



-Clinical Perspective-

The Role of Stress in the Current Metabolic Crisis

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The past century has seen dramatic advances in medical science. Over that time, Western societies have realized significant improvements in life-expectancy and quality of life. However, in the past few decades those advances have slowed and even been reversed in some populations. The recent emergence of metabolic-related chronic disease patterns is on the verge of overwhelming a medical model which has been designed to manage acute and infectious disease patterns. Perhaps the past century has not been as kind to our health as we once thought.

The advances of the past century have been accompanied by many negative health trends as well. Increased caloric intake, especially of refined and processed foods, has led to a population which is “over-nourished” while at the same time deficient in important micronutrients. Sedentary lifestyles resulting from less physical labor have reduced population fitness while increasing adiposity. Changes in working patterns, sleep and social demands have added unprecedented demands on the body’s stress response mechanisms. Environmental toxins have also placed a heavy burden on our detoxification systems leading to an array of sensitivities and syndromes unknown to previous generations. We have now learned that these factors are inter-related and synergistic, producing negative health outcomes much earlier in this generation than ever before. Solutions to this healthcare crisis will involve understanding the complex matrix of the metabolic inter-relationships that are driving these disorders and will require fundamental investment in lifestyle-directed therapies.

It is therefore no surprise that metabolic disorders once only associated with aging adults are now routinely diagnosed in young adults and adolescents. The CDC predicted that if current trends hold, 1/3 of children born in the year 2000 would be diagnosed with type 2 diabetes within their lifetime. A recent study in Latino youth, one of the most vulnerable populations, showed that for each additional component of the metabolic syndrome they possessed, the higher their level of morning cortisol.¹ In fact, an increasing amount of data is now linking this stress hormone with insulin resistance, visceral adiposity, obesity, hypertension and lipid abnormalities.^{2,3} The inter-relationship between stress (hypothalamic-pituitary-adrenal-HPA axis over-stimulation) and glycemic dysregulation is perhaps one of the most over-looked contributors to metabolic abnormalities.

When we think of stress we often think of major life events, those often found on a life-stress inventory (divorce, death of spouse, major health concern). While these episodic stressors have negative consequences, the most common stressors are ones which often go unrecognized, operating chronically at low levels resulting in profound negative clinical outcomes. One of these common, unrecognized stressors is glycemic dysregulation. This should come as no surprise, since one of cortisol’s main functions is related to glucose regulation during stress. While these functions are important during episodes of acute stress (as a secondary mechanism to the fight or flight response), long-term cortisol production results in peripheral insulin resistance, inhibition of growth hormone, gonadotropin and thyrotropin hormone and increased gluconeogenesis. When we add to this that visceral adipose tissue, a consequence of chronic overproduction of cortisol and insulin, produces increasing levels of

inflammatory mediators (IL-1 β , IL-6, TNF- α) which drive HPA-cortisol production; we can see why it is so difficult to determine which is the cause and which is the effect.^{4 5,6,7} The key, however, is to break the cortisol-insulin-adiposity-inflammation-stress cycle; preferably *without* pharmaceutical intervention. Here are some of the keys that should be considered:

1. Reduce Glycemic Impact of Diet

The glycemic impact of the diet is vitally important to maintain appropriate insulin and cortisol levels. Both hyperglycemia and hypoglycemia are stressors which signal HPA axis production of cortisol. Chronic dysglycemia results in chronic high cortisol levels placing the individual in an ongoing catabolic state. This is exacerbated when obesity and insulin-resistance have already set in.

Most people are familiar with glycemic index (GI); a number that reflects the glycemic effect of *available carbohydrates* in food relative to the effects of an equal amount of glucose. Glycemic Load (GL) is defined as the amount of carbohydrate exposure over a certain length of time. It is calculated by taking the GI/100 and multiplying this by the weight of the food and the percent of available carbohydrates in the food. Both the GI and GL are based on relative units, not correlating easily to grams of total carbohydrates or calories consumed. So while they may be helpful in the controlled environment of a clinical trial or for making general diet recommendations; what is needed is a number that helps an individual know the true glycemic impact of the meal they will consume.⁸ This requires understanding the impact of the all the other macronutrients (proteins, fats, non-digestible carbohydrates, fermentable fibers) and micronutrients (vitamins, minerals, phytonutrients) that impact glucose disposal and insulin secretion.

