Oxygen Homeostasis

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Oxygen, Insulin Toxicity, Inflammation, and the Clinical Benefits of Chelation Part 2

Insulin Reduction and EDTA Chelation: Two Potent and Complementary Approaches for Preventing and Reversing Coronary Disease

In 1923, the German physician E. Kylin published a paper titled "Studies of the hypertension-hyperglycemia-hyperuricemia syndrome," clearly linking derangements of glucose metabolism to cardiovascular disorders.[1]

Since then, the link between hyperinsulinemia and cardiovascular disease (CVD) has been explored with an enormous number of experimental and clinical studies.[2-8] The prevailing view attributes this association to combined pro-inflammatory effect of glucose and anti-inflammatory effect of insulin. This is a serious error. Consider the following from a 2006 review article published in *Seminars in Thoracic and Cardiovascular Surgery*[9]:

> In this article we discuss data demonstrating an anti-inflammatory effect of insulin and a pro-inflammatory effect of glucose and free fatty acids and provide a mechanistic justification for the benefits of maintaining euglycemia with insulin infusions in the hospitalized patient.

The above quote summarizes well the prevailing – and grievously erroneous, in my view – notion of the glucose/insulin dynamics. Two recent large trials published in the *New England Journal of Medicine*, the ACCORD trial (10,251 patients) and the NICE-SUGAR trial (6,104 patients), clearly showed that the greater use of insulin and insulin-increasing drugs was associated with higher morbidity and mortality.[10,11] The investigators failed to recognize clear evidence of insulin toxicity. Indeed, the editorial accompanying one of the articles considered the more-insulin-higher-mortality association as a "quandary."

In 1968 as a pathology resident, while I learned about three types of lesions, the crucial significance of each escaped me. The first was fatty change of the liver in type 2 diabetes that is characterized by hyperinsulinemia. I did not see this abnormality in type 1 diabetes in which there is an absence or severe deficiency of insulin. Neither my professors nor pathology texts explained that fatty change was due to persistently elevated levels of insulin. The second histopathologic abnormality was fat necrosis in soft tissues of diabetics. Again, hyperinsulinemia was not identified as the cause of the lesion. The third type of lesion was ground-glass appearance of the nuclei of liver cells as evidence of gluconeogenesis seen in type 2 diabetes. My professors and books did not link it with adverse effects of excess insulin.

In Part 1 of this column (May 2010), I documented cases of normalization of blood pressure in some cases of hypertension when blood insulin levels were reduced. In cases of prostate cancer coexisting with hepatitis and hyperinsulinemia, reduction of blood insulin levels is associated with significant drops in liver enzymes and PSA values. (unpublished personal observations)

Insulin influences the behavior of several vasoactive moieties in the endothelial cells, as well as within the circulating blood. For example, it stimulates endothelial release of endothelin-1 and nitric oxide.[12] Hyperinsulinemia and not glucose level is the predisposing factor to endothelial dysfunction.[13] The plasma levels of cell adhesion molecules change in hyperinsulinemia and modulate some vasoactive mediators.[14] Hyperinsulinemia induces overactivity of some cytokines in in-vitro cell studies.[15]

Relative Toxicities of Hyperglycemia and Hyperinsulinemia

In a previous article, I presented the dysox model of diabetes and demonstrated that all known biochemical, histopathologic, and clinical aspects of diabetes are rooted in the primary disruptions of oxygen homeostasis and the consequent derangements of oxidosis, acidosis, and clotting-unclotting dysequilibrium.[16] Here, I bring that perspective to bear on the present context of relative toxicities of hyperglycemia and hyperinsulinemia. Mitochondrial ATP generation drives all major events involving cellular

development, differentiation, detoxification, and demise. At the level of fundamental energetics, all reactions involve electron transfer events. It is true that glucose autooxidizes in biologic systems to initiate and perpetuate electron transfer chains; however, the rates of such oxidation, uninitiated and uninfluenced by insulin, are minimal under physiological conditions. By contrast, insulin-driven electron transfer chains constitute the principal mode of glucose oxidation in the Krebs cycle. It follows that hyperinsulinemia inflicts oxidative molecular and cellular injury to a far greater degree than hyperglycemia.

Notwithstanding the above clinical, histopathologic, and biochemical aspects of insulin excess, the fundamentals of insulin toxicity escape the notice of clinicians. Indeed, results from a Google search for "insulin toxicity" did not include a single paper from clinicians (other than those posted by the author). This, in my view, is an enormously important and neglected subject, which I address in my forthcoming book *Oxygen, Gila Monster, and Insulin Toxicity*.[17]

In a series of publications, my colleagues and I have documented the efficacy of EDTA chelation for reversal of coronary artery disease.[18–21] The dysox model of coronary artery disease requires that all elements that disrupt oxygen homeostasis be effectively addressed, including nutritional therapies.[22] Hyperinsulinemia is common in patients with cardiovascular disorders, and our protocols eliminate or decrease its degree. However, in past studies we did not investigate insulin metabolism. In Part 1 of this column, I presented aspects of 122 four-hour insulin and glucose profiles to document some unusual patterns of insulin pathobiology and certain unanticipated findings. Here, I review the clinical benefits of EDTA chelation and normalization of insulin homeostasis to clarify the complementarity of these two potently beneficial clinical approaches.

