Beyond Insulin Resistance and Syndrome X: The Oxidative-Dysoxygenative Insulin Dysfunction (ODID) Model – Part III

by Majid Ali, MD

Darwin, Dysoxygenosis and ODID

Some readers may have difficulty with the word dysoxygenative in the title of this article. They might accept the evidence I present and my deductive reasoning concerning the oxidative phenomena that lead to pathophysiologic derangements of insulin metabolism. However, they might challenge my emphasis for the role of dysoxygenosis in the proposed ODID model. My simple answer is that oxidosis theoretically can be corrected rapidly by the addition of the required reducing equivalents. But we know from empirical experience that such attempts do not lead to rapid reversal of chronic disorders characterized by chronic oxidosis, including the oxidative-dysoxygenative insulin dysfunctions. That is so because oxidatively-hampered functions of enzymes and other regulatory proteins cannot be expeditiously restored merely by using anioxidant therapies. A systematic and comprehensive approach is required that addresses all the elements that led to the ODID state. Other readers might express concern about the true-to-life value of the ODID model in terms of reversing type 2 diabetes mellitus. Later, I cite several studies by integrative practitioners as well as some published in prestigious journals (including *The New England Journal of Medicine*[285]) to show that to be the case for many type 2 diabetics. Also, I include a case study of one of my recent patients with type 2 diabetes to illustrate the clinical value of the ODID model. The eventual effects of all therapies employed in those programs was to reduce oxidosis and correct dysoxygenosis (though the authors of those papers did not directly address the issues of oxidosis and dysoxygenosis).

It is important to point out that the ODID model may not be fully comprehended within the prevailing Western deterministic-reductionist model of medicine, Rather, one needs to consider it within the larger context of the Darwinian notion of ecologic relationships, nutrition, and time-honored aspects of self-regulation in the health/disease/disease continuum. I include below brief comments about those aspects of ODID.

Darwin went around the world and recognized that the parts are inseparable from the whole as the whole is inseparable from its parts. He also recognized that nature selects and wondered whether there were any recognizable mechanisms operating in that selection. Finally, he propounded his theory of the *mechanisms* involved. Natural selection is an *ecologic* notion. Below, I reproduce some text from an earlier article titled, "Darwin, Oxidosis, Dysoxygenosis, and Integration"[27] to highlight the issue.

Three issues will dominate medicine in the next century: accelerated oxidative injury (oxidosis), abnormal cellular oxygen metabolism ("dysoxygenosis"), and an integrative view of the human microecologic cellular and macroecologic tissue-organ systems. And that medicine will grow under Darwin's glow. Among the ecologic shifts, oxidosis and dysoxygenosis will be the core *issues in basic and clinical research. Integration of empirical and experimental observations will be the mainstay of all therapeutic strategies. Prediction is a risky business; still, those three predictions seem entirely safe.*

Oxidative insulin dysfunction is a spreading epidemic among children and adolescents.[49] *The ecologic, nutritional, and lifestyle changes during the last century which set the stage for that epidemic, are all oxidative-dysoxygenative in nature.* The genetic factors (gene induction, gene silencing, gene suppression, and gene mutation, in certain cases) are clearly secondary to those oxidative-dysoxygenative stressors. The long-term effects of lifestyle changes on the pathophysiology of oxidative insulin dysfunction can be well illustrated by a comparative study of the Pima Indians of Southwestern United States and an Indian tribe in Northern Mexico with close genetic similarity.[64,65,286] A single case of diabetes was documented among Pima Indians in 1908. Elliott Joslin (founder of Joslin Clinic) recorded 21 cases thirty years later. By 1954, the number of cases had climbed to 283, and to over 500 in 1965. In late 1990s, over 60% of the Pima population were reported to have developed diabetes mellitus (mostly of type 2). By contrast, the genetically similar Mexican Indians continue to have an extremely low incidence of diabetes.

