



Oxygen Homeostasis

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Oxygen, Insulin Toxicity, Inflammation, and the Clinical Benefits of Chelation Part 1

In this article, I will describe some aspects of a series of consecutive 125 four-hour insulin profiles to present what I consider to be evolutionary insulin design. This design is disrupted by the trio of toxicities of foods, environment, and thoughts that cause the trio of molecular states of acidosis, oxidosis, and clotting-unc clotting disequilibrium (CUD). The insulin design so disrupted leads to insulin resistance, hyperinsulinemia, and insulin-toxic states – obesity, fatty change of the liver, diabetes, cardiovascular disorders, and others – which, in turn, set the stage for diverse metabolic, inflammatory, and degenerative, including cardiovascular disorders. These subjects are presented at length in the Darwin and Dysox trilogy (2009), the 10th, 11th, and 12th volumes of my textbook *The Principles and Practice of Integrative Medicine*.¹⁻³

Some of the data presented may stretch the credulity of those who have not studied insulin well in clinical medicine. The profound relevance of this evolutionary design to the pathogenesis of insulin-toxic states – obesity, fatty change of the liver, diabetes, cardiovascular disorders, and others – is underscored. Four case studies are furnished: the first two illustrate the evolutionary insulin design, and the remaining two demonstrate serious consequences of

the disruption of this design, as well as dramatic clinical benefits of insulin reduction.

The Crank-Crankshaft Model of Insulin Toxicity

In a previous publication, I proposed that a crank-crankshaft model of insulin resistance hyperinsulinemia develops as the pancreas gears up hormone production to overcome developing resistance of the cell membrane to insulin.⁴ Succinctly stated, in this model the crank of insulin (5,808 daltons) fails to move (activate) the crankshaft of insulin receptors in the hardened cell membranes – the crankshaft is rusted, turned, and twisted, so to speak – so rendering insulin dysfunctional. The crankshaft of insulin receptors is roughly 70 times larger than the insulin crank, including two alpha subunits 135 kD each and two beta subunits of 95 kD each.

To explain hardening of cell membranes, I proposed the Grease and Detergent Model in which biomembranes and matrix are covered with cellular grease due to insufficient detergent functions of the body.⁵ The grease is composed of cellular waste, molecular debris, rancid (oxidized) lipids, sticky sugars (glycosylated proteins and lipids), and pulped (misfolded) proteins. The primary detergent in the body is oxygen,

with secondary oxydetergents, such as hydrogen peroxide, nitric oxide, hydroxyl radicals, oxygen-activated enzymes, and grease-eating phagocytes.

Evolutionary Insulin Design

Evolution optimized insulin homeostasis and cellular bioenergetics with such economy that extremely small amounts are required to keep fasting blood glucose levels in the normal range of 70 to 85 mg/dL. Surprisingly, 24 patients (19.6%) in this series had fasting insulin levels of less than 2 uIU/mL, clear evidence that evolution designed the beta cells of the pancreas to rest during sleep (Table 1, p. 112). Notably, another 27 patients (22.1%) showed insulin values between 2 and 5, adding to the strength of my conclusion. The data in Table 2 (p. 112) show a surprise finding of considerable clinical significance: while only 19.6% of the subjects had a low fasting insulin level of less than 2 uIU/mL, 64.7% had the peak insulin level of over 50 uIU/mL (the peak insulin values of several optimal insulin profiles in the series were below 30 uIU/mL; examples shown in Tables 3 and 4, p. 112). The main inference I draw from these data is that fasting insulin levels often hide delayed hyperinsulinemia.



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Case 1: Optimal Insulin Profile

An 82-year-old 5'8" woman weighing 185 lbs. was seen for severe fatigue developing after resection of an abdominal abscess associated with a ruptured colonic diverticulum. She had been treated for hypertension and atrial fibrillation for over 20 years. Her fasting insulin level of 6 units reveals, with stunning clarity, the evolutionary insulin design: the beta cells of the pancreas were designed to rest at night, even for a markedly overweight elderly woman.

Case 2: Optimal Insulin Profile

A 51-year-old 5'2" woman weighing 120 lbs. consulted me for hypothyroidism, allergy, and sinusitis. She was disabled with chronic fatigue syndrome ten years earlier following divorce and working as a single mother. She became committed to her health and rigidly followed a low-glycemic-index diet. She said, "Life has been good. If I were not so devoted to my health, I think I would be very sick. Adversity, if it doesn't kill you, liberates you."

