Diabetes – A Glucose Metabolism Problem

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Diabetes is fast becoming a global pandemic and diabetic complications are moving upwards as the top seven cause of death. Diabetes is a chronic disorder of glucose metabolism. Studies in the UK show that proper change in diet, daily exercise and brisk walking can greatly aid to reduce blood sugar levels that are not too far above the healthy levels. A blood sugar reading of 10.4 can drop to 9.2, a decline by 12% by a twenty minute brisk walk. A change in the fat:protein:bone ratio with reduction in total body fat and a reduction in the girth circumference by 8-12% can reverse the diabetic condition in borderline cases. The primary issue here is the conversion of fat into glucose that is then utilized in cells to yield energy. Unfortunately many diabetics suffer a further problem in glucose metabolism when they are put on drugs that block the conversion of lipids into glucose. Over a short time, their blood lipid profile begins to change, adding a new risk to health.

Diabetes is now the leading condition associated with blindness, end-stage renal disease and non-traumatic amputations. Treating diabetic wounds and infections in diabetics is a problem because of the slow healing as well as due to the fact that antibiotics compound the glucose metabolism problem. Giving antibiotics to diabetics with infections can lead to rising of blood sugar levels, sometimes doubling it or raising it even higher. Healthcare costs for the diabetic population in the US alone may reach a staggering USD100 billion. Diabetics are very likely to develop arthritis in 6-8 years and that adds another USD40 billion. They will also have a higher risk to getting strokes that adds to healthcare costs as well as contributes to loss of incomes and gainful employment. Cancers are on the rise and diabetics have a higher risk to cancers that balloons the healthcare cost.

There is a more urgent need to look at the human diet and the antioxidant intake from food sources. The dietician's concept of a balanced meal comprising fats, carbohydrates, meats and vegetables can be thrown out of the window. Humans are primates and we need to study the primate patterns of our wild cousins in the undisturbed forests. These primates are lean and certainly not obese and do not suffer a glucose metabolism problem. They lead active lives, foraging throughout the day on fruits, nuts, berries, flowers, shoots, leaves and tubers that ensures a broad range of antioxidants, polysaccharides, bioavailable minerals and soluble fibers. They rest in the afternoons and have well regulated sleep patterns. A fifteen minute siesta or snooze around midday will do a lot of good and eating five smaller meals comprising fruits and raw vegetables as the major portion with some nuts will provide a better dietary support for the healthy biochemistry in the human body, rather than load the digestive system with heavy meals. Eliminating white sugar, trans-fatty acids and long chain fatty acids while adding some medium fatty acids into the diet will only add positively to a turn around in health. Small amount of unpolished is preferred in contrast to large amounts of polished (white rice). Traditional diets are far better than the modern western diet of processed foods that contain preservatives and artificial sweeteners and artificial flavors. Cigarettes and excess alcohol trigger oxidative damage in the body and accelerate aging. They also accelerate all the degenerative conditions while increasing the risk of diabetes, arthritis, skin problems and cancers by depressing the immune system. Type II diabetes is a condition that is strongly associated with a sedentary lifestyle and the modern western diet (Metabolic Support, Comparative Guide to Nutritional Supplements p48). Most of these foods are deficient in chromium and low in selenium, manganese, copper and zinc, leading to a sub-clinical deficiency that is widespread in North America. The modern western diet is also

low in chromium, natural vitamin E, natural vitamin B and folate. All of these antioxidants are factors in the healthy metabolism of glucose in cells that promotes the formation of the Glucose Tolerance Factor and prevents the accumulation of sorbitol.

Sorbitol is about 60% as sweet as sugar and is often used as a sweetener in diet foods such as carbonated diet drinks and ice creams and sugar-free chewing gum. Sorbitol is also often used in modern cosmetics as a humectant and thickener. Some transparent gels can only be made with sorbitol. It is also known as glucitol or sugar alcohol. It also occurs naturally in many stone fruits and berries from trees of the genus Sorbus (Lehninger, Principles of Biochemistry, Nelson and Cox, Fourth Edition). Unfortunately, sorbitol metabolizes slowly in the body. Large amounts of sorbitol may cause gas. Ingesting large amounts of sorbitol can lead to gas and some abdominal pain, and mild to severe diarrhea.

Oral sorbitol can have the following side-effects:- nausea, gas, diarrhea, stomach cramps or anal irritation, rectal bleeding, vomiting, weakness, dizziness, persistent urge to empty the bowel. Commercially produced sorbitol may be more harmful as it is a racemic mixture of L and D-form sorbitol. The reduction of glucose by changing the aldehyde group to an additional hydroxyl group yields sorbitol. Complete reduction of sorbitol yields toxic compounds such as alkanes and hexane that are part of tumor cell biochemistry and can also be used as biofuel. The two main biochemical reactions with regard to sorbitol may be summarized as follows:-

1. Sorbitol (in high antioxidant environment + without ONOO-) → Fructose
2. Sorbitol (in excess free radical environment + with ONOO-)→ Toxic metabolites

The second reaction yielding toxic metabolites deplete antioxidants in cells leading to an increase in superoxide and DNA fragmentation that can initiate cancer cell development. This process puts the diabetic patient with excess sorbitol at a higher risk of cancers and explains the higher incidence of cancers in the diabetic population. Accordingly, the reduction of accumulated sorbitol in cells leads to NADPH depletion which is a significant biochemical change within the cell that contributes to the observed pathological changes (see: Burg MB, 1995, Molecular basis of osmotic regulation, Am. J. Physiol, 268,F983-F996: Hotta N, 1997, New concepts and insights on pathogenesis and treatment of diabetic complications: polyol pathway and its inhibition, Nagoya J. Med. Sci, 60,89-100) as NADPH, is required for the detoxification of oxidants (Kinoshita and Nishimura,1988, The involvement of aldose reductase in diabetes complications, Diabet Metab Rev, 4:323 –337). The real problem is sorbitol accumulation and low antioxidant intake. Sorbitol itself provides much of the hydrogen required for the transformation to yield large amounts of carbon dioxide.

$$19\ C_6O_6H_{14} \rightarrow 13\ C_6H_{14} + 36\ CO_2 + 42\ H_2O$$

Hexane is mildly toxic. It is also a mild anesthetic. Inhalation of high concentrations produces first a state of mild euphoria, followed by somnolence with headaches and nausea. Hexane toxicity due to large amounts of hexane in humans is uncertain and the toxicity may not be due to hexane itself but on account of one of its metabolites, hexane-

2,5-dione, that may react with the amino group in the lysine residues in proteins to yield cross-linked proteins and a consequent loss of protein function.