The epidemic of type 2 diabetes among the Hispanic-Americans is as frightening as that among the Pima Indians. Among them, the prevalence of type 2 diabetes tripled between 1979 and 1988. Alarmed at the published data in January 2000 MSNBC reported that type 2 diabetes "could easily become the preeminent US public health problem."[287] Earlier, I referred to the epidemic of low-body-weight type 2 diabetes in India.[51-54] Clearly, many of our assumptions about the association of obesity with type 2 diabetes in the West do not hold any water in India.

Genes legislate life, the environment interprets the laws set forth by them. I chose that as the title of one of the chapters in *RDA: Rats, Drugs and Assumptions.*[288] It is self-evident that the genes among the Pima Indians, Hispanic Americans, and Indians in India have not undergone such tectonic shifts during the last five decades that we can attribute every aspect of epidemics of type 2 diabetes to them. Even when we can demonstrate activation of genes involved with glucose energetics and insulin pathways, the question still remains: What triggered those genes? That must be accepted as the central question.

I submit that the two primary issues involved in the epidemics of type 2 diabetes in Pima Indians, Hispanic Americans, and Indians of India are oxidosis and dysoxygenosis. Those are the fundamental molecular lesions caused by ecologic, nutritional, and lifestyle stresses that lead to oxidative-dysoxygenative insulin dysfunction.

The plight of the Pima Indians[64,65,286] and Hispanic-Americans[47,287] cannot be understood by a merely deterministic-reductionist study of diabetes. What is needed is some lessons from the Dene peoples of the North American subarctic. I include below some text from one of my editorials for *The Journal of Integrative Medicine* about the Dene peoples:

The earlier peoples (mistakenly regarded as "primitive" by some) demonstrated a profound ecologic awareness in their lives. Their "language of ecology" was different from ours in that it was metaphorical and ritualistic, but in many ways it was far richer, spiritual, and ennobling. Ecologists often relate "an exact moment of birth" of the science of ecology to a definition of ecosystem put forth by Tansley in 1935. That, of course, is not uncommon for those unfamiliar with the deep "ecologic beliefs" of the ancients in the inseparability of people, animals, lands, and waters. Human perceptions of ecologic issues and insights into their impact on human life are as old as humankind itself. For instance, the term nde (ndeh) of the Dene peoples of the North American subarctic is often translated

as land. But that is not what Dene mean by ndeh. For them, ndeh is the integrated whole that surrounds and permeates their beings. It is the relatedness of that whole to everything with which they celebrate life – of people, animals, air, fire, water, the deep earth, and the most high sky. Ndeh is anything and everything for them. The concept of the discrete is alien to them; so were such notions to most peoples of earlier eras.[289]

Darwin, in essence, figured out how *ndeh* was preserved and evolved under the organizing influence of what he called the *Infinite Wisdom.*

As indicated earlier, I coined the term dysoxygenosis for a *cellular* state of functional impairment of enzymes involved with oxygen metabolism.[27,28] I briefly summarize here previously published morphologic, biochemical, and clinical evidence for the ODID model.[11,15,27,28]

Morphologic

Morphologic alterations in the circulating blood associated with dysoxygenosis are readily observed with high-resolution, phase-contrast microscopy. In 1997, my colleague, Omar Ali, and I introduced the term oxidative coagulopathy for those microscopic abnormalities.[9] In a subsequent series of articles, we described and illustrated at length various morphologic patterns of oxidative coagulopathy, including microclot and microplaque formation (Figures 5-10). The reversal of those changes with oxygenative therapies was the subject of other publications.[5-11] In essence, all solubilized proteins in the human body are under constant threat of being insolubilized by myriad phenomena related to oxygen and redox homeostasis. Under physiologic condition, the proteolytic pathways provide a vigorous counterbalance, "digesting" and dissolving those insolubilized protein forms. We introduced the term oxidative lymphopathy for similar stresses on lymph proteins that result in microclot formation.

