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Cardiometabolic disease in men: an integrative medicine approach to managing hormonal risk factors

Keywords

Cardiometabolic disease

Hormonal risk factors

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Abstract

This article reviews the known pathophysiology of cardiometabolic disease (CM) and discusses methods of diagnosis and evaluation of male patients who may be at risk for CM disease. The usefulness of integrative medicine treatment is also reviewed.

These topics are illustrated by means of an actual case of a 55 year-old Caucasian male with no significant past medical history who presented to an integrative medicine clinic complaining of generalized fatigue and weight gain of 30 pounds during the preceding 4 years. After a comprehensive work-up, the patient was diagnosed with metabolic syndrome and advised to begin an exercise program, improve his diet, and lose weight.

The patient was prescribed various supplements in addition to testosterone replacement. He was also advised on stress management techniques.

After 3 months, the patient had successfully lost 25 pounds through dietary modifications, recommended dietary supplements, and exercise. He reported less daytime fatigue, particularly after meals, and improved sleep at night. His stress levels remained unchanged but he felt 'more even' and less susceptible to stressful events on the l-theanine. He had no adverse side effects from the medications or supplements and PSA levels remained unchanged. He was scheduled to return to the clinic in 3 months for re-evaluation. © 2010 WPMH GmbH. Published by Elsevier Ireland Ltd.

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Case

A 55 year-old Caucasian male with no significant past medical history presented to our integrative medicine clinic complaining of generalized fatigue and weight gain of 30 pounds during the preceding 4 years. Initial evaluation by his primary care physician 2 months prior was unremarkable, and he had a fasting glucose of 102 mg/dl. Laboratory studies included a normal comprehensive metabolic panel, complete blood count with platelets, iron studies, thyroid studies, and prostate specific antigen (PSA) level. Serum lipids were within normal limits except a triglyceride level of 203. Biometric measurements demonstrated central obesity with a waist circumference of 42 inches, a body mass index of 40.4, and a blood pressure of 137/83. The patient was diagnosed with metabolic syndrome and advised to begin an exercise program, improve his diet, and lose weight. No further instructions were provided, and a follow-up appointment was scheduled in 6 months to assess progress.

The patient reported significant work-related stress due to the poor economy, and his job commanded frequent travel that made

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it difficult for him to eat a healthy diet and exercise routinely. He was interested in further medical evaluation since his fatigue had increased to the point of interfering with his daily tasks. He complained of afternoon 'lows' especially after his mid-day meal. He was convinced 'something was wrong' and requested advice on appropriate dietary strategies, natural products, and hormonal therapies that may address his physical concerns, while avoiding prescription medications if possible.

The patient's review of systems was positive for 'brain fog', low libido, loss of stamina, and poor muscle tone. He denied any urinary complaints, and his PHQ 9 Depression Survey was negative for significant depression. Review of systems was otherwise negative. Current medications included aspirin 81 mg daily and he had no known drug allergies. He is married, has 2 children, and denies smoking or alcohol intake. His family history is negative for heart disease, diabetes, or cancer. Physical exam revealed a healthy-appearing, overweight male with no abnormal physical findings. His blood pressure was 135/85 and his weight was unchanged.

Definitions

Cardiometabolic Disease

Obesity has become an epidemic in both developed and developing nations and is the sixth most important risk factor contributing to the overall burden of disease worldwide [1]. The average American consumes over 135 lb of sugar per person per year whereas the average German ingests 75 lb per person per year [2]. Central adiposity plays a critical role in the development of cardiometabolic (CM) disease, and the extensive metabolic activity of visceral fat is increasingly recognized in the medical literature. Once thought of as merely a repository for excess calories, adipose tissue is now viewed as an endocrine gland capable of secreting numerous bioactive substances including hormones, growth factors, and cytokines that contribute directly to the development of heart disease and type 2 diabetes [3]. Additionally, new data has emerged linking these same biochemical factors, and in particular insulin resistance, with cancer [4].