The grave problem is also associated with excess carbon dioxide from such reactions in the body. The biological effects of peroxynitrite have been recently considered to be largely dependent on its reaction with carbon dioxide, which is present in high concentrations in intra- and extracellular compartments. Peroxynitrite anion ($ONOO^-$) reacts rapidly with carbon dioxide, forming an adduct called the nitrosoperoxocarboxylate ($ONOOCO_2^-$), whose decomposition has been proposed to produce reactive intermediates such as the carbonate radical ($CO_3^{\cdot-}$) (Marcelo et al, 1999, Direct EPR Detection of the Carbonate Radical Anion Produced from Peroxynitrite and Carbon Dioxide, J Biol Chem, Vol. 274, Issue 16, 10802-10806, April 16). In the carbon dioxide radical, most of the electron density is on the carbon atom, whereas in the carbonate radical, most of the electron density is on the oxygen atoms (Chantry et al, 1962, Mol. Physiol. 5, 589-599: Bisby et al, 1998, J. Chem. Soc. Faraday Trans. 94, 2069-2072). Peroxynitrite reacts rapidly with carbon dioxide to form nitrogen dioxide and bicarbonate radical, which can be even more damaging than the overly promiscuous hydroxyl radical (Joseph S. Beckman, editorial, 2001, Rebounding From Nitric Oxide, Circulation Research. 2001;89:295).

These radicals could contribute to oxidative damage especially in patients with low glutathione-catalase activity that allows hydrogen peroxide concentrations to build up in cells. It is well known that excess hydrogen peroxide (H_2O_2)-induced copper-catalyzed fragmentation of proteins follows a site-specific oxidative mechanism mediated by hydroxyl radical-like species (*i.e.* Cu(I)O, Cu(II)/$^{\cdot}OH$ or Cu(III)) that ends in increased carbonyl formation and protein fragmentation (see: Dario et al, 2005, Copper-catalyzed Protein Oxidation and Its Modulation by Carbon Dioxide, Enhancement of Protein Radicals In Cells, J. Biol. Chem., Vol. 280, Issue 29, 27402-27411, July 22). Copper-catalyzed oxidations and alteration of tissue components have been implicated in organ damage in many of pathologies (Beshgetoor and Hambidge, 1998, Am. J. Clin. Nutr. 67, (suppl.) 1017S-1021S: Schumann et al, 2002, Eur. J. Clin. Nutr. 56, 469-483). Copper-catalyzed oxidations are also demonstrated in most of the site-specific mechanism of oxidative damage to proteins and other biomolecules (Gaetke and Chow, 2003, *Toxicology* 189, 147-163: Berlett and Stadtman, 1997, J. Biol. Chem. 272, 20313-20316). Supplements with copper and iron from inorganic sources could be detrimental to health, more so, when taken in excess. Indeed, the occurrence of loosely bound copper ions has been reported for a number of clinical samples from pathological conditions involving oxidative stress and inflammation, such as in Wilson disease plasma during an episode of fulminant hepatitis, rheumatoid arthritis synovial fluid, Parkinson disease cerebrospinal fluid, senile plaques of Alzheimer disease (Gaetke and Chow, 2003, Toxicology, 189, 147-163: Schumann et al, 2002, Eur. J. Clin. Nutr. 56, 469-483).

Research suggests that CO_2 plays a key role in (bi)carbonate-enhanced, H_2O_2-induced, copper-catalyzed Fenton chemistry in biological systems as well as CO_2 and the hydroperoxide anion (-OOH) reactions as shown below (see: Dario et al, 2005, Copper-

catalyzed Protein Oxidation and Its Modulation by Carbon Dioxide, Enhancement of Protein Radicals In Cells, J. Biol. Chem., Vol. 280, Issue 29, 27402-27411, July 22).

$$CO_2 + {}^{-}OOH \rightleftarrows HOOCO_2^{-}$$

In short, there are Fenton reactions that serve as mechanisms modulating radical formation that are triggered by excess carbon dioxide. That means an excess consumption of carbonated drinks could also trigger Fenton reactions that, if sustained over time, will generate oxidative stress and oxidative damage to biomolecules and cells and harm healthy biochemistry. Such research clearly indicates a role for CO_2 as a mediator and/or modulator of H_2O_2-induced, metal-catalyzed oxidative damage to cellular proteins under pathophysiological conditions involving copper-mediated oxidative stress. Only L-form scavengers of free radicals protect against oxidative damage and oxidative fragmentation of proteins in biological systems to promote health, ruling out a role for drugs and any other chemical stressors in proper therapy orchestrating biological repair in conditions caused by Fenton chemistry and Fenton chemistry catalyzed by free metals in biological systems, as drugs themselves generate free radicals in biological systems.

Drugs in patients with heavy metal loads or free metals such as copper or iron can become even more toxic. Free copper will participate in the Fenton reaction as follows,

$$Cu^{1+} + H_2O_2 \rightarrow Cu^{2+} + {}^{-}OH + {}^{\bullet}OH$$

to yield the free radicals by reacting with excess hydrogen peroxide in cells. Later, administering a drug that generates superoxide can produce harmful effects.

Very small amounts of inorganic copper or a chemical stressor like paraquat alone causes little detectable radical adduct formation in healthy living biological systems, in particular when the natural antioxidant activity is strong but a heavy metal, from an inorganic source that remains free together with a strong chemical stressor in large amounts can produce oxidative damage to the membranes of cell organelles as the crucial event in toxicity (see: Ronald et al, 1994, Detection of Oxygen-derived Radicals in Biological Systems Using Electron Spin Resonance, Environ Health Perspect 102(Suppl 11) :33-36). Hence, it is important to first prepare the patient receiving a drug that is a strong chemical stressor with an intervention of biochelator such as alpha-lipoic acid from organic sources to remove the free metals and enter into a safer phase for the drug administration.

Diabetics who have been diabetics for more than a year may suffer from another problem – excess sorbitol in their cells. Excess sorbitol ingestion can aggravate irritable bowel syndrome and block fructose absorption (Reports, The British Medical Journal, see sorbitol, Wikipedia). Apart from dietary sorbitol, cells also produce sorbitol naturally. When too much sorbitol is produced inside cells, it can cause damage such as diabetic retinopathy and neuropathy (Sorbitol: A Hazard for diabetics? Nutrition Health Review). These conditions may relate to excess sorbitol in the cells of the eyes and nerves.