Biochemical

The most direct and illuminating biochemical evidence for dysoxygenosis may be drawn from an analysis of 24-hour urinary excretion of urinary organic acids. In one study, urinary excretion of organic acid metabolites of the Krebs cycle were found in nearly 80% of subjects, with the remainder showing increased excretion of a variety of metabolites of oxygen (Tables 4, 5, and 6). Table 7 shows evidence of dramatic reversal of dysoxygenosis following successful use of oxygenative therapies.

Clinical

In the preceding section, I addressed the critical issues of what some others may deem as non-insulin-glucoregulatory events in the bowel, blood, and liver ecosystems that profoundly affect not only the digestive-absorptive aspect of carbohydrate metabolism but also glucose disposal in peripheral tissues.

Table 4 – The Frequency of Increased Urinary Excretion of Metabolites of Glycolysis *and* Krebs Cycle in 84 Patients with Dysoxygenosis

Krebs Cycle	
Citric acid	36
Succinic acid	11
Aconitic acid	5
Fumaric acid	0
2-oxo-glutaric acid	0
Glycolysis	
Glyceric acid	32
2-Hydroxybutyric acid	22
Lactic	7
Pyruvic	1

Table 5 – The Frequency of Increased Urinary Excretion of Metabolites of the Krebs Cycle *Only* in 84 Patients with Dysoxygenosis

Citric acid	38
Succinic acid	5
Aconitic acid	4
Fumaric acid	0
2-oxo-glutaric acid	0

Table 6 – The Frequency of Increased Urinary Excretion of Metabolites of Glycolysis *Only* in 84 Patients with Dysoxygenosis

Glyceric acid 8	8
2-Hydroxybutyric acid	5
Lactic 2	2
Pyruvic zero	0

A large number of recent reports of oxidative phenomena involving reactive oxygen species, reactive nitrogen species, products of glycation, and oxidant and prooxidant molecules have elucidated the essential oxidative nature of myriad pathophysiology changes involving carbohydrate and insulin metabolism. Those observations provide additional strong support for the oxidative insulin dysfunction. Specifically, antioxidant enzymes are proteins and like other functional proteins, are vulnerable to oxidative injury or destruction leading to loss of their enzymatic functions.[41,42] In the context of oxidative insulin dysfunction, the oxidants of central importance are the reactive oxygen species, reactive nitrogen species, and products of glycation reaction. Among the antioxidant enzyme systems of central importance, the glutathione peroxidase system (GPx) is selectively inactivated by SNAP and is especially sensitive to functional loss by superoxide and the glycation reaction. Both reversible (involving nitrosation of a thiol) and irreversible (involving the formation of sulfur-seleno bridge) reactions are involved in GPx inactivation. Inactivation of glutathione peroxidase and many other antioxidant enzyme systems involved in insulin pathophysiology form the core of the oxidative insulin dysfunction model. A specific example of this, as mentioned earlier, is the induction of pancreatic beta cell apoptosis by nitric oxide.

Earlier in this article, I defined oxidative-dysoxygenative insulin dysfunction as impairment of any or all aspects of insulin synthesis, release from beta islet cells, and signaling pathways as well as any or all derangements of metabolic pathways triggered, perpetuated, or interrupted by oxidative-dysoxygenative stresses. It is evident from the preceding discussion that insulin is predominantly anabolic under some sets of conditions and predominantly catabolic under other sets of conditions. It is a mediator of proinflammatory responses that can also serve anti-inflammatory roles. Indeed, it seems highly probable to me that insulin will eventually be demonstrated to influence – and be influenced by – all mediators of inflammatory and healing responses. The same will hold for all apoptotic phenomena and carcinogenesis. Those statements may be seen as too broad to be of real value. However, my opinion is defensible in light of the preceding presentation of diverse genetic, nutritional, ecologic, and inflammatory influences of insulin pathophysiology. ➤