Table 1: Distribution of Fasting Insulin Levels, Expressed in uIU/mL, in Consecutive 122 Four-Hour Insulin Profiles

	< 2 uIU/mL (n = 24)	2–5 uIU/mL (n = 27)	6–15 uIU/mL (n = 49)	16–25 uIU/mL (n = 13)	26–60 uIU/mL (n = 9)
Females (n = 78)	15 (12.3%)	16 (13.1%)	33 (27%)	8 (6.5%)	6 (5.3%)
Males (n = 44)	9 7.3%	11 9.0%	16 13.1	5 4.1%	3 2.4%

Table 2: Distribution of Peak Insulin Levels (in 50 uIU/mL) of 122 Profiles in Six Categories

Insulin uIU/mL	< 50	51–100	101–150	151–200	201–300	>300
Females (n = 78)	26 (21.3%)	33 (27%)	16 (13.1%)	1 (0.8%)	1 (0.8%)	1 (0.8%)
Males (n = 44)	14 (11.4%)	13 (10.6%)	15 (12.3%)	0	2 (12.3%)	0

Table 3: Optimal Insulin Profile (Peak Value, 29 uIU/mL) of an 82-year-old 5'8" Woman Weighing 185 lbs. with Hypertension, Atrial Fibrillation, and Diverticulitis

	Fasting	1 Hr	2 Hr	3 Hr	4 Hr
Insulin uIU/mL	6	27	29	9	4
Glucose	87	97	111	65	79

Table 4: Optimal Insulin Profile (Peak Value, 11.8 uIU/mL) of a 51-year-old 5'2" Woman Weighing 120 lbs. who Consulted Me for Hypothyroidism, Allergy, and Sinusitis

	Fasting	30 M	1 Hr	2 Hr	3 Hr	4 Hr
Insulin	3.2		11.8	2.4	1.9	1.5
Glucose	85	110	75	70	52	91

Pathology and Clinical Aspects of Insulin Toxicity

Insulin in excess is a potent toxin – fattening, pro-inflammatory, immunosuppressive, pro-stroke, pro-heart disease, pro-degenerative disorders, pro-cancer, and pro-premature aging. Not unexpectedly in this light, it impedes oxygen-driven mitochondrial energetics and myriad oxygen signaling pathways. Insulin toxicity is the unrecognized spreading pandemic of our time. Unfortunately most doctors rely on fasting blood sugar values within the reference range – a regrettable practice that often masks insulin derangements (personal unpublished data) – and the consequences of insulin toxicity go unrecognized. Notable among such consequences are:

- fatty change of the liver;
- insulin-induced fat necrosis (a type of tissue death);
- insulin dermatitis, including gray-yellow discoloration;
- neuropathy; and
- higher vulnerability and mortality from cardiovascular events.

Strong evidence for increased morbidity and mortality from the cardiovascular consequences of increased insulin activity is drawn from two recent and massive trials: the ACCORD trial, which included 10,251 patients, and the NICE-SUGAR Study, which included 6,104 patients.^{6,7}

The Only Reliable Test for Insulin Toxicity

My analysis of 122 four-hour insulin profiles revealed that it is not safe to rely on the fasting or random blood insulin level determinations. As indicated earlier, 67% of the subjects in this series had hyperinsulinemia that was not suspected or proven by their previous doctors. Remarkably, six individuals without prior diagnosis of diabetes were found to be diabetic using the standard blood sugar criteria – insulin profiles included four-hour glucose profiles as well.

Table 5: Reduction in Insulin Levels Correlate with Changes in Liver Enzyme Activities, and Blood Pressure of a 67-year-old 5'7" woman weighing 215 lbs. With Hypertension, Chronic Fatigue Syndrome, GERD, IBS, Fatty Change of the Liver, and Allergy

	Fasting	30 Min	1 Hr	2 Hr	3 Hr	4 Hr	AST IU/mL	ALT IU/mL	BP
Insulin	51.4	61.9	115	84.8	30	25.6	95	138	166/100* 150/96**
Glucose	98	190	122	124	68	51.5			
				31.3			44	61	130/80

*right arm ** left arm

Table 6: Reduction in Insulin Levels Are Correlated With Improvement in Liver Enzyme Activities, and Blood Pressure of a 63-year-old 5' 11.5" Man Weighing 211 lbs. With Hypertension, Hepatitis C, Cirrhosis, and Hypertrophic Cardiomyopathy