The enzyme that causes problems is called aldose reductase. In the body, the enzyme called aldose reductase converts glucose into a related sugar called sorbitol - a process that occurs all the time to a small extent in all humans. Sorbitol does not exit from cells very fast. It attracts water that accumulates in the cells. Uptake and accumulation of sorbitol is probably the reason for the stability of the cell shape (Kay Marin, 2006, Osmotic stress in *Synechocystis* sp. PCC 6803: low tolerance towards nonionic osmotic stress results from lacking activation of glucosylglycerol accumulation, Microbiology 152, 2023-2030) which means it must be regulated. Excess sorbitol causes the cells to swell, and its toxic metabolites can result in nerve, eye, kidney and blood vessel damage, as well as aid in the development of cataracts. Conversion of glucose to sorbitol is greatly accelerated in diabetics, a process that can cause health complications over time. More sorbitol in cells with low levels of antioxidants means relatively more toxic metabolites.

Diabetics and obese persons have relatively higher population of free radicals in their bodies that put them, as a group, at a higher risk to oxidative damage and a higher incidence of:

1. Hypertension and cardiovascular disease.
2. Arthritis
3. Erectile dysfunction
4. Neuropathies
5. Cancers
6. Renal disease
7. Stroke
8. Cardio-vascular disease
9. Varicose veins
10. More prone to headaches

Part of the problem biochemistry in diabetics starts with reduced ability of insulin to bind at its receptor sites on cell surfaces. Oxidatively damaged insulin molecules cannot bind to their receptor sites to facilitate the entry of glucose into the cells where it is routed into the pathway to yield energy. Instead, sorbitol accumulation takes place in the cells of diabetic patients, known to be associated with chronic complications in diabetic patients. A high dose vitamin C (2000mg per day) has been shown to reduce the accumulation of sorbitol (Davie et al, 1992, Effect of Vitamin C on Glycosylation of Proteins, Diabetes 41:167-73). The antioxidant vitamin C is known to suppress the polyol pathway activity induced by high glucose (Vinson et al, 1989, In vitro and in vivo reduction of erythrocyte sorbitol by ascorbic acid, Diabetes, 38:1036–1041) but why are such high doses necessary? In plasma, ascorbate maintains its antioxidant activity, even at very high concentrations (Rehan et al, 1984, Evidence for the role of oxygen radicals in acute nephrotoxic nephritis, Lab Invest, 51:396–403). In most species, cells in the liver produce L-ascorbic acid from metabolism of glucose through the glucoronic pathway. In man, however, the absence of one enzyme in that pathway (Burns et al, 1956, Missing step in guinea pigs required for the biosynthesis of L-ascorbic acid. Science 124: 1148–1149) necessitates the dietary intake of a micronutrient, termed vitamin C, to prevent scurvy and

oxidative stress that relates to insulin and its ability to bind at its receptor sites on the cell surface.

The binding activity of insulin is facilitated by chromium. Insulin must first form a complex known as Glucose Tolerant Factor (GTF) that is formed in the presence of chromium. This complex enables the insulin to bind to its receptor site (Anderson et al, 1996, Beneficial Effects of Chromium for People with Type II Diabetes, Diabetes 45 (suppl 2) 124A/454: Offenbacher and Strunger, 1980, Beneficial Effects of Chromium rich Yeast on Glucose Tolerance and Blood Lipids in Elderly Patients, Diabetes 29: 919-25: Mertz, 1969, Chromium Occurrence and Function in Biological Systems, Physiol Rev 49: 163-237). If there is a lack of chromium or if the insulin molecule is oxidatively damaged, the GTF complex cannot be formed and only high doses will remove the oxidative stress to facilitate the formation of the GTF. L-ascorbic acid will always work better in biological systems than a racemic mixture of L and D-forms. Since diabetics have relatively higher population of free radicals, there is consequently a higher population of glycosylated proteins and studies also show that vitamin C supplementation inhibits glycosylation thereby reducing the risk of the formation of sugar-protein complexes – a process that is elevated several-fold in diabetics (Davie et al, 1992, Effect of Vitamin C on Glycosylation of Proteins, Diabetes 41:167-73). Spontaneous generation of superoxide *in vitro*, is increased in patients with quiescent disease compared with normal healthy donors, that can be reduced with the administration of a combination of the antioxidants vitamins E and C which is associated with an increase in the total antioxidant capacity and vitamin C concentrations, increasing the body's ability to prevent free radical-mediated oxidative damage (see:Harper et al, 2002, Adjuvant treatment of patients with antineutrophil cytoplasmic antibody-associated vasculitis with vitamins E and C reduces superoxide production by neutrophils, Rheumatology (Oxford Journals) 2002; 41: 274-278). Oxygen radicals are directly toxic to endothelial cells and have been documented to cause renal injury in animal models. Antioxidant enzymes and/or oxygen radical scavengers protect animals with antiglomerular basement membrane glomerulonephritis from proteinuria and glomerular damage.

There is growing evidence that the use of antioxidants can prevent cardiovascular disease and cancer and have an anti-inflammatory effect (Lefer and Granger, 2000, Oxidative stress and cardiac disease, Am J Med, 109:315–23). Reactive oxygen radicals increase oxidation of low density lipoproteins (LDL) which may lead to accelerated atherosclerosis and “the administration of vitamins E and C can reduce oxidative damage in patients with moderate renal impairment due to various causes” (Nuttall et al, 1999, Vitamin supplementation reduces oxidative stress in conservatively managed patients with chronic renal failure, J Am Soc Nephrol, 10:83A). A recent study of vitamin C in patients with coronary artery disease (CAD) demonstrated a marked improvement in endothelial function with no detectable change in oxidative stress (Gokee et al, 1999, Long-term ascorbic acid administration reverses endothelial vasomotor dysfunction in patients with coronary artery disease, Circulation, 99:3234–3240). Improvement in endothelial function is a necessary step to achieve in the diabetic patient as it lowers peroxynitrite levels and increases available nitric oxide for its various regulatory roles in different tissues.

Vitamin C reduces oxidative stress, increases flow-mediated dilation (FMD) and, when given long term, decreases neutrophil O_2^- generation (Gethin et al, 2000, Neutrophil superoxide anion–generating capacity, endothelial function and oxidative stress in chronic heart failure: effects of short- and long-term vitamin C therapy, A Clinical Study, J Am Coll Cardiol, 36:1474-1482) but other natural antioxidants are required for better effects. Vitamin C is actively transported into cells through an insulin-dependent transport system and can achieve intracellular concentrations in the 1 to 10 mmol/liter range, at which it is an effective scavenger of O_2^- (Wolf G, 1993, Uptake of ascorbic acid by human neutrophils, Nutr Rev, 51:337–338). Thus, its scavenging effects may be largely intracellular. Aside from its scavenging actions, vitamin C spares intracellular glutathione from oxidative degeneration (Bendich et al, 1986, The antioxidant role of vitamin C, Adv Free Radic Biol Med, 2:419–444). Natural antioxidants have an important role as adjuvant therapy and a potential role in reducing disease morbidity but synthetics will not yield the expected positive results. Long-term therapy with vitamin C reduced the ability of neutrophils to generate O_2^- but intravenous vitamin C administration did not have this effect (Gethin et al, 2000, Neutrophil superoxide anion–generating capacity, endothelial function and oxidative stress in chronic heart failure: effects of short- and long-term vitamin C therapy, A Clinical Study, J Am Coll Cardiol, 36:1474-1482).