Table 7 – Effect of Nutritional and Anti-PLF Therapies on PLF Population and Urinary Excretion of Organic Acids in a 4-year-old Autistic Child

Name	Pre-treatment	Post-treatment (Reference Range)
Tartaric acid	423	32 (0-16)
Arabinose	427	24 (0-115)
Furan-2,5-dicarboxylic acid	155	7 (0-50)
Furancarbonylglycine acid	88	0 (0-60)
5-hydroxymethyl-2-furoic acid	421	42 (0-80)
3-hydroxy-3-methylglutaric acid	259	11 (0-36)
Lactic acid	98	61 (0-100)
Pyruvic acid	3.6	2.6 (0-50)
5-hydroxyindoleacetic	1.5	5 (0-20)
Oxalic	39	142 (0-100)
Succinic	3	43 (0-20)
2-hydroxyphenylacetic	0.25	0.28 (0-10)
2-hydroxyphenylacetic	6	10 (0-50)

Insulin Dysfunction

The thread that holds the enormous kaleidoscope of insulin pathophysiology together evidently is oxygen homeostasis. Also, in my view, no attempts to delineate individual molecular steps in that kaleidoscope can be fruitful unless seen through the prisms of oxygen and states of dysoxygenosis. Indeed, many who have attempted that in the past have been forced to think differently by newer knowledge in the exploding fields of genomics and proteonomics. Consider the following statement of a researcher at the Joslin Diabetes Center, quoted in *Science: "We used to think type 2 diabetes was an insulin receptor problem, and it's not. We used to think it was solely a problem of insulin resistance, and it's not. We used to think that muscle and fat were the primary tissues involved, and they are not."*[290]

What should also be amply clear from the preceding is that the simplistic notions of preventing and treating disorders of glucose-insulin metabolism with one or more drugs must be relinquished. Chronic and unrelenting sugar overload, abrupt hyperglycemic-hypoglycemic shifts, rapid glucose-insulin-adrenergic responses, obesity, insulin resistance, pre-diabetes, and overt diabetes must now be seen as demonstrable and interrelated segments of myriad kaleidoscopic molecular mosaics. The thread that holds those mosaics together is accelerated oxidative molecular injury which, in turn, impedes or destroys myriad enzymatic and regulatory protein functions involved in preserving the oxygen metabolism. Thus, unrelenting oxidosis results in dysoxygenosis.

It should be evident to the reader by now that the ODID model sheds considerable light on one of the most perplexing questions of insulin pathophysiology and the spreading epidemic of obesity-associated and low-body-weight type diabetes mellitus: How can we reconcile the fact that in the former (obesity-associated) type 2 diabetes, insulin appears to predominantly serve anabolic roles while in the latter (low-body-weight) type 2 diabetes, it appears to serve predominantly a catabolic role? The ODID model holds that the pathogenetic factors in both forms of types 2 diabetes are essentially oxidative-dysoxygenative in nature. Insulin serves variable roles within different contexts of nutrition, environment, and lifestyle.

Prevention and Reversal of ODID

Articles on insulin resistance and type 2 diabetes often open with comments about the epidemic and frightening spread of those two disorders. Nearly always, such articles then move on to discussions of pharmacologic agents that might block molecular and genetic pathways that are believed to cause diabetes. Amazingly, the nutritional, environmental, and stress-related factors that set the stage for the development of insulin resistance and diabetes are rarely, if ever, discussed. Nor is any consideration given to the essential oxidative-dysoxygenative factors that set the stage for ODID. Furthermore, a large body of literature[78,275,276,291,292] demonstrating the efficacy of dietary changes, nutrient supplementation, and phytoregulatory substances is ignored.