CM risk is an expansion of underlying risk factors linked to the metabolic syndrome (MeS). Insulin resistance and visceral obesity are the hallmarks of MeS, with hypertension and hypertriglyceridemia (typically with abnormalities in high-density lipoprotein (HDL) cholesterol) also serving as important co-contributors. CM risk is amplified by other known cardiovascular markers such as high sensitivity-CRP (hs-CRP). While a unified model of CM disease remains incomplete, it is now clear that inflammation, hormonal derangements, stress, central obesity, nutritional deficiencies, and high oxidative burdens underlie the progression towards insulin resistance, diabetes, and heart disease.

Prevalence of Cardiometabolic Disease

The term CM disease is relatively new, and accurate estimates on prevalence are not well defined in the literature. In contrast, the statistics on MeS, diabetes and heart disease provide insight into the problem since they act as proxies for the underlying features of CM risk. It is estimated that 20% of the US population has metabolic syndrome and nearly 21 million people have diabetes. The Centers for Disease Control and Prevention (CDC) report that diabetes is the sixth leading cause of death in the US. Additionally, heart disease continues to be the primary cause of morbidity and mortality in the US affecting more than 1 out of 5 adult men. The 2006 estimates show that 80 million people in the US had one or more forms of cardiovascular disease (CVD) [1].

Integrative Medicine

Nearly one-half of the US adult population utilizes integrative therapies to treat various medical conditions and modify disease risk, including risks for CM disease [5]. Patients demonstrate reliance on these modalities out of philosophical interest in 'natural approaches' to augment conventional medical therapy and to improve their levels of well-being. Unfortunately, because of the negative stigma associated with 'non-traditional' treatment approaches, nearly 70% of patients do not tell their physician about use of integrative approaches [5].

Integrative medicine is an evidence-based combination of conventional, alternative, and complementary therapies. Integrative

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medicine makes use of conventional medicine and surgery in combination with herbs, supplements, manual therapies, mind–body techniques and other modalities to allow patients to achieve optimal health and healing while being actively involved in their own care [6].

Over 45 academic centers in the US have established integrative medicine programs, and 75% of medical schools now teach these approaches to medical students. The annual budget of the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health is now over $120 million [7].

Pathophysiology of Cardiometabolic Disease

CM disease results from a complex combination of etiologies derived from hormonal derangements in primarily insulin, cortisol, and testosterone. In addition, inflammatory mediators (e.g. interleukin-6 (IL-6), tumor necrosis factor-α (TNFα), leptin, adiponectin, hs-CRP), nutritional deficiencies (magnesium, chromium, Vitamin D and Co-enzyme Q10), hypercoagulability (plasminogen activator inhibitor-1 (PAI-1), fibrinogen), oxidative stress, environmental toxins, genetic polymorphisms, poor lifestyle habits, disrupted sleep, and psychosocial stress also play important roles. This case study will focus on the more influential hormonal derangements of insulin, cortisol and testosterone amplifying underlying CM risk and central obesity.

Visceral Obesity, Insulin Resistance and Inflammation

Visceral adipocytes release inflammatory markers known as adipocytokines into the circulation. These adipocytokines include TNFα, IL-6, leptin, adiponectin, and non-esterified fatty acids (NEFAs), all of which contribute to insulin resistance and cardiovascular risk [8]. White adipose tissue is located around the viscera and has been shown to generate higher amounts of adipocytokines compared to subcutaneous fat, thereby highlighting its role in the development of central obesity and consequently type 2 diabetes and heart disease [9].

Both hyperinsulinemia and insulin resistance have been implicated in CM disease. Elevated serum insulin is a well-recognized precursor to diabetes and heart disease, and it may be a stronger predictor of CVD and MeS than insulin resistance alone [9]. Perpetuation of tissue resistance to insulin causes the pancreas to be placed under duress as it increases insulin production as a compensatory mechanism to sustain normoglycemia. Excess NEFAs are transported to the liver where they are converted into very low-density lipoproteins (VLDLs) and triglycerides, thereby inducing hyperlipidemia. Insulin elevation also stimulates the sympathetic nervous system thereby leading to sodium and water retention and vasoconstriction resulting in an increase in blood pressure [8].