Intravenously administered vitamin C has a different effect. When its ascorbate radical enters bacterial cells and cancer cells, its metabolism in these cells produces hydrogen peroxide that is cytotoxic to such cells. The National Institutes of Health scientists have confirmed that vitamin C is selectively toxic to cancer cells and that tumor-toxic levels of vitamin C can be attained using intravenous administration. “These findings give plausibility to intravenous ascorbic acid in cancer treatment” (Chen et al, 2005 Sept, Pharmacologic ascorbic acid concentrations selectively kill cancer cells: Action as a pro-drug to deliver hydrogen peroxide to tissues. Proc Natl Acad Sci USA, 20;102(38):13604-9, Epub 2005 Sep 12). Earlier research showed that it cytotoxic to cancer cells (Cameron and Pauling, 1976 Oct, Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer, Proc Natl Acad Sci USA, 73(10):3685-9). Other researchers show that tumor-toxic levels of vitamin C could be achieved only by giving the vitamin intravenously. Their research published in the British Journal of Cancer, describe in detail the pharmacokinetics of high doses of intravenous vitamin C (Casciari, et al, 2001, Cytotoxicity of ascorbate, lipoic acid, and other antioxidants in hollow fibre in vitro tumours, British J Cancer. 2001, 84(11), 1544-1550) but this is also achievable by extracts from tamarind leaves obtained in the nano form. Tamarind is rich in L-ascorbic acid.

White sugar interferes with L-ascorbic acid activity in the body. Niacin, or vitamin B3, is important in the formation of the glucose tolerance factor (GTF) and it prevents oxidative damage in the insulin-producing beta-cells within the pancreas (Anderson et al, 1994, Nocotinamide prevents Interleukin I-effects on the accumulated Insulin release and Nitric Oxide Production in Rat Lsles of Langerhans, Diabetes 43:770-77). Flavonols, found in citrus fruits work synergistically with natural vitamin C and are antithrombotic because they are bound selectively to mural platelet thrombi and, because of their free radical-scavenging properties, modify damaged endothelial cells and permit normal prostacyclin

and NO synthesis (Gryglewski et al, 1987, On the mechanism of antithrombotic action of flavonoids, Biochem Pharmacol, 36**:** 317-322). So, flavanols may be combined with L-ascorbic acid for better free radical scavenging activity. Such modifying properties that result in improved cell function are termed as biological repair.

"Vitamin C is an electron donor for enzymes involved in collagen hydroxylation, biosynthesis of carnitine and norepinephrine, tyrosine metabolism, and amidation of peptide hormones; its deficiency causes scurvy. The amount of vitamin C necessary to prevent scurvy may not be adequate to maintain optimal health. The ability of vitamin C to donate electrons also makes it a potent water-soluble antioxidant that readily scavenges free radicals such as molecular oxygen, superoxide, hydroxyl radical, and hypochlorous acid. In this setting, several mechanisms could account for a link between vitamin C and heart disease. One is the relation between LDL oxidation and vitamins C and E. Vitamin C in vitro can recycle vitamin E, which can donate electrons to prevent LDL oxidation in vitro. As the lipid-phase vitamin E is oxidized, it can be regenerated by aqueous vitamin C. Other possibilities are that vitamin C could decrease cholesterol by mechanisms not well characterized, or could improve vasodilatation and vascular reactivity, perhaps by decreasing the interactions of nitric oxide with oxidants" (ref: Sebastian and Mark Levine, 2000 May, Vitamin C and myocardial infarction: the heart of the matter, American Journal of Clinical Nutrition, Vol. 71, No. 5, 1027-1028).

The key factor in L-ascorbic acid dietary intake is the fact that vitamin C entry into cells is insulin mediated and consequently, diabetics do not have sufficient L-ascorbic acid in their cells. This chronic deficiency of vitamin C within the cells in diabetic patients despite adequate intake as per normal standards does not help them as much as a very high intake and the prolonged deficiency of vitamin C in the diabetic is problematic and leads to vascular disorders, elevated blood cholesterol and depression of the immune system (Davie et al, 1992, Effect of Vitamin C on Glycosylation of Proteins, Diabetes 41:167-73). Accordingly, the primary approach for the diabetic patient is:-

1. Reduce the excess superoxide (OFR), and rapidly eliminate the secondary radicals, such as ONOO- and the hydroxyl radical and the radicals of carbon dioxide, and
2. Reduce the risk of hydrogen peroxide build-up in cells, and
3. Inhibit and reverse the process of glycosylation, and
4. Reduce the accumulation of sorbitol in their cells, and
5. Continue to provide energy to cells through ways that are not insulin mediated.

High doses of L-ascorbic acids and a broad range of dietary antioxidants become important to initiate biological repair to improve healthy biochemistry. Recent studies reveal that high dose vitamin C, alone can provide an effective means of correcting sorbitol accumulation than current pharmaceutical approaches (Murray and Pizzorno, 1998, Encyclopedia of Natural Medicine, Puma Health, Rocklin CA p 417: Cunningham et al, 1994, Vitamin C. An Aldose Reductase Inhibitor that Normalizes Erythrocyte Sorbitol in Insulin-Dependent Diabetes Mellitus, J Am Coll Nur 4:34-50). The role of L-ascorbic acid may lie in its ability to inhibit aldose reductase as well as its ability as an antioxidant to drive the antioxidant-driven pathway that converts sorbitol into fructose by promoting the activity of sorbitol dehydrogenase. The polyol pathway is a two-step

metabolic pathway in which glucose is reduced to sorbitol, which is then converted to fructose.