A different approach to the problem of insulin-resistant cell membranes is to restore the cell membrane function by integrative nutritional, herbal, and oxygenative therapies. It is generally not recognized in pharmacologic medicine that many cases of hyperinsulinemia and type 2 diabetes can be successfully managed with natural therapies and without drugs. In integrative management plans, it should be evident by now, my colleagues focus on all relevant oxidative-dysoxygenative issues and have several examples of excellent glucose homeostasis in our files.

Following are the major components of our integrative management protocols in use at the Institute: (1) patient education of all major ecologic, nutritional, oxidative-dysoxygenative, and other issues concerning the cause and reversal of the ODID state; (2) optimal food choices with maximum possible carbohydrate restriction; (3) oral redox-restorative nutritional and herbal protocols designed to arrest and reverse oxidative-dysoxygenative stressors (see Tables 8 and 9); (4) intramuscular and intravenous protocols to potentiate the various enzymatic pathways of the body, especially those involved in oxygen transport and utilization, acid-base equilibrium, and hepatic detoxification, in selected patients with other associated chronic disorders; (5) oxygenative therapies, especially bi-weekly EDTA infusions (see footnote after Table 8 for rationale of EDTA use and ref. 9 for detailed discussion of molecular dynamics of oxidative coagulopathy and efficacy of EDTA for its control); (6) specific protocols for restoring microecologic cellular and macroecologic tissue-organ ecosystems, especially the bowel, blood, and liver ecosystems (including such empirically effective therapies as castor oil liver packs, cayenne/ginger vapor protocol, and hydrogen peroxide baths (for details, see www.MajidAli.com); (7) support for the thyroid, adrenals, and pancreas trio[293]; (8) support for sex hormones, neurotransmitters, and hypothalamus-limbic system; and (9) stress management with self-regulation, meditation, and limbic stretching. The principles of integrative medicine, scientific basis of integrative treatment protocols, and details of therapies employed have been presented previously.[7,26-18,22]

A. Education

We recognized a special need to educate patients in the study of three specific areas: (1) philosophy, principles and practice of integrative medicine (focus on the whole person rather than his diagnostic category); (2) the true nature of the ODID state and the oxidative-dysoxygenative phenomena that cause it; (3) the essential need for slow, and sustained (limbic) exercise[294]; and (4) spiritual surrender with effective methods for stress control and meditation.[295] For patient education in those areas, we used the Institute's own lending library of books,

monographs, videos, and audio tapes (see listing at www.MajidAli.com).

B. Optimal Food Choices and Dietary Guidelines

In our dietary approach to prevention and reversal of ODID, we recommend the minimum possible intake of starches and increase the use of high-quality proteins with abundant use of cold-pressed oils *taken cold.* Optimal hydration with periods of overhydration in the morning (three to four quarts daily) is an essential part of the program.

Among the carbohydrates consumed, the choice of carbohydrates is often very important in many cases. For example, one patient recently reported the morning blood sugar range of 225 to 275 mg/dL when taking wheat products and only 125-150 mg/dL when she consumed the same quantity of starch in a combination of rice, buckwheat, and soy. The metabolic individuality of a person in this context is often not given due consideration. For additional information on dietary plans, the reader is referred to *The Butterfly and Life Span Nutrition*[7] (See www.Glycemic.com for detailed information on the glycemic index of various foods).

Detailed discussions of the principles and practice of clinical nutrition as employed in our program have been described in *The Butterfly and Life Span Nutrition.*[34] Briefly, the essentials of our recommendations for food choices are the following: (1) diligent avoidance of foods that generate sudden hyperglycemic-hypoglycemic shifts and cause rapid surges of insulin and catecholamines; (2) partially-hydrolyzed protein formulations containing 85-90% amino acids used to further relieve stress on glucose-insulin dynamics; (3) ample supplies of essential oils (cold-pressed olive, flaxseed, sesame and pumpkin oils taken cold with salad, uncooked vegetables or other cold foods); (4) avoidance of foods with oxidized, denatured fats; (5) frequent consumption of foods such as ginger, garlic, onions, turmeric, lentils, beans, and others that are empirically known to improve bowel function and health; (6) liberal nutrient supplementation of vitamins, minerals, and redox-restorative substances that support the various enzyme systems of the body, especially those involved in redox homeostasis, oxygen transport and utilization, and acid-base equilibrium.

