the liver to peripheral tissues, thus it brings cholesterol to cells. Lowering LDL is often a primary focus of treatment in the prevention of cardiovascular disease. Populations with lifetime LDL-cholesterol levels <100 mg/dl are associated with a very low risk for CHD. Thus an LDL <100 mg/dl is considered optimal, while a level of less than 130 mg/dl is considered near optimal.[7] Specific recommended levels are based on your number of risk factors of heart disease.

5. Triglycerides

Triglycerides are the chemical form in which most fat exists in food as well as in the body. They are present in blood plasma and, in association with cholesterol, form the plasma lipids. Triglycerides in plasma can also be made by the body from other energy sources like excess carbohydrates or protein calories that are not used immediately by tissues, and get converted to triglycerides. Triglycerides, from fat tissue, help to meet the body's needs for energy between meals. Unfortunately, if triglycerides get too high, as in hypertriglyceridemia, it becomes a risk factor for cardiovascular disease. The American Heart Association recommends triglycerides should be < 150 md/dl.[7]

The risk of cardiovascular disease and metabolic syndrome can be reduced by several modifiable habits.[7, 8] These include:

- Lowering saturated and trans fats
- Increasing monounsaturated and polyunsaturated fats (such as omega-3 fatty acids)
- Increasing soluble fiber (by increasing whole grains, fruits and vegetables)
- Ensuring adequate intake of B vitamins and antioxidant nutrients
- Increasing plant sterols
- Maintaining an ideal weight
- Increasing exercise
- Stopping smoking
- Avoiding excess alcohol intake
- Avoiding very high-carbohydrate diets (>60 percent of total energy)

Estrogen Metabolites

6. 2-hydroxyestrone (2-OHE1)
7. 16- hydroxyestrone (16-alpha-OHE1)
8. 2/16 ratio

Researchers have found that the body metabolizes estrogens into several different forms that can impact cancer development. One form, 2-hydroxyestrone (2-OHE1), tends to inhibit cancer growth and has been referred to as the "good" estrogen. Another, 16-alpha-hydroxyestrone (16-alpha-OHE1), actually encourages tumor development, and has been referred to as the "bad"estrogen.

Studies have shown that measuring the ratio of these two forms of estrogen provides an important indication of risk for future development of breast cancer.[9] This ratio of "good to bad estrogen" is determined from a single urine specimen. Studies have shown that women with low Estronex™ 2/16 ratios have much higher rates of breast cancer. Low Estronex 2/16 ratios also indicate increased long-term risk for other estrogen-sensitive cancers, including uterine, ovarian, cervical, and even head and neck cancers. Though a woman's biochemical individuality certainly affects how much of each form of estrogen is produced, in many women the primary cause of a low 2/16 ratio is related to dietary factors. Consuming more foods containing indole-3-carbinol (I3C) can raise the Estronex 2/16 ratio.[10] I3C is found in cruciferous vegetables, like broccoli, cauliflower, cabbage, and Brussels sprouts. Nutritional supplements containing I3C or diindolylmethane (DIM), a supplement closely related to I3C, have also been shown to raise the Estronex 2/16 ratio. Follow-up testing is strongly recommended to ensure that the treatment plan is effective over time. Other potentially favorable dietary changes are addition of ground flax seed or soy isoflavones and fish oils (omega-3 fatty acids), which can help to increase the Estronex 2/16 ratio.[10]

Cell Regulation

Nitric Oxide Regulation

9. Arginine

Arginine is a conditionally essential amino acid that is critical for cardiovascular health and detoxification functions. Arginine is used to make the powerful blood vessel regulator nitric oxide. Nitric oxide acts to lower blood pressure. Too little arginine can lead to high blood pressure. Too much arginine can lead to increased aging from oxidative damage. Arginine is measured in blood and markers of arginine insufficiency are measured in urine. High citrate, isocitrate, cis-aconitate, or orotate (Organix profile analytes) can indicate arginine insufficiency. The essential amino acid lysine needs to be present in amounts balanced with arginine to ensure healthy immune system function.