Limiting carbohydrate and white sugar intake is critical in patients with sorbitol accumulation because when intracellular glucose rises, aldose reductase activity is stimulated and catalyzes the formation of sorbitol, which can be oxidized to fructose by sorbitol dehydrogenase (Stevens et al**,** 2000, The sorbitol-osmotic and sorbitol-redox hypothesis. In: LeRoith D, Taylor SI, Olefsky JM, eds. Diabetes mellitus: a fundamental and clinical text. Philadelphia, Lippincott Williams & Wilkins, 972–983). Increased polyol pathway flux through AR, which reduces glucose to sorbitol with the aid of NADPH, is a major contributing factor in the early signs of diabetic neuropathy, possibly through depletion of glutathione, increased superoxide accumulation, increased JNK activation and DNA damage (Eric et al, 2006, Aldose Reductase–Deficient Mice Are Protected From Delayed Motor Nerve Conduction Velocity, Increased c-Jun NH_2-Terminal Kinase Activation, Depletion of Reduced Glutathione, Increased Superoxide Accumulation, and DNA Damage, Diabetes, 55:1946-1953). The increased flux of glucose through the polyol pathway augments oxidative stress (Sato et al., 1979, Lipid peroxide level in plasma of diabetic patients, Biochem Med**,** 21**:** 104-107; Hunt et al., 1993, Oxidative alterations in the experimental glycation model of diabetes mellitus are due to protein-glucose adduct oxidation, Some fundamental differences in proposed mechanisms of glucose oxidation and oxidant production. Biochem J, 291**:** 529-535). Increased AR activity leads to a decreased level of glutathione and consequently to more severe diabetic neuropathy (Yagihashi et al, 2001, Neuropathy in diabetic mice overexpressing human aldose reductase and effects of aldose reductase inhibitor, Brain, 124:2448–2458). The other problem of sorbitol accumulation is the accumulation of water in the cells and its toxic metabolites. Hence, aldose reductase inhibition by No and mediated by natural antioxidants prevents complications of diabetes and associated conditions that develop after the onset of diabetes or more accurately after sorbitol accumulation.

“Early experiments aimed toward elucidating the mechanistic basis of chronic diabetic complications focused on sorbitol accumulation and accompanying cellular damage. Glucose is converted to sorbitol via augmented polyol pathway. The enzyme responsible, aldose reductase, has been shown to be upregulated in all tissues affected by chronic diabetic complications. Increased intracellular concentrations of sorbitol can cause osmotic changes, cell swelling, and abnormalities in myoinositol metabolism and can lead to impairment of NaC,KCATPase. Aldose reductase inhibition has been shown to prevent hyperglycemia-induced damage in diabetic retinopathy, neuropathy, and nephropathy to some extent. The mechanism by which aldose reductase inhibition prevents development of vascular complications is not fully understood. Aldose reductase requires NADPH for the conversion of glucose to sorbitol. Sorbitol is then converted to fructose by sorbitol dehydrogenase. The latter step requires NADC reduction for the enzymatic conversion. This suggests that an imbalance in the redox state, that is, altered NADH:NAD and NADPH:NADP might cause endothelial dysfunction secondary to increased aldose reductase activity (King and Brownlee, 1996, The cellular and molecular mechanisms of diabetic complications, Endocrinol. Metab. Clin.North. Am.,

25**,** 255–270: Williamson et al, 1993, Perspectives in diabetes: Hyperglycemic pseudohypoxia and diabetic complications, *Diabetes,* 42**,** 801– 813: Pugliese et al, 1991, Glucoseinduced metabolic imbalances in the pathogenesis of diabetic vascular disease. Diabetes Metab. Rev.*,* **7,** 35–59). Interestingly, depleted NADPH may also lead to reduced NO production as the enzymatic reaction of NO synthesis requires NADPH." (Subrata Chakrabarti, 2002, Alteration of Endothelins: A Common Pathogenetic Mechanism in Chronic Diabetic Complications, Int. Jnl. Experimental Diab. Res., 3:217–231) that partly explains why diabetics develop hypertension. These observations and findings point to the need to address the redox balance within cells as a therapeutic model to find ways that promote healthy biochemical reactions in the living biological systems. This redox balance clearly appears to be one of the mechanisms for maintaining a stable cell shape that controls the amount of water in cells.

Increased dietary intake of antioxidants from food sources and high doses of L-ascorbic acid alters the biochemical equilibria that effectively scavenges free radicals and alters the redox balance that works to reduce the amount of glucose that is converted to sorbitol and promotes the conversion of sorbitol to fructose. If fructose is produced, it can be utilized easily by cells to yield citrate or palmitate. Another more effective way is to pass L-ascorbic acid rapidly into cells is through topical sprays that contain this vitamin together a few other antioxidants and minerals in the nano form, so that they can quickly enter cells through other channels and no insulin mediation is required. So, while there is a solution to the sorbitol problem due attention must also be given to the issue of insulin resistance and the possible factor or factors causing it or associated with this observed condition.

"In type 2 diabetes both insulin resistance and hyperglycemia may promote atherosclerosis and its complications, while insulin resistance is likely a key underlying factor driving the complications of metabolic syndrome including atherosclerosis. Hyperinsulinemia is an independent risk factor for atherosclerosis in some but not all epidemiological studies. Because hyperinsulinemia is often associated with other risk factors such as dyslipidemia, it may be difficult to segregate out independent effects of insulin resistance in such studies. An alternative view to the central role of insulin resistance is that in obesity and metabolic syndrome an inflammatory reaction in adipose and blood vessels drives atherosclerosis and its complications" (ref: Chien-Ping Liang et al, 2007, The Macrophage at the Crossroads of Insulin Resistance and Atherosclerosis, Circulation Research, 100:1546). This is free radical induced inflammation caused by the 'robbing' of electrons by the free radicals from molecules in the cell membrane, thereby raising their cell membrane potential. It is pertinent to note that insulin resistance occurs in both hyperinsulinemia and dyslipidemia. Dyslipidemia refers to an irregularity of the lipid profile, covering a variety of disorders relating to abnormal levels of total cholesterol, LDL-C, HDL-C, or triglycerides. Dyslipidemia is attributable to problems with lipoprotein particles, apolipoproteins, or enzyme deficiencies – ie declining cell function and cell output, including low levels of repair proteins that finds its origin in low entry of glucose into cells to generate energy. The common factor is the inability of the insulin to bind at its receptor sites and an alternative view is that the problem lies in the formation of the GTF. Nitric oxide (NO) is also involved in regulating aldose reductase

activity and its role must also be considered in therapy. NO regulates sorbitol accumulation in cells whereas reduced availability of NO activates the synthesis of aldose reductase by S-thiolating AR from its inactive state. Increasing NO synthesis in the body and thereby increasing bioavailability is a useful way for reversing diabetes-induced changes in this polyol pathway. In healthy conditions, sorbitol synthesis represents a minor (>3%) fate of glucose in nonrenal tissues but during diabetes, 30-35% of the glucose could be converted to sorbitol, leading to degenerative changes. This increase in the polyol pathway has been linked to several pathological changes in insulin-insensitive tissues such as those in the blood vessels, peripheral nerves, renal medulla, blood cells, and ocular lens and the extent of inhibition of sorbitol accumulation was comparable to the extent of inhibition of AR activity (Kota Ramana et al, 2003, Nitric oxide regulates the polyol pathway of glucose metabolism in vascular smooth muscle cells, The FASEB Journal, 2003;17:417-425). Conversely, sorbitol dehydrogenase deficiency produces a significant increase of sorbitol accumulation in red cells incubated in high-concentration glucose (Alvarez et al, 1993, Membrane-bound sorbitol dehydrogenase in human red blood cells. Studies in normal subjects and in enzyme-deficient subjects with congenital cataracts, J Inherit Metab Dis, 6(1):67-72). Reversing sorbitol accumulation will be better facilitated when aldose reducatase is inactivated and sorbitol dehydrogenase is activated.