C. Oral Redox-Restorative Substances (RRSs) and Herbal Protocols

The choice of RRSs and the selection of dosage of individual RRS was made with the following three considerations: (1) the established structural and functional aspects of RRSs in biology; (2) the established roles of such RRSs in health preservations; and (3) the empirical experience with the clinical uses of RRSs in the management of chronic ecologic, immunologic, nutritional, and degenerative disorders. The authors hold that the notions of Recommended Daily Allowances for prevention of nutrient deficiency syndromes are utterly irrelevant to the clinical uses of RRSs as therapeutic agents in integrative medicine. Thus, the participating physicians who prescribed the various management protocols agreed to follow general guidelines concerning the use of the Institute protocols, and not to limit their use of RRSs to any algorithms. The complete listings of oral nutrient and herbal protocols have been published.[48]

The major RRSs and nutrient prescriptions were as follows: chromium, 400-600 mcg; selenium, 400-600 mcg; molybdenum, 400-600 mcg; support for the liver ecosystem: glutathione, 600-800 mg; acetylcysteine, 600-800 mg; MSM, 1,000 to 1,500 mg; lipoic acid, 300 to 500 mg; magnesium, 1,500 to 1,500 mg; calcium, 1,000 to 1,500 mg; potassium, 400 to 600 mg; taurine, 1,500 to 2,000mg, and coenzyme Q10, 100 to 150 mg.

Table 8 – Range of Daily Doses of Vitamins, Minerals, and Important Redox-Restorative Substances for Prevention and Reversal of ODID

Vitamins	C, 3,000 to 5,000 mg; E, 400 to 800 IU; A, 10,000 to 15,000 IU; D, 100 to 250 IU; B-complex, 30-50 mg; B12, 250 to 1,000 mg
Minerals	magnesium, 1500 to 2,500 mg; calcium, 1,000 to 1,500 mg; potassium, 400 to 600 mg; chromium, 400-600 mcg; selenium, 400-600 mcg; molybdenum, 400-600 mcg;
Redox-Restorative Substances	Glutathione, 600-800 mg; N-Acetylcysteine, 600-800 mg; Methylsulfonylmethane, 1,000 to 1,500 mg; lipoic acid, 300 to 500 mg; taurine, 1,500 to 2,000 mg; coenzyme Q10, 100 to 150 mg; pycnogenol, 100 to 150 mg; EDTA infusions*

*Intravenously administered EDTA arrests oxidative coagulopathy, is a vasodilator and cell membrane stabilizer, and has been long known to prevent premature aging of mitochondrial enzymes. EDTA also lowers the body burden of toxic metals, such as lead and mercury, which are known to increase the risk of coronary artery disease. In recently reported animal experiments, EDTA prevented diffuse reperfusion injury in tissues subjected to rapid freezing. (references summarized in Ref. 9, 11, and 13).

Insulin Dysfunction

Table 8 shows guidelines for RRSs, other nutrients, and phytoregulatory substances prescribed at the Institute.

Case Report of Reversal of ODID

A 47 year-old man presented at the Institute with recently diagnosed type 2 diabetes mellitus. He was highly motivated and eager to test the efficacy of non-pharmacologic therapies for normalizing his blood sugar levels. A program of diet, exercise, self-regulation, nutrients, and herbal protocols was instituted following the above guidelines. Table 8 shows the results of a four-hour glucose tolerance study and insulin levels. Figure 13 shows the data for blood glucose control. The arrow in the figure points to an outlying blood glucose value on the day when the patient, in his words, "wanted to test the effect of consuming two large bread rolls."