Soluble fibers and fermentable fibers (carbohydrates that can be fermented into short-chain fatty acids by gut micro-flora) seem to have an especially profound effect, not only on the glycemic response of the initial meal consumed, but on subsequent meals consumed. Researchers at the Lund University in Sweden have recently published data showing that a single breakfast meal consisting of high amounts of soluble and fermentable fibers will decrease the glycemic impact of the subsequent lunch and dinner meals.⁹ This effect was also noted for fibers consumed in the evening; impacting the glycemic response of the breakfast meal.^{10,11} Add this to the data recently published in the NEJM showing low-carbohydrate and Mediterranean-style diets improve glycemic control, weight, and lipid parameters over a two-year period- dietary changes must play a primary role in improving long-term outcomes.¹²

Dietary patterns that should be encouraged:

- Model the basic diet after the Mediterranean where possible.¹³ (Read : Eat, Drink and be Healthy- Willett)
- Reduce glycemic impact by reducing refined carbohydrates, soft drinks and other sweetened beverages and increasing the use of whole grains
- Do Not Skip Breakfast- This meal sets the foundation for glycemic control for the entire day and helps ensure the normal transition from high morning cortisol production.

- Supplement the diet, if necessary, with soluble and fermentable fibers (FOS, inulin etc.)
- Increase phytonutrients: use brightly colored vegetables, spices and herbs to improve insulin sensitivity.

2. Measure Insulin sensitivity early.

Fasting serum tests (especially fasting serum glucose) are ineffective ways to discover insulin sensitivity impairments in at-risk populations. Impaired glucose tolerance often begins years before changes in fasting glucose levels will suggest a problem. Use of oral glucose tolerance tests or other post-prandial tests will identify at-risk patients earlier and allow lifestyle approaches to have their greatest impact. In fact, getting baseline insulin sensitivity for all patients where there is a family history of diabetes, obesity or heart disease would be advisable. Advanced lipoprotein analysis will also reveal signs of insulin resistance. Insulin resistant patients will most often have an elevated triglyceride:HDL-C ratio¹⁴ (suspect insulin resistance when ratio is above 3.5), elevated small-dense LDL particles, elevated large triglyceride-rich VLDL particles, smaller HDL particles and increased C-reactive protein levels. All of these measurements are routinely available through numerous laboratories at reasonable (and often reimbursable) rates.

3. Measure cortisol/DHEA levels in all obese patients regardless of age.

Measuring cortisol and DHEA levels by saliva sampling is the best way to monitor the diurnal nature of the HPA-axis. All stressors, regardless of origin will result in episodic or chronic elevations in cortisol. Chronic HPA-axis stimulation by stress directly impairs insulin function and stimulates caloric intake (especially of comfort foods).^{15,16} By assessing HPA function using salivary cortisol and DHEA it enables the patient to begin assessing other potential stressors that may be driving cortisol output. These may be related to chronic inflammatory conditions (allergies, food allergies, GI inflammation, injury etc), relationships, work stress, financial worries, chronic illnesses or glycemic dysregulation. Without adequate management of stress-signaling over time, an individual will begin showing signs of adrenal fatigue or exhaustion where the output of cortisol is no longer elevated or even well below normal (even though the pituitary output of ACTH still remains high). These individuals will likely have severely depressed levels of DHEA leading to an abnormally high cortisol:DHEA ratio.

Once assessment of the HPA axis is accomplished through testing and symptom evaluation, improvements can be suggested for lifestyle, diet and natural therapies. Recall that obesity itself, through inflammatory signaling, will drive the HPA signal for cortisol. Weight loss of any amount will help balance the HPA axis, improve insulin sensitivity and improve self-image.

4. Maintain adequate sleeping pattern

Over the past few decades, sleep time (primarily less sleep before midnight) and regularity (weekday vs. weekend) has been reduced in both children and adults. Poor sleep quality and quantity is directly related to visceral adiposity and HPA axis dysfunction.¹⁷ In fact sleep deprivation is often used in laboratory studies to invoke HPA axis stress.¹⁸ Additionally,

obese patients have elevated risk for sleep apnea, which often goes undiagnosed, adding to an already burdened physiology. Patients (as well as those with whom they sleep) should be questioned about sleeping patterns, duration, and symptoms of sleep apnea. Maintaining regular patterns of sleep for at least 7 hours per night should be recommended.

5. Set realistic improvements in lifestyle measurements

Lifestyle management programs most often fail due to diminishing adherence over time. Most studies show weight loss will maximize 6 months into a program and then subjects begin to creep back to their starting weight. Even so, these individuals still have improved metabolic parameters over those who never lost the weight in the first place. It should be emphasized to patients that even small decreases in their weight or increases in their physical activity can have tremendous benefits. Emphasis should be placed upon improving insulin sensitivity and decreasing inflammation which is less personal than specific weight or BMI targets.