Excess sorbitol attracts too much water into cells and hyperosmotic stress induced by sorbitol rapidly stimulated apoptosis in cultured cardiomyocytes (Gálvez et al, A rapid and strong apoptotic process is triggered by hyperosmotic stress in cultured rat cardiac myocytes, Cell Tissue Res., 2001 May;304(2):279-85). Dysregulated apoptosis has been implicated in the genesis and development of several human diseases, including cardiovascular conditions such as congestive heart failure and myocardial ischemia (Narula et al, 1996, Apoptosis in Myocytes in End-Stage Heart Failure, N. Engl. J. Med,. 335**,** 1182–1189: Kajstura et al, 1996 Jan, Apoptotic and necrotic myocyte cell deaths are independent contributing variables of infarct size in rats, Lab Invest., 74(1):86-107) and inhibition of aldose reductase is cardioprotective. AR inhibition also protected diabetic hearts from ischemic injury (Ramasamy et al, 1988, Am. J. Physiol, 275**,** H195–H203: Trueblood and Ramasamy, 1998, Aldose reductase inhibition improves altered glucose metabolism of isolated diabetic rat hearts, Am. J. Physiol, 275**,** H75–H83).

Treatment with N^G-nitro-L-arginine methyl ester (L-NAME), an inhibitor of NO synthesis, enhanced aldose reductase (AR) activity and prevents sorbitol accumulation in tissues of nondiabetic rats. Experimental research suggests that NO maintains AR in an inactive state and this repression is relieved in diabetic tissues. Thus, increasing NO availability may be a useful strategy for inhibiting the polyol pathway and preventing the development of diabetes complications (Deepak Chandra et al, 2002, Nitric Oxide Prevents Aldose Reductase Activation and Sorbitol Accumulation During Diabetes, Diabetes 51:3095-3101). When excess superoxide reacts with nitric oxide, it forms the peroxynitrite oxidant (ONOO-) which binds nitric oxide and reduces the availability of NO, that in turn enhances the activity of aldose reductase and sorbitol accumulation begins to occur in cells. Converting the peroxynitrite back to NO and oxygen becomes a necessary intervention while preventing excess superoxide-NO reactions and endothelial health becomes a primary concern in health, as the endothelial lining in the major arteries

produce the bulk of NO, so that the availability of NO is maintained at optimal levels for sorbitol level regulation as well as for vaso-regulation.

Endogenous NO may be the body's most important "healing" molecule. Increasing the amount of bioavailable NO within the body increases the body's potential for anti-tumor activity. Tumor cells are rich in superoxide that maintains the high acidic value of the cytoplasm in cancer cells. NO is a very small molecule that can enter cancer cells. Upon entry into tumor cells, it is very rapidly converted to ONOO- which is cytotoxic to tumor cells. Continuous availability of endogenous NO is crucial for such benefit.

Nitric oxide can modify proteins via different biochemical processes. NO interacts with and modifies a wide variety of other molecules: free radicals such as the superoxide anion, key redox regulators such as glutathione, and macromolecules (DNA and proteins). This lends a basis for NO to regulate crucial processes within the cell such as the response to redox perturbations, protein function, and gene expression through non-enzymatic modifications. S-nitrosylation of proteins is one potential mechanism (Antonio Martínez-Ruiz and Santiago Lamas, 2004, S-nitrosylation: a potential new paradigm in signal transduction, Cardiovascular Research 2004 62(1):43-52).

Intracellular activity of AR is regulated by redox-sensitive reactions. When glutathione levels decline, hydrogen peroxide accumulates in cells of the tissue causing the enzyme to be S-thiolated and the altered pylol pathway converts glucose to sorbitol that accumulates in the cells. Deficiency in erythrocyte catalase, an enzyme responsible for the removal of H_2O_2, is associated with increased frequency of diabetes (Goth et al, 2001, Blood catalase deficiency and diabetes in Hungary, Diabetes Care 24:1839–1840: Goth and Eaton, 2000, Hereditary catalase deficiencies and increased risk of diabetes, Lancet 356:1820–1821).

By increasing the glutathione levels, this process can be slowed down but in order to reverse the process, the production of peroxynitrite must be shut down to make more NO available that promotes S-nitrosation of the enzyme. Rapid free radical scavenging activity, through extracts from fruits, flowers, vegetables and spices obtained in the nano form, the superoxide is quickly converted into oxygen and the hydrogen peroxide is rapidly converted to water and oxygen while NO levels increase, that in turn inhibit S-thiolation and inhibit sorbitol synthesis. Simultaneously, the production of peroxynitrite is shut down to make NO available for nitrosylation to alter the function of the enzyme so that sorbitol is converted to fructose and water begins to move out of the cells. If the fructose production increases sharply, it could result in a greater amount of fructose being emptied into the large intestine and fructose clearance is necessary. Since uptake of fructose by the liver is not regulated by insulin, in this type of situation, the fructolytic pathway can be driven to yield pyruvate which enters the Krebs cycle for conversion to citrate. In this approach, the fructose ends up in the Krebs cycle where it is utilized to yield precursors of many compounds. This process creates a sharp demand in energy in cells and in the diabetic patient, the blood glucose levels can increase. These can be brought down over time with teas formulated with coconut powder, grapeseed, milk thistle, chlorella, etc that increase blood antioxidant levels and increase glutathione levels

in the liver and blood. High blood antioxidant levels will prevent or reduce oxidative damage to the insulin and glucose molecules and help promote glucose metabolism, provided there is no mineral deficiency of such minerals as managanese, copper, zinc, iron and magnesium.