10. ADMA

As the principal endogenous inhibitor of nitric oxide synthase, ADMA (asymmetric dimethylarginine) regulates rates of nitric oxide (NO) formation. Nitric oxide acts as a signal molecule in the nervous system, as a weapon against infections, as a regulator of blood pressure, and as a gate keeper of blood flow to the organs. Elevated ADMA is a risk factor for hypertension, cardiovascular disease, renal failure, and erectile dysfunction.[11, 12]

11. Arginine/ADMA ratio

A number of standard heart disease risk factors (smoking, hypertension, hyperlipidemias) are related to vasodilatory impairment, but the strongest correlation may be the ratio of arginine to ADMA in plasma.[13] This ratio has been used to assess the balance of stimulatory and inhibitory effects on NO synthesis.[14] Elaboration of endothelium-derived nitric oxide affects the behavior of circulating T lymphocytes and monocytes. Mononuclear cell adhesiveness is inversely correlated with the plasma L-arginine/ADMA ratio, and the effect is reversed by restoration of the ratio to control levels with oral administration of 14–21 grams of arginine.[15]

Eicosanoid Balance

The proper fats and oils are necessary for cell membranes, nerve coverings, hormone production, vitamin absorption, and more. Most of us get a lot of fat in our diet, but it is often not the quality of fat we should be getting. We need to eat more "good" fats from fish, seeds, nuts, vegetables, and healthy oils (omega- 3, 6, and 9), and less of the trans, saturated fats found in processed foods.

12. Eicosapentaenoic Acid

Deficiency of eicosapentaenoic acid (20:5n3) is likely the most prevalent fatty acid abnormality affecting the health of individuals in western societies. Low levels in plasma or especially in erythrocytes indicate insufficiency. Low levels have been associated with arthritis, heart disease, depression and general aging.[16-18] Eicosapentaenoic acid (EPA) is anti-inflammatory and should balance the levels of pro-inflammatory arachidonic acid. Although EPA can be produced from the essential fatty acid, alpha linolenic acid (ALA), dietary intakes of this fatty acid are generally poor. The conversion also requires the action of the delta-6 desaturase enzyme that may be low due to inadequate Zn, Mg, or vitamins B3, B6, and C. Such an enzyme impairment would be indicated if EPA is low and ALA is normal or high. High levels of saturated, monounsaturated, trans fatty acids, and cholesterol also slow the conversion of ALA to EPA (as well as GLA to DGLA).

13. Docosahexaenoic Acid

The growth and development of the central nervous system is particularly dependent upon the presence of an adequate amount of the very long chain, highly unsaturated fatty acids, docosapentaenoic (22:5n3) and docosahexaenoic acids (22:6n3).[19, 20] Attention deficit hyperactivity disorder and failures in the development of the visual system in EFA deficiencies are two examples of this dependency.[21] Docosahexaenoic acid (DHA) is an important member of the very long chain fatty acids (C22 to C26) that characteristically occur in glycosphingolipids, particularly in the brain. Since this fatty acid is so important in early development, it is worth noting that the levels in breast milk are correlated with the mother's intake of fish oils, which are rich sources of both of these fatty acids.[22] DHA intake may also help to lower blood pressure and the risk of cardiovascular disease.[23, 24]

14. Arachidonic Acid

Because of the prevalence of corn and corn oil products in feed for cattle and hogs, diets high in these red meats are rich in arachidonic acid (20:4n6). Arachidonic acid (AA) is a 20-carbon or fatty acid that serves as the principal pro-inflammatory fatty acid. Its synthesis is inhibited by non-steroidal anti-inflammatory drugs (NSAIDs). High AA promotes gallstone formation by stimulating mucin production in the gallbladder mucosa.[25]

15. AA/EPA (Omega-6/Omega-3) Ratio

AA and EPA are the most critical fatty acids for maintaining the ratio of the omega-6 and omega-3 classes because they compete for enzymes that make cell regulators. A high ratio indicates an overabundance of the pro-inflammatory, omega-6 fatty acid, AA. An overabundance of AA is quite common in Western high meat and corn oil diets and can result in an imbalance in the AA/EPA ratio. This is one of the indicators that extra omega-3 fatty acids, including EPA of fish oils, would be beneficial.

Cell Protection

Cell Membrane Oxidation

16. Lipid peroxides

Also known as TBARS (thiobarbituric acid reactive substances), lipid peroxides are a product of oxidative damage to the fatty acid portion of cell membranes. LDL appears to have the highest susceptibility to lipid peroxide damage. Lipid peroxides can aid in monitoring the tissue damaging effects of oxidative stress. Lipid peroxide levels are positively correlated with smoking, high triglycerides, body mass index, and fibrinogen, and negatively correlated with HDL and vitamin C.