Conclusion:

Over the next few decades, the looming epidemic of cardio-metabolic risk will either overwhelm the current medical paradigm or a new paradigm will emerge to combat this risk. If such a new paradigm emerges it must include the understanding of the complex matrix which links glucose control, adiposity and stress. Functional tests which allow for HPA axis assessment and measurements of insulin sensitivity should be performed earlier, especially in patients with a BMI over 28 or with a family history of Type II diabetes. Dietary recommendations should emphasize insulin sensitivity, glycemic impact and reducing inflammation- for which the Mediterranean diet (with a reduced carbohydrate-impact emphasis) is well suited. Within this paradigm- stress management is paramount, because the hypothalamus-pituitary axis (adrenal, thyroid, gonad, growth hormone) controls so much of the biological matrix. Lastly, clinicians who will manage patients under this new paradigm must not only understand the new paradigm, they must model it for their patients.

References:

1. Weigensberg, M.J.; Toledo-Corral, C.M.; and Goran, M.I. Association between the metabolic syndrome and serum cortisol in overweight Latino youth. *J Clin Endocrinol Metab.* 2008; 93(4):1372-1378.
2. Dallman, M.F.; la Fleur, S.E. et al. Minireview: glucocorticoids--food intake, abdominal obesity, and wealthy nations in 2004. *Endocrinology.* 2004; 145(6):2633-2638.
3. Dallman, M.F.; Pecoraro, N.C. et al. Glucocorticoids, chronic stress, and obesity. *Prog Brain Res.* 2006; 153:75-105.
4. Kyrou, I.; Chrousos, G.P.; and Tsigos, C. Stress, visceral obesity, and metabolic complications. *Ann N Y Acad Sci.* 2006; 1083:77-110.
5. Elenkov, I.J.; Iezzoni, D.G. et al. Cytokine dysregulation, inflammation and well-being. *Neuroimmunomodulation.* 2005; 12(5):255-269.
6. Andrews, R.C.; Herlihy, O. et al. Abnormal cortisol metabolism and tissue sensitivity to cortisol in patients with glucose intolerance. *J Clin Endocrinol Metab.* 2002; 87(12):5587-5593.

7. Andrews, R.C. and Walker, B.R. Glucocorticoids and insulin resistance: old hormones, new targets. *Clin Sci (Lond)*. 1999; 96(5):513-523.
8. Monro, J.A. and Shaw, M. Glycemic impact, glycemic glucose equivalents, glycemic index, and glycemic load: definitions, distinctions, and implications. *Am J Clin Nutr*. 2008; 87(1):237S-243S.
9. Nilsson, A.C.; Ostman, E.M. et al. Effect of cereal test breakfasts differing in glycemic index and content of indigestible carbohydrates on daylong glucose tolerance in healthy subjects. *Am J Clin Nutr*. 2008; 87(3):645-654.
10. Nilsson, A.C.; Ostman, E.M. et al. Including indigestible carbohydrates in the evening meal of healthy subjects improves glucose tolerance, lowers inflammatory markers, and increases satiety after a subsequent standardized breakfast. *J Nutr*. 2008; 138(4):732-739.
11. Nilsson, A.; Ostman, E. et al. Effects of GI vs content of cereal fibre of the evening meal on glucose tolerance at a subsequent standardized breakfast. *Eur J Clin Nutr*. 2008; 62(6):712-720.
12. Shai, I.; Schwarzfuchs, D. et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med*. 2008; 359(3):229-241.
13. Sofi, F.; Cesari, F. et al. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ*. 2008; 337:a1344-
14. Li, C.; Ford, E.S. et al. Does the association of the triglyceride to high-density lipoprotein cholesterol ratio with fasting serum insulin differ by race/ethnicity? *Cardiovasc Diabetol*. 2008; 7:4-
15. Dallman, M.F.; Warne, J.P. et al. Glucocorticoids and insulin both modulate caloric intake through actions on the brain. *J Physiol*. 2007; 583(Pt 2):431-436.
16. Dallman, M.F.; Pecoraro, N.C.; and la Fleur, S.E. Chronic stress and comfort foods: self-medication and abdominal obesity. *Brain Behav Immun*. 2005; 19(4):275-280.
17. Van, C.E. and Knutson, K. Sleep and the epidemic of obesity in children and adults. *Eur J Endocrinol*. 2008;
18. McEwen, B.S. Sleep deprivation as a neurobiologic and physiologic stressor: Allostasis and allostatic load. *Metabolism*. 2006; 55(10 Suppl 2):S20-S23.
19. Integrative Practitioner On-Line Newsletter. December 3, 2008. www.integrativepractitioner.com