Other antioxidants like probucol and α-tocopherol also restore high glucose–induced insulin resistance by their antioxidative effects (Kenichi et al, 1999, Antioxidants Improve Impaired Insulin-Mediated Glucose Uptake and Prevent Migration and Proliferation of Cultured Rabbit Coronary Smooth Muscle Cells Induced by High Glucose, Circulation, 99:1370-1378). Also, conversely, "the ability of antioxidants to protect against the effects of hyperglycemia and free fatty acids (FFA) *in vitro*, along with the clinical benefits often reported following antioxidant therapy, supports a causative role of oxidative stress in mediating and/or worsening these abnormalities" (Joseph et al, 2002, Oxidative Stress and Stress-Activated Signaling Pathways, A Unifying Hypothesis of Type 2 Diabetes, Endocrine Reviews 23 (5): 599-622) and the protection is mediated by prevention of oxidation of the glucose, insulin, protein and lipid molecules as well as from the benefit of removing oxidative stress and promoting biological repair, if a broad range of antioxidants are present in the blood in relatively high levels. High levels of natural antioxidants also drive biochemical pathways for healthy biochemistry.

Shutting down peroxynitrite formation is critical also because it is a powerful oxidant that can react with a wide range of targets to cause oxidation of membrane phospholipids, protein and nonprotein thiols, results in single-strand DNA breaks, and nitrates tyrosine residues (Beckman and Koppenol, 2006, Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and the ugly, American Journal of Physiology - Cell Physiology, 271(5 part 1):C1424–C1437). It can injure mitochondria leading to increase in mitochondrial pore opening and consequently apoptosis (Behar-Cohen et al, 1996, Peroxynitrite cytotoxicity on bovine retinal pigmented epithelial cells in culture, Biochemical and Biophysical Research Communications, 226(3):842–849: Radi et al, 2002, Peroxynitrite reactions and formation in mitochondria, Free Radical Biology and Medicine, 33(11):1451–1464). Natural antioxidants can be used to improve endothelial function and prevent the formation of peroxynitrite. Drugs cannot work in this direction as they generate free radicals in biological systems. Drugs developed by the pharmaceutical industry have thus far been associated with toxicity and side effects, which is why natural substances are of increasing interest (Stig Bengmark, 2006, Curcumin, An Atoxic Antioxidant and Natural NFKB, Cyclooxygenase-2, Lipooxygenase, and Inducible Nitric Oxide Synthase Inhibitor: A Shield Against Acute and Chronic Diseases, Journal of Parenteral and Enteral Nutrition, Vol. 30, No. 1, 45-51).

It clearly becomes apparent that NO is not a signaling molecule that it is made out to be but is a reactive molecule that plays a direct regulatory role in the body's biological system by reacting with proteins to alter their function and alter the biochemical pathway and the resultant yields of biochemical pathways in biological systems. Exposure to NO donors increased protein glutathiolation. NO regulates protein glutathiolation (Matthew et al, 2006, Protein glutathiolation by nitric oxide: an intracellular mechanism regulating redox protein modification, The FASEB Journal, 20:1715-1717.) and S-nitrosylation appears as

the effector mechanism by which NO reversibly regulates protein structure and function (Hess et al, 2005, Protein *S*-nitrosylation: purview and parameters, Nat. Rev. Mol, Cell. Biol, **6**,150-166: Stamler et al, (2001) Nitrosylation, the prototypic redox-based signaling mechanism, Cell, 106,675-683). A significant feature of NO bioreactivity is that its nitrosylation of glutathione yields S-nitrosoglutathione that subsequently allows protein glutathiolation and alters the protein function for healthy biochemistry. Protein-glutathione adducts accumulate during oxidative stress (Thomas et al, 1995, Protein sulfhydryls and their role in the antioxidant function of protein *S*-thiolation, Arch. Biochem. Biophys. 319,1-9: Ziegler DM, 1985, Role of reversible oxidation-reduction of enzyme thiols-disulfides in metabolic regulation, Annu. Rev. Biochem, 54,305-329) and glutathiolated actin appears in many pathological conditions that are associated with oxidative stress (Eaton et al, 2002, Detection, quantitation, purification, and identification of cardiac proteins S-thiolated during ischemia and reperfusion, J. Biol. Chem, 277). Actin is readily glutathiolated by S-nitrosoglutathione and if selenium or glutathione levels are low, free circulating actins may be detected which is an indication of chronic oxidative stress as in chronic malnutrition or AIDS patients. The cytoprotective role of gluthiolated-protein relates to their functional significance. For instance, "studies have shown that NO-dependent glutathiolation of aldose reductase decreases the reduction of glucose to sorbitol (Townsend et al, 2006, A glutathione *S*-transferase π-activated prodrug causes kinase activation concurrent with *S*-glutathionylation of proteins, Mol. Pharmacol, 69,501-508).

NO is therefore an important molecule for regulatory processes in the body, other than for vaso-regulation. In the healthy state, when hydrogen peroxide does not accumulate in cells, AR is maintained in an inactive, S-thiolated state. Further, when NO availability is reduced by its loss to the formation of ONOO-, as in the diabetic patient, the enzyme is liberated from this repression and is converted to aldose reductase and glucose is converted to sorbitol that accumulates in cells (see:Nishikawa et al, 2000, Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage, Nature, 404 :787 –790). Diabetics have relatively higher levels of free radicals and the superoxide reacts with NO to form the peroxynitrite (ONOO-) and consequently less NO is available. During diabetes NO availability is decreased (even though the NO synthesis per se may be enhanced), and therefore the net effect will be further yields of AR and increased sorbitol synthesis and even a small fraction of AR remaining uninhibited during diabetes could result in profound sorbitol accumulation while enhancing NO leads to AR inhibition and reduced sorbitol accumulation (see:Deepak Chandra et al, 2002, Nitric Oxide Prevents Aldose Reductase Activation and Sorbitol Accumulation During Diabetes, Diabetes 51:3095-3101). An increase in AR activity results in sorbitol accumulation which potentially disrupts cellular integrity and this may be one of the reasons why diabetics lose minerals. Antibiotics also cause the loss of minerals which means treatments with antibiotics in diabetics must be followed up with mineral replacement from organic sources. Excess sorbitol and activation of aldose reductase also decreases expression of the antiapoptotic protein Bcl-xL, increases DNA fragmentation and glutathione depletion (Anita Galvez et al, 2003, Aldose Reductase Induced by Hyperosmotic Stress Mediates Cardiomyocyte Apoptosis, J. Biol. Chem., Vol. 278, Issue 40, 38484-38494, October 3) that explain the development of diabetes complications including degenerative pathologies

and cancers. The mineral and glutathione depletion explains the degenerative changes and apoptosis of cells in the diabetic.