Elemental Cofactor Status

17. Magnesium (Mg)

Magnesium serves as a cofactor in approximately three hundred enzyme systems, making this element a critically important nutrient for many bodily functions. Deficiency conditions are associated with a wide variety of problems including hypertension, diabetes, and pre-menstrual syndrome. Magnesium plays a vital role in normal cardiac function, and deficiency has been increasingly associated with cardiovascular disease. Some suggest hypomagnesemia is in itself atherogenic. Magnesium has also been found to be useful in the treatment of congestive heart failure, tachycardia, and other arrhythmias. Magnesium deficiency in humans is rarely severe, although symptoms of marginal deficiency may be many and varied. The magnesium content of red blood cells is a good indicator of short-term magnesium status. Because magnesium is required by many enzymes involved in energy transfer, magnesium deficiency affects all tissues. As the largest energy user, nervous tissue shows the earliest signs of deficiency, with the appearance of dullness and listlessness, nausea and loss of appetite, alopecia (rapid hair loss), and tremors. The major dietary sources of magnesium are nuts, beans, and dark green vegetables.

18. Zinc (Zn)

Growth and tissue repair are dependent on zinc as an activating cofactor for DNA/ RNA. For this reason, zinc is vital to the normal healing of wounds and skin disorders. Dermatoses related to low zinc status are well-known; acrodermatitis enteropathica is a severe deficiency seen in infants, and a milder form is seen in adults. Zinc is required for normal immune function. In fact, there are many similarities between the immunologic affects of zinc deficiency and those of AIDS. Low zinc is associated with low T-helper lymphocytes. If

intake of calcium, copper, or iron is excessive, tissue zinc may become depleted. If zinc is elevated, problems that might occur include iron non-responsive anemia due to related copper deficiency and increased vascular disease risk from lowered HDL cholesterol. Sources of zinc in the diet include whole grains, nuts, seeds, and seafood, especially shellfish.

Metabolic Markers[26, 27]

B-Vitamin Insufficiency

The B-complex vitamins are necessary for many enzymes in the body to function properly. The body uses enzymes to extract energy from food, build new tissue, remove toxins, and maintain the immune system.

19. Pyruvate

Pyruvate may be elevated when B vitamins, particularly B1 and B5, are insufficient. In order for pyruvate to move into the mitochondria to enter the Krebs cycle it must be broken down by pyruvate dehydrogenase enzyme. The pyruvate dehydrogenase enzyme requires several B vitamins to function correctly, such as vitamins B1, B2, B3, B5 and lipoic acid.

When both lactate and pyruvate are high, there may be insufficient lipoic acid, a type of B vitamin. Lipoic acid is an important antioxidant, so low levels can lead to aging-related illnesses. Many studies have shown that lipoic acid is helpful in treating diabetes and for assisting the liver with removing toxins from the body

Alpha-Keto-acids

20. Alpha-Ketoglutarate
21. alpha-Ketoisovalerate
22. alpha-Ketoisocaproate
23. alpha-Keto-ß-methylvalerate

These keto acids also require vitamins, B1, B2, B3, B5 and lipoic acid to prevent their accumulation and spilling into urine. Thus elevations of these organic acids, and pyruvate may indicate insufficiency of these B vitamins.

24. Xanthurenate

Your body needs vitamin B_6 (pyridoxine) to utilize amino acids derived from dietary protein. Inadequate vitamin B_6 is one factor that leads to increased concentrations of xanthurenate in urine. Xanthurenate is a product of amino acid breakdown that cannot be further metabolized in the absence of vitamin B_6. Abnormal levels of kynurenate can have direct effects on brain function in addition to showing a need for vitamin B_6. Deficiency of vitamin B_6 can result in high levels of these compounds. Vitamin B_6 deficiency may also result in elevated concentrations of homocysteine in blood, which leads to increased risk of heart disease.

25. ß-hydroxyisovalerate

Until recently, biotin deficiency was very difficult to determine in humans because this vitamin deficiency affects health in ways that mimic many other conditions. Doctors were likely to overlook biotin deficiency until the beta-hydroxyisovalerate was discovered. It is a specific and sensitive metabolic marker for functional biotin deficiency. As your biotin intake decreases, your ß-hydroxyisovalerate excretion increases. Biotin is especially important for healthy nerves, skin and digestive function.