Accumulation of adipose tissue in the abdominal area is associated with CVD as well [8]. Adipocytokines generated by these centralized adipocytes create a state of chronic systemic and local vascular inflammation, enhanced coagulation, and endothelial dysfunction [8]. Inflammatory markers contributing additional risk for atherogenesis include hs-CRP, PAI-1, and fibrinogen. When combined with modifiable traditional risk factors such as hyperlipidemia, smoking, and hypertension, the potent mixture of visceral obesity, insulin abnormalities, and inflammation contribute directly to the development of CM disease.

Stress and Hypothalamic–Pituitary–Adrenal Dysregulation

Stress is a critical mediator of CM risk. Integrity of the hypothalamic–pituitary–adrenal (HPA) axis function is essential for maintaining homeostasis [10–12]. Exposures to any stressors results in the stimulation of the ''stress system'' thereby inducing a myriad of adaptive hormonal responses designed to re-establish disrupted homeostasis and promote survival. These primitive ''fight or flight'' responses are intended to ensure survival of the organism. Stress-induced HPA axis dysfunction has been shown to intensify insulin resistance, inflammation, endothelial dysfunction, neurological damage, and immunological damage [13].

Stress, via adrenally released cortisol, has been linked to the development and/or exacerbation of diabetes and heart disease. Cortisol directly affects insulin release and glucose regulation [14]. Cortisol increases insulin levels, and the co-elevation of these two hor-

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mones promotes visceral adipose deposition. Visceral fat has abundant glucocorticoid receptors and is very sensitive to the effects of cortisol and insulin [15,16]. This cycle of events inevitably plays a role in the development of insulin resistance, hyperlipidemia, hypertension and ultimately cardiometabolic disease [10,17].

Although many of the deleterious effects of chronic stress have been attributed to elevated levels of cortisol, there is ample medical evidence also suggesting a link between chronic stress, hypocortisolism and/or low corticotropin-releasing hormone (CRH) release [13,18]. Hypocortisolism is the paradoxical suppression of the HPA axis under conditions of chronic stress and is usually reported by patients as generalized fatigue. More commonly found in adults, hypocortisolism is felt to represent the cumulative effects of chronic stressors and mediates the progression of major chronic diseases such as cardiovascular disease, cancer, cognitive and mood disorders, auto-immune diseases as well as overall vitality and energy [13].

Low cortisol production in response to chronic stress leads to loss of glucocorticoid receptor ligand activity [18] and an increase in pro-inflammatory cytokines, including IL-6 [19]. The increase in inflammatory signaling due to loss of counter-regulation by normal glucocorticoid activity is a crucial physiologic component of CM disease.

While stress has long been associated with development of diabetes and heart disease, the links between cortisol, insulin resistance, visceral adiposity, and increased inflammation have only recently been more fully appreciated.

Testosterone deficiency

Testosterone deficiency is a significant contributing risk factor to CM disease. It can result from any number of causes and affects men of all ages. The clinical signs and symptoms of this disorder depend upon the age of the patient at onset and the degree of the deficiency. Testosterone deficiency in men typically manifests as symptoms of decreased erectile function and libido. Physiologically, testosterone plays a critical role in the regulation of normal growth, bone metabolism, and body composition [20].

Qualitative CT imaging has confirmed that testosterone deficient men have a systemic increase in adipocyte deposits. Studies have confirmed the significant relationship between serum free testosterone levels and the volume and distribution of body fat in both healthy and obese male subjects. Free testosterone levels have been shown to be inversely correlated with obesity in a number of studies, and the link between low testosterone and central obesity has been particularly striking [21].

The relationship between central obesity and total testosterone is even more pronounced when combined with the presence of low sex hormone binding globulin (SHBG) levels. Since SHBG binds free serum testosterone, an increase in serum SHBG leads to even lower free testosterone levels in obese men. In a subgroup of the men in the HERITAGE family study, low total testosterone and SHBG were predictors of greater obesity and visceral fat levels on CT scan [22].

Hypogonadism plays an important adjunctive role with central adiposity in the development of glucose intolerance and cardiovascular risk [23]. Low serum testosterone levels are associated with both worsening insulin resistance as well as progression of atherosclerosis. Men with low testosterone levels have also been shown to be at higher risk for coronary artery disease, hypertension and myocardial infarction.