In *Oxygen, Darwin's Drones, and Diabetes* (2010), I marshal evidence for my view that in metabolic and cardiovascular disorders, insulin toxicity is the primary event and hyperglycemia is secondary.[22] The evolutionary insulin design is perverted by the trio of toxicities of foods, environment, and thoughts. These disruptions set the stage for insulin-toxic states – dysfunctional insulin receptor function, insulin resistance, obesity, fatty change of the liver, hyperinsulinemia, prediabetes, diabetes, renal insufficiency – that culminate into cardiovascular disorders. The metabolic, inflammatory, and degenerative aspects of these disruptions are presented at length in Darwin and Dysox Trilogy (2009), the 10th, 11th, and 12th volumes of my textbook series *The Principles and Practice of Integrative Medicine*.[23–25]

Complementary Benefits of Insulin Reduction and EDTA Chelation

The ACCORD and NICE-SUGAR trials provide incontrovertible evidence of insulin toxicity for patients with cardiovascular disorders. A close examination of the spectrum of insulin toxicity – pathological inflammatory response being the most evident aspect – not only sheds light on the insulin–CVD link but also on the mechanisms underlying the additive benefits of integrating insulin homeostasis with EDTA chelation infusions. Specifically,

1. Hyperinsulinemia induces oxidative coagulopathy; causes oxidative stress on the circulating blood plasma, platelets, erythrocytes, and leukocytes; and causes atherogenesis. EDTA infusions arrest oxidative coagulopathy.[17,22,26]
2. Hyperinsulinemia exerts procoagulative effects by activating inflammatory mediators.[27]
3. Some serpins – a super family of clot-busters and inflammation suppressors – are insulin-sensitizing.[28] EDTA counters such procoagulative influences.[26]
4. Hyperinsulinemia increases lipid peroxidation reactions.[29] EDTA counters such reactions, which mostly require the participation of transitional metallic ions – iron, copper, and others – by binding and sequestering them.[26]
5. Hyperinsulinemia impairs mitochondrial efficiency by creating local dysox conditions.[30] EDTA preserves mitochondrial enzymes (specifically, it completely or partially restores the ischemia-induced mitochondrial defects).[31]
6. In states of systemic inflammation, hyperglycemia impairs neutrophil degranulation and potentiates coagulation, whereas hyperinsulinemia inhibits fibrinolysis.[32] EDTA inhibits pathologic inflammatory responses.[26]
7. Hyperinsulinemia affects the activities of many vasoactive substances, including tumor necrosis factor alpha, endothelin-1 and nitric oxide.[33] Hyperinsulinism can be expected to disrupt homeostasis of these crucial regulators of endothelial function and vascular flow. EDTA restores these functions.[26]
8. Hyperinsulinemia induces overactivity of some cytokines in in-vitro cell studies.[34] EDTA prevents such overactivity.[26]

CUE, CUD, and Chelation

Oxygen is the king of human biology. It maintains law and order in the body by organizing and coordinating its three "executive branches": acid–alkali balance, oxidant and antioxidant regulation, and clotting–unclotting equilibrium (CUE).[23–25] The oxygen's order of biology is threatened by the trio of toxicities of environment, foods, and thoughts. The failure of its executive branches lead to acidosis, oxidosis, and clotting–unclotting dysequilibrium (CUD), respectively. Notwithstanding the explosive growth of literature on redox chemistry, it is ironic that crucial issues of redox regulation are not addressed by mainstream doctors. Such doctors liberally prescribe aspirin and yet they are adamant against measures for insulin reduction and EDTA chelation, two approaches that can reverse clotting–unclotting dysequilibrium, which is the hallmark of cardiovascular disorders.

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On March 24, 2010, I saw Sherry L., a 94-year-old woman with a sharp mind and a strong heart. Her lipid profiles included the following: cholesterol, 318 mg/dL; HDL cholesterol, 102 mg/dL; and LDL cholesterol, 197. On March 30, a 68-year-old, 5'10" man weighing 268 lbs. told me that his insurance company had denied coverage of a four-hour insulin test which I had ordered for him. On March 31, a front-page story in the *New York Times* reported on the government's support for a statin drug for healthy people with normal cholesterol levels. Three days later, C-Span spent an hour promoting statin drugs. It had the executive director of the Center for Science in Public Interest, who talked about cholesterol-clogging coronary arteries over and over. No, he didn't once mention statins; but the message to the viewers was not lost. That night I had a dream about the cholesterol-statin industrial complex, which I posted on www.ethics7.org.