Table 10
Blood Glucose and Insulin Levels of a 47-Year Old Man After 100 Gram Glucose Load

Time	Glucose mg/dL	Insulin mcU/mL
Fasting	102	5.5
1/2 hour	274	–
1 hour	320	31.5
2 hour	189	39.6
3 hour	49*	15.6

One of the major strengths of the ODID model is its ability to explain all known complications of diabetes and, through that understanding, to allow formulation of rational ➤

Table 9 – Phytoregulatory Substances, Nutrients, and Minerals of Empirical Value for Prevention and Reversal of ODID*

Gymnema Sylvestre (500 to 750 mg) Ginkgo biloba (25-75 mg)	Neem extract (50-100 mg), Huckleberry leaf (100-250 mg ginger, garlic Fresh or cooked	Bitter Melon Channa Water (Black Skin Garbanzo bean)
Chromium 400-1,000 mcg	Molybdenum 200-500 mcg	Selenium 400-1,000 mcg
EDTA infusions** Methylsulfonyl methane (500-1,000 mg)	Arginine 250-500 mg	Vanadyl sulfate 10-30 mg. Lipoic acid for neuropathy 250 to 750 mg
Aminoguanidine 300 mg	Proanthocyanidine (grape seed and others) 100-250 mg	Acetyl-L-carnitine 500 to 1000 mg

*Other nutrients of substantial empirical value include coenzyme Q10, fatty acids (GLA and EPA), magnesium, lysine

➤

and logical integrative management plans to prevent and/or reverse those sequelae. Specifically, cardiac, cerebral, peripheral vascular, renal, ophthalmic, and neurologic complications – as well as those related to diminished resistance against microbial species – can be directly attributed to oxidative coagulopathy induced by hyperglycemia. The generation of reactive oxygen species, reactive nitrogen species, and oxidative products of glycation involved in the pathogenesis and perpetuation of oxidative coagulopathy also inflict oxidative injury to enzymes and regulatory proteins involved in oxygen metabolism, eventually leading to the oxidative-dysoxygenative insulin dysfunction. That leads one to the obvious conclusion: all efforts for prevention and reversal of the ODID state must address *all* factors involved in oxidosis and dysoxygenosis.

Notwithstanding progress in blocker drugs – as is amply documented earlier in this article – the epidemics of type 1 and type 2 diabetes are rampant and there is no indication of a let-up in the foreseeable future. Furthermore, the drug-blockade approach exacts a heavy toll in chronic illness. To cite one example, 85,000 *preventable* heart attacks and episodes of heart failure were recently ascribed to the use of calcium channel drugs.[259]

My primary purpose in proposing the oxidative-dysoxygenative insulin dysfunction (ODID) model is to: (1) focus on those issues of nutrition, environment, and lifestyle stress that lead to ODID; (2) marshall evidence for my view that the essential pathogenetic mechanism involved in all those factors are oxidative-dysoxygenative in nature; and (3) address the potential of nonpharmacologic measures that can prevent and, in many cases, reverse the ODID state.