26. Methylmalonate
27. Formiminoglutamate

The most common dietary deficiency leading to homocysteine elevation (possibly associated with increased heart disease risk) involves vitamin B_{12} and folic acid. You can have normal blood levels of these vitamins but still not have enough for your body's enzymes to function properly. Dietary deficiency of vitamin B_{12} and folic acid are associated with increased risk of many diseases, including anemia and the associated chronic

fatigue. Methylmalonate is a sensitive functional marker for vitamin B_{12}; high levels of methylmalonate indicate vitamin B_{12} deficiency. Formiminoglutamate (abbreviated FIGLU) is a compound made from the amino acid histidine. Insufficiency of folic acid leads to high urinary FIGLU. Folic acid is especially critical for prenatal and childhood development. It is important for lowering the risk of cardiovascular disease and cancer.

Cellular Energy

Cellular energy is derived from the biochemical processes in the cellular powerhouses called mitochondria. Failing mitochondrial function is associated with obesity, diabetes, and aging. Markers included in the Women's Health Profile allow detection of multiple levels of potential interference with mitochondrial function.

28. Adipate
29. Suberate
30. Ethylmalonate

Adipate, suberate, and ethylmalonate elevations indicate metabolic blocks. Carnitine is needed to move fatty acids into the mitochondria where they are converted to energy using

riboflavin (vitamin B_2). When insufficient levels of carnitine or vitamin B_2 slow down this process, other parts of the cellular machinery take over and make adipate and suberate. A similar block in another pathway causes high ethylmalonate. Since most of the body's energy is produced from the burning of fatty acids, the muscles and brain suffer when this cellular energy pathway is blocked. Supplementation of carnitine and vitamin B_2 may be needed when these compounds are too high. Insufficiency of vitamin B_2 is implicated in impaired carbohydrate metabolism, migraines, and dementia. Carnitine supplementation has been documented to improve Alzheimer's, age-related cognitive decline, and cardiac function.

Although not an essential amino acid, carnitine helps the body use fatty acids for energy. The body makes small amounts of carnitine, but if it is not enough, fatty acids are not processed normally, and urinary excretion of the by-products adipate and suberate increases. Ethylmalonate, which comes from a different carnitine-dependent pathway, would also accumulate with carnitine insufficiency.

31. ß-hydroxybuterate

Elevated beta-hydroxybutyrate, commonly called ketone, means that there is extra metabolic stress on mitochondria to process fatty acids. The metabolic stress can come from poor sensitivity to (or lack of) insulin or from very low carbohydrate intake. These factors cause lowered flow of cellular glucose that increases need to oxidize fatty acids.

32. Succinate
33. Fumerate
34. Malate

Succinate, fumarate, and malate, along with lactate serve as functional markers to indicate whether the body is able to produce energy efficiently by utilizing coenzyme Q10. When these markers are elevated it may be indicating a need to supplement with Q10. Q10 is a nutrient that enables the body to use oxygen to generate energy. Since the body can make coenzyme Q10, it is not called a vitamin. If there is enough present to meet tissue demand, supplementation is not needed. However, because its production involves so many steps and nutrient co-factors, many people do not make enough coenzyme Q10.

35. Hydroxymethylglutarate (HMG)

Hydroxymethylglutarate (HMG) is used by cells to make CoQ10 – and cholesterol. Cholesterol-lowering statin drugs block this process, causing HMG to become elevated and inhibiting the cell's production of CoQ10. While there can be other causes for this metabolic block, high levels of HMG generally indicate need for CoQ10 supplementation.

Neural Function

This category relates to neurotransmitters, the chemicals the nervous system uses to function and communicate with the body. The first three compounds, 37, 38, 39, in this category are significant if they are either low or high. Abnormalities in this area can relate to symptoms of mental, emotional, and behavioral problems.

36. Vanilmandelate (VMA)
37. Homovanillate (HVA)

Vanilmandelate and homovanillate are breakdown products from neurotransmitters involved in hormone and nerve impulse transmission. When these compounds are low, it indicates the body is not making enough of these neurotransmitters. Symptoms associated with this condition are depression, sleep disturbances, inability to deal with stress, and fatigue. Treatments to improve digestion, along with supplementation of the precursors tyrosine or phenylalanine, can help improve the ability to keep up with demand for these neurotransmitters. Elevations of VMA and HVA indicate an overactivation of nervous system function involving these neurotransmitters. This can be for various reasons, but is most commonly associated with stress – both internal (e.g., mental/emotional) and external (e.g. environmental toxins). Addressing the source of stress and improving the body's ability to handle stress are useful in these cases.