Serpents, Serpins, and Statins

In addition to nitric oxide, endothelins, and adhesion molecules mentioned earlier, there are serpins, a superfamily of protease-inhibitors. Thirty-six serpins are known to exist in humans (including antithrombin, kinin, some coagulation factors) among the over 1000 known, including those of fungi, bacteria, and certain viruses.[35,36] By some estimates, 10% of all plasma proteins belong to this family. The acronym *serpin* – short for serine protease inhibitors – was coined to underscore the importance of the serine-protease nature of chymotrypsin and antitrypsin, the original members of the family identified for their key roles in controlling blood coagulation and inflammation, respectively. It seems safe to predict that excess insulin will be found to affect most, if not all, serpins, adding to the growing CUE-CUD complexity.

Not unexpectedly, in light of nature's preoccupation with complementarity and contrariety, serpins also perform diverse nonproteolytic functions, including hormone carriage proteins (thyroxine-binding globulin, cortisol-binding globulin), tumor suppressor genes (maspin), and storage (ovalbumin, in egg white). In this broader context, serpins serve the Oxygen King as senior officials in its CUE executive branch, commonly with overlapping roles. Contrast this with the simple-minded – and misguided – notion of preventing cardiovascular events with statins, which block one specific enzyme and carry a significant risk of liver injury, rhabdomyolysis (muscle cell death), and fatigue. Statins also increase the risk of cancer.[37]

The kaleidoscope of the CUE-CUD dynamics is vast. Evolution perfected the CUE homeostasis over hundreds of million years. This equilibrium is remarkably resilient but still vulnerable to a vast number of disruptive elements. Mythological serpents killed their victims by curdling their blood, as some snake venoms do. Other venoms induce fatal systemic bleeding. Yet other venoms kill by triggering concurrent thrombohemorrhagic events. I see a parallel of that diversity in human CUE-CUD dynamics, albeit not so dramatic in most clinical states except in acute cases of disseminated intravascular clotting. Evolutionary considerations are as humbling as they are enlightening. They compel us to look beyond one-enzyme-one-blocker-drug model of the statin industry, and to learn from empirical experiences of diligent and astute clinicians. I know that I have only a partial understanding of the exact mechanisms of clot-busting herbs (which have scores of components) and nutrients that I use in my integrative protocols to achieve insulin reduction and EDTA chelation; however, that lack of knowledge does not invalidate their empirical and clinical value.[18,19]

In 1997, my colleague, Omar Ali, and I marshaled 13 lines of evidence to support our assertion that cholesterol is a minor player in atherogenesis.[38] In 2007, the *Lancet* published an analysis of published data for over 40,000 women who were given statin drugs for primary prevention of coronary heart disease.[38] Consider the following quote from that review of the subject in *Lancet*[38]:

> The last major revision of the US guidelines, in 2001, increased the number of Americans for whom statins are recommended from 13 million to 36 million, most of whom do not yet have but are estimated to be at moderately elevated risk of developing coronary heart disease. In support of statin therapy for the primary prevention of this disease in women and people aged over 65 years, the guidelines cite seven and nine randomized trials, respectively. Yet not one of the studies provides such evidence.

Yet not one of the studies provides such evidence! This comment should surprise only those who have never critically examined the statin data published during the last few decades.

Integrated Protocols for Insulin Reduction

Hyperinsulinemia, as I explained in Part 1, is caused by dysoxygenosis resulting from the trio of toxicities of foods, environment, and thoughts. It follows that integrated protocols for a lifelong plan for insulin reduction must address all relevant oxygen issues. Clinical benefits of many natural remedies that improve insulin function – cinnamon, bitter gourd (karela, bitter melon), *Gymnemia sylvestre*, chromium, and others – are well recognized. However, in my view, the issues of chronic anger, excessive gut fermentation, leaky gut state, impaired hepatic detox pathways, and other non-pancreas-related pathologies are deep and pervasive. Simple remedies, such as mentioned above, rarely yield long-term satisfactory results. I refer interested readers to "Dr. Ali's Insulin Reduction Program" at www.ethics7.org.

In closing, the questions concerning the bioenergetic basis of the insulin–CVD link are explored. Evidence is marshaled to support a hypothesis that insulin toxicity is

a major, if not the primary, mechanism of atherogenesis in individuals with hyperinsulinism. The mechanisms underlying the added clinical benefits of insulin-reducing and EDTA chelating therapies are considered to support this combined approach.

Notes

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