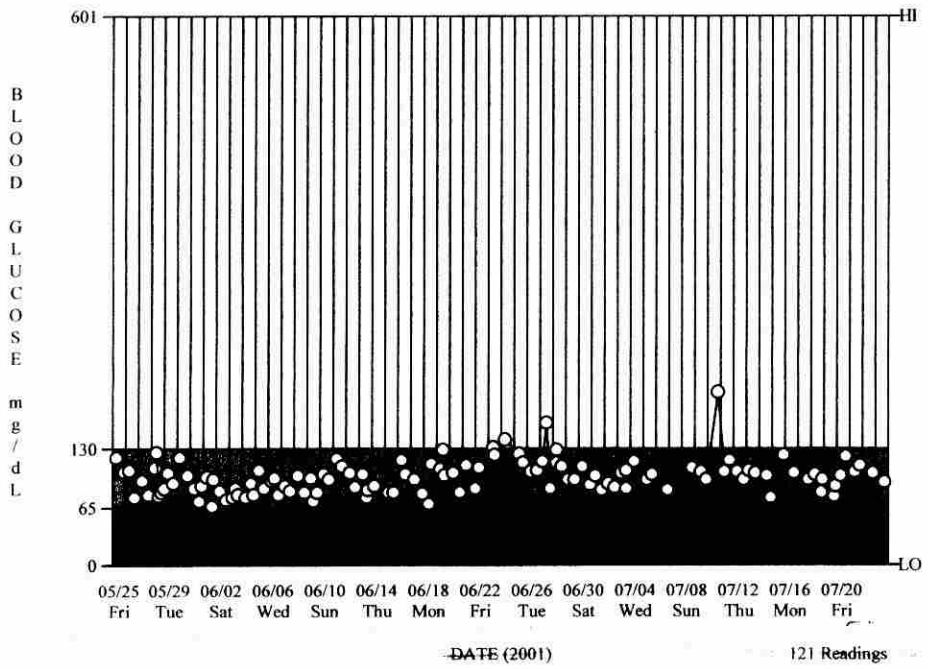
Summary

Clinical, biochemical, and genetic aspects of glucose and insulin metabolism and counterregulatory pathways are reviewed. Enormous complexity of the involved molecular and signaling pathways is highlighted. The glucose-insulin pathways are intricately intertwined, not only with those of metabolism of lipids and proteins, but also with developmental, inflammatory, coagulative, healing, and aging pathways. The epidemic of low-body-weight-associated type 2 diabetes in the Orient further calls into question several assumptions generally made about the pathogenesis of obesity-associated type 2 in the West. Accelerated oxidative molecular injury to myriad pathways is recognized as the common denominator in all such aspects. The oxidative-dysoxygenative insulin dysfunction (ODID) model is put forth as a synthesis of diverse oxidative-dysoxygenative dynamics that involve the various glucoregulatory mechanisms. The ODID model also addresses the "non-insulin" dynamics of bowel, blood, and liver ecosystems that profoundly affect the energetic metabolism of glucose and insulin homeostasis but are rarely, if ever, addressed by diabetologists and insulin researchers.

Genes set broad biologic limits on energetic glucose metabolism, functionalities of insulin and insulin-like molecules, and counterregulatory pathways. However, environmental factors and nutritional choices determine the state of the health/dis-ease/disease continuum. In the Western deterministic-reductionistic medicine, all notions of pathogenesis of insulin resistance, syndrome X, and diabetes mellitus, as well as of treatment plans, are based on an assumption that all atoms, molecules, and cells involved with glucose-insulin dynamics play *fixed and consistent* roles in health and disease. That assumption is challenged here with an extensive review of the functional complementarity and contraryness of molecules involved in those pathways.

The ODID model has a strong explanatory power for all known aspects of the pathogenesis of the spreading epidemics of obesity-associated type 2 diabetes in the West and low-body-weight-associated type 2 diabetes in the Orient. It also sheds considerable light on all known complications of diabetes mellitus. Furthermore, it provides a rational basis for integrative management plans for prevention and reversal of insulin resistance, syndrome X, and diabetes mellitus in its early stages. Addressing all relevant issues of redox dysregulation and dysoxygenosis significantly reduces the frequency and extent of cardiovascular, renal, neurologic, ophthalmic, and other sequelae of diabetes.

Figure 13. Excellent Glucose Control Obtained with an Integrative Plan without Drug Therapies (see Table 5 for Glucose Tolerance Test for the Patient)



Correspondence:
Majid Ali, MD
95 East Main Street, Suite 101
Denville, New Jersey 07834 USA
973-586-4111 / Fax 973-586-8466

References for all three parts available on the *Townsend Letter* website www.townsendletter.com

◆