Oxygen metabolism is essential for sustaining aerobic life but healthy cellular biochemistry yields reactive oxygen species (ROS) and elimination of ROS is essential and is an integral part of healthy biochemistry. Problems begin with the failure to quickly eliminate ROS, as when superoxide dismutase (SOD) levels decline and excess ROS begins to produce oxidative stress in cells. Oxidative stress, a cytopathic consequence of excess ROS leads to the production of secondary radicals and reactive oxidants such as the peroxynitrite and the development of many diseases, including Alzheimer's disease, and diabetes and its complications. Neuropathies, nephropathy, retinopathy and myocardial injury are debilitating complications of diabetes. These metabolic abnormalities are initiated and influenced by elevated oxidative stress. Mitochondrial superoxide production initiates a cascade of damaging events via the production of more superoxide, hydrogen peroxide, hydroxyl radicals, and peroxynitrite which injure macromolecules either at or near the site of their formation (Bergamini et al, 2004, Oxygen, reactive oxygen species and tissue damage, Current Pharmaceutical Design, 10(14):1611–1626). Chronic excess of ROS in the retina results in aberrant mitochondrial functions in diabetes (Kowluru RA, 2005, Diabetic retinopathy: mitochondrial dysfunction and retinal capillary cell death, Antioxidants & Redox Signaling, **7**(11-12):1581–1587) which is due to low levels of superoxide dismutase (SOD). Damage to the mitochondrial lipid membrane by ROS increases the permeability of the organelle, and the modulation of the permeability transition of mitochondrial membrane represents another dysfunction caused by ROS. Increased swelling of the mitochondria is observed in the retina of diabetic mice (Kanwar et al, Oxidative damage in the retinal mitochondria of diabetic mice: possible protection by superoxide dismutase, submitted to Investigative Ophthalmology & Visual Science,cf-Kowluru and Pooi-See Chan, Oxidative Stress and Diabetic Retinopathy, Exp Diabetes Res. 2007; 2007: 43603). Such swelling of mitochondria is expected in all cases of complications of diabetes and hence, in biological therapy, oxidative stress must be rapidly removed to facilitate biological repair to restore organelle function and membrane function – which is at the nano level. Drugs cannot perform biological repair. In the diabetic patient, there may be other issues and the next issue in diabetics is the issue of insulin resistance.

Many studies show that oxidative stress is not only associated with complications of diabetes, but has been linked to insulin resistance *in vivo* (defined as a subnormal response to a given amount of insulin). *In vivo*, studies in animal models of diabetes indicate that antioxidants, especially LA, improve insulin sensitivity. Several clinical trials have also demonstrated improved insulin sensitivity in insulin-resistant and/or diabetic patients treated with the antioxidants vitamin C, LA, vitamin E, and glutathione (ref: Joseph et al, 2002, Oxidative Stress and Stress-Activated Signaling Pathways: A Unifying Hypothesis of Type 2 Diabetes, Endocrine Reviews 23 (5): 599-622). Oxidative damage to insulin and oxidative stress that prevents the formation of the GTF are key underlying factors in developing insulin resistance. Also, “oxidative stress alters the plasma lipoprotein profile (particularly low- density lipoproteins), the coagulative parameters (with an increased thrombotic risk), the endothelium (with a decrease in

prostacyclin synthesis and an increase of thromboxane production) and the cell membranes (which undergo peroxidation). In diabetic patients, an altered oxidative pattern is present not only in the fasting state but also especially after food intake. In particular, food intake induces a decrease in the total radical-trapping antioxidant parameter (TRAP) and an elevation of hydroperoxides and thiobarbituric acid reactive substances (TBARS)" (Caimi et al, 2003, Diabetes Mellitus: Oxidative Stress and Wine**,** Curr Med Res Opin 19(7):581-586, Medscape).

When too much antibiotics are administered to clear an infection, they also kill the symbiotic (good) bacteria in the gut that keep the candida in check. As the candida begins to flourish, the afflatoxins they produce may reach levels to produce thrush or candida infections. Even before these levels are reached, the afflatoxins can interfere with the formation of GTF leading to low cell output and sorbitol begins to accumulate in cells. Hence, GTF formation is central to therapy for the diabetic patient as well as the insulin-resistant patient and this approach must include the strategies to scavenge excess free radicals, lower sorbitol accumulation etc. and where appropriate, to keep the candida in check. Mineral deficiencies may also be associated with insulin resistance.

Minerals from organic sources, especially manganese, copper, zinc and iron are required in enzyme activity in the biological systems to convert the superoxide into oxygen through SOD activity and to convert the hydrogen peroxide into water and oxygen through glutathione-catalase activity as soon as they are formed in cells so as to prevent the formation of secondary radicals that are disruptive to healthy biochemical pathways and cause oxidative damage to molecules and cell membranes leading to hypertension, CVD, arthritis and diabetic complications. insulin resistance in diabetes and hypertension, It has been suggested that the depletion of intracellular free magnesium common to both hypertension and diabetes may help to explain their frequent clinical association as all channels regulating insulin action are magnesium-dependent (Mario et al, Effects of Vitamin E and Glutathione on Glucose Metabolism, Role of Magnesium, 1999, Hypertension, 34:1002-1006) and magnesium supplementation may lower blood pressure (Widman et al, 1993, The dose dependent reduction in blood pressure through administration of magnesium: a double blind placebo controlled cross-over trial, Am J Hypertens, 6:41–45: Paolisso et al, 1993, Effects of magnesium and nifedipine on insulin action, substrate oxidation and blood pressure in aged subjects, Am J Hypertens, 1993;6:920–926) and improve circulating glucose levels and tissue glucose oxidation in subjects with NIDDM (Paolisso et al, 1994, Changes in glucose turnover parameters and improvement of glucose oxidation after 4-week magnesium administration in elderly noninsulin-dependent (type II) diabetic patients, J Clin Endocrinol Metab, 78:1510–1514). Diabetes is a multifactorial condition induced by excess free radicals and prolonged oxidative stress that can lead to loss of minerals and it is not caused by magnesium deficiency but magnesium deficiency is a factor in the progression of the condition and its complications and mineral deficiency must be properly addressed in diabetics.

As far as meeting the need to provide energy to cells in the diabetic patient as an alternative to glucose, is concerned, this can be met with fruit juices that contain sucrose and fructose. Adding one or two tablespoons of medium chain fatty acids can be very

beneficial to health as these fatty acids are easily broken down into monoglycerides by lingual lipase activity and these compounds can be readily metabolized to yield energy in the liver. This approach prevents energy starvation of cells in the diabetic patient and can continue until the sorbitol accumulation clears up and blood sugar levels decline while a 20 minute brisk walk helps to lower circulating glucose on a daily basis as part of the glucose lowering management process.