	Fasting	1 Hr	2 Hr	3 Hr	4 Hr	AST IU/mL	ALT IU/mL	Hep C Count
Insulin	15.8	57.2	132	20	51	42	73	9.7 million
Glucose	79	165	115	40	11.8			
Insulin	4	48.3	44.2	10.2	2.9			3.6 million
Glucose	61	148	99	50	409	41	37	

The reason why insulin toxicity is neglected in clinical medicine is that doctors do not look for it with a four-hour insulin profile performed after a 75 gram glucose load. Most of more than 10,000 patients whom I saw during the last 30 years had complex chronic problems and had seen multiple specialists. Not more than 20 of them had four-hour insulin profiles performed before I saw them. Notably, none of the previous doctors had undertaken robust bowel and liver detox procedures to address hyperinsulinemia. Indeed, some aspects of these data are likely to stretch the credulity of doctors who have not studied insulin well in their practices.

Case 3: Insulin Toxicity

A 67-year-old 5'7" woman weighing 215 lbs. presented with hypertension, chronic fatigue syndrome, GERD, IBS, fatty change of the liver, and allergy. The highest recorded blood pressure in the past was 240/110. The results of four-hour insulin and glucose profiles are presented in Table 5. Other pertinent laboratory data included the following: AST, 95; ALT, 138; A1c,

6.1%; vitamin D, 21 IU; decreased values of multiple urinary steroid metabolites; and increased urinary excretion of cadmium, mercury, and lead. I prescribed my integrated insulin reduction protocol (described later). Note the fall of the pretreatment two-hour postprandial insulin value of 84.8 units to posttreatment value of 31.3 units, and the pretreatment

blood pressure values of 166/100 and 150/96 to posttreatment value of 130/80 (Table 5).

Case 4: Insulin Toxicity

A 63-year-old 5' 11.5" man weighing 211 lbs. presented with a history of hepatitis C, cirrhosis, hypertrophic cardiomyopathy, GERD, eczema, onychomycosis, and leg

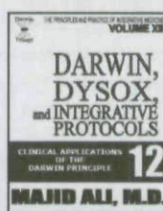
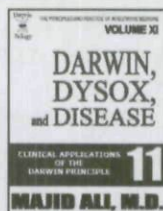
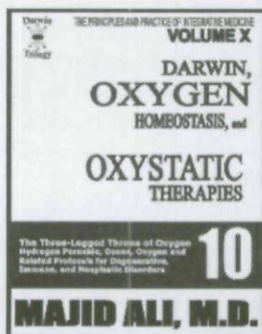
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edema. He had received interferon therapy six years earlier, which was tolerated poorly and failed to reduce the viral load long term. In January 2010, seven years later, it was planned to enter him in the trial of a caspase inhibitor drug at a New York University hospital. He responded so well to our integrative treatment plan that the trial team found him unsuitable for inclusion. He lost 24 pounds. His BP values changed from 145/90 to 125/80, and hepatitis C viral count fell from 9.7 million copies in September 2009 to 3.6 million copies in January 2010. Changes in insulin profiles and liver enzymes are shown in Table 6 (p. 113).

To summarize, I describe aspects of a series of consecutive 125 four-hour insulin profiles to put forth evolutionary insulin design, and discuss the clinical significance of insulin toxicity which results when this design is thwarted. The risks of relying on fasting or random insulin levels

are highlighted. I consider a four-hour insulin profile the single most important laboratory test for assessing not only the glucose metabolism but also for the early detection and quantification of the insulin-toxic states, such as obesity, fatty change of the liver, prediabetes, diabetes, prehypertension, hypertension, neuropathy, incipient renal failure, and cardiovascular events. In Part 2, I will discuss the EDTA-insulin dynamics and present the details of my insulin-reduction program.

Notes

1. Ali M. *Darwin, Oxygen Homeostasis, and Oxystatic Therapies*. Principles and Practice of Integrative Medicine 3. 3rd ed. New York: Institute of Integrative Medicine Press; 2009.
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4. Ali M. Beyond insulin resistance and syndrome X: The oxidative-dysoxygenative insulin dysfunction (ODID) model. *J Capital Univ Integr Med*. 2001;1:101-141.
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6. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545-2559.
7. The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283-1297.

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