Diagnosis and Evaluation

Evaluation of male patients who may be at risk for CM disease includes not only identifying the presence of traditional cardiac risk factors but also delineation of underlying hormonal status. Identification of important hormonal abnormalities including insulin resistance and hyperinsulinemia, HPA axis dysregulation and testosterone deficiency, is essential. Furthermore, in patients who already have MeS, evaluation of these hormones is particularly important in CM risk stratification.

Various authoritative organizations have provided differing diagnostic criteria of MeS. Certain guidelines include insulin resistance as part of MeS (World Health Organization (WHO) [24], American College of Endocrinology [25], whereas the diagnostic criteria of

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other groups (National Cholesterol Education Program (NCEP)) [26], do not. Nevertheless, the underlying presence of MeS serves as a useful trigger when evaluating patients with some of the underlying modifiable factors that shape CM risk.

In summary, NCEP criteria require three of five markers for MeS:

- waist circumference >40″ men, 35″ women
- triglycerides > 150 mg/dl
- HDL-C <40 mg/dl in men and 50 mg/dl in women
- BP ≥ 130/85 mm Hg
- Fasting blood sugar (FBS) ≥ 100 mg/dl

The WHO MeS criteria include the homeostasis model of assessment index (HOMA) in the top quartile and FBS ≥110 mg/dl. The HOMA evaluates the degree of insulin resistance by applying a basic calculation to measured glucose and insulin levels (see calculation below). While insulin resistance has been independently associated with both metabolic syndrome and atherosclerosis [27], questions remain about standardizing a definition of an abnormal HOMA (upper quartile or another cut-point) as well as adjustments for age, ethnicity, or other risk factors.

Insulin Resistance

Various measures exist to assess insulin sensitivity with the gold standard being the hyperinsulinemic euglycemic clamp. Other more readily available measures include fasting insulin or calculation of the HOMA. Elevated fasting insulin above the 75th percentile (normal 5–25 μU/ml) has been associated with the development of CM disease and may be a stronger predictor of risk than insulin resistance [28]. Insulin resistance can be estimated using the HOMA, and is calculated by the following equation:

$$\textit{fasting glucose mmol}/1 \times \textit{fasting insulin } \mu U/ml \div 22.5.$$

Another highly utilized and appropriate diagnostic test is the 2-hour insulin tolerance test. A standard proxy for abnormal insulin response is also the two-hour glucose tolerance test, but more direct measures of insulin have gained favor due to interest in capturing underlying risk in patients whose glucose remains normal in the early phases of CM disease progression.

HPA Dysregulation

Under normal conditions, the HPA axis maintains a predictable pattern of diurnal variation under the influence of many factors. Cortisol is integral to normal HPA axis function and typically peaks before awakening and gradually decreases during the course of the day [29]. A growing body of research has positively correlated an association between alterations in rhythmicity of cortisol release and various comorbid conditions including post-traumatic stress disorder [30], depression [31], chronic fatigue syndrome/fibromyalgia [32], metabolic syndrome [33], cardiometabolic disease [34], cancer [35], and memory impairment [13,36].

It is not only the loss of the normal diurnal pattern of cortisol release but also flattening of the normal diurnal cortisol curve that negatively impacts multiple physiological systems, including the cardiovascular system, metabolic regulation of energy balance, and sites of fat deposition [35–38].

Although serum and urinary testing of cortisol and its metabolites has been traditionally utilized to diagnose the extremes of adrenal gland dysfunction, salivary cortisol testing has emerged as the preferred method of routine diagnostic testing [39]. Salivary cortisol levels have been shown to correlate predictably with serum levels and allow determination of free cortisol levels by eliminating interference from serum cortisol binding globulin that precludes determination of the serum free cortisol fraction. Advantageous aspects to salivary testing include its non-invasive, convenient and 'stress free' method of collection [40]. Typically, salivary testing includes four samples during the course of a single day to determine the slope of cortisol production. Twenty-four hour urine testing may also be used, however this method does not allow for observation of the diurnal variation in cortisol.

Testosterone Deficiency

The use of total testosterone as the initial assessment of hypogonadism in men has been advocated by the Institute of Medicine and in several recent guidelines [41]. No formal consensus exists on the presence of CM disease and how it is correlated with measurements of

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total testosterone, although low testosterone is present in 15–30% of men with obesity and diabetes.