38. 5-Hydroxyindolacetate (5-HIA)

5-Hydroxyindolacetate is a breakdown product of the neurotransmitter, serotonin. Low 5-HIA indicates inadequate production of serotonin. Associated symptoms can include constipation, depression, fatigue, insomnia, and attention deficit and behavioral disorders. High 5-HIA may occur when there is an increased utilization and breakdown of serotonin. Many antidepressant medications can cause a significant increase in the amount of serotonin that is made and broken down. This stimulation will contribute to loss of the essential amino acid, L-tryptophan, from which serotonin is made. Dietary therapy should focus on protein digestion via stomach acid and pancreatic enzymes, and on consumption of high tryptophan foods such as turkey and bananas.

39. Kynurenate
40. Quinolinate

Elevations can indicate an insufficiency of vitamin B6, especially

when xanthurenate is high. Quinolinate elevations are caused by inflammatory processes induced by the immune system, such as during infection (especially viral). High quinolinate levels in the brain can cause insomnia, irritability, and nervousness. These effects may be improved by removing the source of inflammation and supplementation with magnesium. Kynurenate can reduce the toxic effects of quinolinate.

Detoxification

Not only does the body use essential nutrients to actively build and maintain itself, it also must eliminate environmental toxins and certain chemicals created in the body itself. This process of detoxification is critical to health. Like a backed-up sewer, an impaired detoxification system can lead to many problems. Brain fog, headaches, insomnia, nausea, chemical sensitivities, and a variety of chronic health problems have been related to toxicity issues.

41. Citrate
42. cis-Aconitate
43. Isocitrate

Citrate, cis-aconitate, and isocitrate, the first three steps in the Krebs cycle, are involved in both energy production and removal of toxic ammonia. High levels can indicate ammonia toxicity. Chronic loss of these valuable compounds can contribute to loss of organ reserve and disturbances in neurological function. If they are low they can indicate a need for essential amino acids, especially arginine.

44. 2-Methylhippurate

2-Methylhippurate is a by-product of detoxification of the common solvent, xylene. Elevations indicate an exposure to this potentially toxic compound found in paint, varnishes, paint thinners, solvents, and many aerosols. Such exposures increase the burden on liver detoxification. An abundant supply of the amino acid, glycine, and vitamin B5 are important for removing xylene from the body.

45. Orotate

Orotate is a sensitive marker of your liver's capacity to convert toxic ammonia to non-toxic urea that the body can excrete. That capacity can be increased by additional arginine. Ammonia toxicity can also be reduced by supplementation with alpha-ketoglutarate, magnesium, aspartic acid, and glutamic acid. Ammonia impairs brain function, causing difficulty with thinking, fatigue, headaches, and increased food sensitivities.

46. Glucarate

Glucarate serves as a biomarker for your exposure to a wide array of potentially toxic chemicals. Glucaric acid is a by-product of the predominant phase I detoxification reactions. Hepatic output of glucarate is accurately reflected by urinary levels, and glucarate excretion is an indicator of overall hepatic detoxification function. High urinary glucarate suggests above normal exposure to pesticides, herbicides, fungicides, petrochemicals, alcohol, pharmaceutical compounds, or toxins produced in the gastrointestinal tract.

47. alpha-Hydroxybutyrate

Alpha-Hydroxybutyrate is elevated when your body attempts to respond to metabolic stress by making additional glutathione. Because glutathione is critical for removing toxins and acts as a powerful antioxidant, your body is constantly making it in large amounts. Many disease processes can be adversely influenced by insufficiency of this vital nutrient. Elevated alpha-hydroxybutyrate indicates high cell demand for glutathione. Supplementation with various sulfur amino acids and glutathione can be used to support adequate levels of this compound.

48. Pyroglutamate

Pyroglutamate elevation indicates the body is using up glutathione to keep from losing amino acids. Glutathione is important for protection of cells from oxidation. Various amino acids, especially methionine and glycine, can help rebuild total body glutathione. Pyroglutamate elevation can also indicate a glycine insufficiency; supplementation with this amino acid may be indicated.

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