The diagnostic threshold of hypogonadism remains a subject of debate. The American Association of Endocrinologists recommends 300 ng/dl (10.4 nmol/l) as the lower limit of serum total testosterone, and initiation of testosterone therapy is recommended when levels are 8 nmol/l (200 ng/dl) or less. Other guidelines recommend initiating testosterone replacement when serum total testosterone levels are between 8 nmol/l and 12 nmol/l and clinical signs and symptoms warrant therapy [42]. Serum testosterone levels, like the other sex hormones, have a circadian rhythm. Since testosterone levels tend to be highest in the morning, it is recommended that testing be conducted at this time. Of note, however, is that several studies have shown that the circadian rhythm is often lost in elderly men [43].

An assessment of serum SHBG levels is also important, particularly in elderly men, obese men, and in men with underlying CM disease. The SHBG can then be used to calculate bioavailable testosterone levels when total testosterone levels are known. The bioavailable testosterone levels provide an assessment of both the free testosterone as well as the weakly bound to albumin portion that is readily available in tissue when needed [41]. A number of different methods are used to calculate bioavailable testosterone, one of the most common [44] is:

$$\left\{\left(\frac{k_{at} \times [\text{albumin} \times [FT]}{1 + k_{at} \times [FT]}\right)\right\} + [FT]$$

Where k_{at} is the association binding constant of testosterone to albumin and *FT* is free testosterone.

Additional hormonal evaluations should include measurements of follicle stimulating hormone (FSH), luteinizing hormone (LH), and prolactin if repeat morning total testosterone remains low [41]. If testosterone therapy is initiated, a baseline PSA and prostate exam should be performed. At the 3-month follow up visit, repeat testing is recommended of total or bioavailable testosterone and SHBG, hematocrit, and PSA (free and total) [45].

Integrative Medicine Treatment

Once a patient with MeS has been identified with underlying hormonal derangements in insulin, cortisol and/or testosterone, several integrative medicine treatment options can be considered. Conventional hormone replacement and medications may be considered as part of an overall treatment plan if necessary.

Insulin

The most important aspect of reducing insulin resistance is through dietary modification and weight loss. In general, low glycemic index diets have become the favored integrative medicine approach in managing insulin-related abnormalities. To supplement dietary strategies, a number of supplements and herbs are available to improve insulin control and reduce glucose intolerance. For example, α-lipoic acid, bitter melon, and chromium have demonstrated either plausible biological mechanisms or positive clinical effectiveness in improving insulin sensitivity.

α-Lipoic acid, also known as lipoic acid (LA) or thioctic acid, and its reduced form, dihydrolipoic acid, are powerful anti-oxidants. LA scavenges hydroxyl radicals, hypochlorous acid, peroxynitrite, and singlet oxygen. There are several possible sources of oxidative stress in CM disease including glycation reactions, decompartmentalization of transition metals, and a shift in the reduction–oxidation status of insulin resistant cells [46,47]. In addition to its anti-oxidant properties, LA increases glucose uptake through recruitment of the glucose transporter-4 to plasma membranes, a mechanism shared with insulin-stimulated glucose uptake. Further, recent trials have demonstrated that LA improves glucose utilization and insulin sensitivity in patients with type 2 diabetes, in addition to associated neuropathies [48,49].

Bitter melon (*M. charantia*) is a green, bitter vegetable from the gourd family, grown in tropical and subtropical regions throughout the Amazon, East Africa, Asia, the Caribbean, and South America. Extracts have been shown to contain poly-peptide P, similar in structure to bovine insulin. Laboratory studies have found that bitter melon may enhance insulin secretion by the islets of Langerhans, reduce glycogenesis in liver tissue, enhance peripheral glucose utilization, and increase serum protein levels [50,51]. Clinical conditions for which bitter melon extracts are currently being used include diabetes, dyslipidemia,

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and microbial infections. These extracts were found to decrease blood sugar levels when injected subcutaneously into type 1 diabetics [52]. Bitter melon supplements utilized for the treatment of diabetes should contain a standardized extract of 10% charantins.

Chromium supplementation has been reported in clinical trials for over five decades to improve insulin regulation and glucose tolerance in people with type 1 and 2 diabetes, gestational diabetes, and steroid induced diabetes [53,54]. Chromium depletion can lead to hyperlipidemia, insulin resistance, fatigue, accelerated atherosclerosis, hypertension, anxiety, impaired wound healing, decreased glucose tolerance and possibly infertility [54]. Some studies have reported negative clinical outcomes in patients supplementing chromium. However, low doses and poorly absorbable forms of chromium used in these studies may have negatively affected the therapeutic outcomes. Chromium is not found in sufficient amounts in food to replenish tissue stores or to affect clinically significant improvement in blood glucose control [54].

Stress, Cortisol and HPA dysregulation

A number of natural products are available to the public advertised as promoting 'adrenal health' or combating stress-related fatigue. These include minerals and vitamins, herbs, and protein glandular extracts. Use of products to alleviate the impact of stress and engender a sense of wellbeing has long been used in many world-healing traditions, including Chinese and Ayurvedic medicine. Often, these substances were considered special, or even magical, in their ability to buffer the individual against stress and support overall health in non-specific ways. More recently, research has shown that these same products are likely influencing the HPA axis in particular to protect the organism against the consequences of acute and chronic stress.

A common category of adrenal support supplements includes plant *adaptogens*, such as *Rhodiola* and Ginseng, which have long been touted as improving the ability of organisms to avoid systemic damage during periods of prolonged exposure to various stressors.

Rhodiola rosea has been one of the most popular adaptogenic herbs used in Asian and European traditional medicine. It directly stimulates selected nicotinic, cholinergic, noradrenergic, dopaminergic, and 5-hydroxytryptaminic receptors thereby enhancing emotional tone, improving memory and concentration, and enhancing learning capabilities [55]. Studies have shown administration of *Rhodiola* and its extract, SHR-5, also enhance the quality of physical working capacity, efficiency and performance, and speed of information perception and processing [56]. *Rhodiola* is also capable of inhibiting the stress induced cortisol response that may play a role in potentiating its anti-fatigue, anti-stress, and anti-depressant effects [55].

Several forms of Ginseng have also been clinically useful as non-pharmacologic anti-stress agents. *Panax ginseng*, also known as *Korean Red Ginseng*, has been shown to favorably affect many systemic metabolic functions including glucose regulation, cerebral function, pain modulation, and immune activity. Through these and other mechanisms, *Panax ginseng* has demonstrated efficacy as an anti-fatigue, anti-stress, and anti-aging adaptogen [57]. *Siberian Ginseng* (*Eleutherococcus senticosus*) has many of the same systemic protective benefits of *Panax ginseng*. Extensive studies have shown its clinical efficacy as an anti-stress adaptogen [58] through mechanisms including decreasing adrenal cortical activity, increasing sympathetic tone, and decreasing parasympathetic nervous system activity during stressful conditions [59].

L-Theanine, a derivative of the major excitatory brain neurotransmitter L-glutamate, is an amino acid found in the tea plant *Camellia sinensis*. Studies have shown L-theanine to inhibit LDL oxidation, counteract the stimulatory effects of caffeine, and lower blood pressure. In its anti-stress capacities, L-theanine increases dopamine and serotonin production [60], decreases norepinephrine concentrations, and induces alpha-brain wave activity [61,62]. It reduces cortisol levels and increases relaxation associated with recovery from a stressful task [63].

Testosterone

Conventional approaches to testosterone replacement are advocated when appropriate to improve insulin sensitivity and reduce visceral fat. A detailed discussion regarding phar-

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macologic supplementation of testosterone is beyond the scope of this manuscript.

Case progression and Resolution

The patient underwent an extensive hormonal evaluation as part of his initial work up. Laboratory results demonstrated elevated fasting insulin of 35 μU/ml, low total testosterone 7.8 nmol/l and a flattened cortisol curve. The patient was encouraged to begin a low glycemic index diet and exercise program. In addition, chromium GTF 1000 μg twice daily and alpha lipoic acid 400 mg twice daily were added to further improve his obesity and hyperinsulinemia.

Stress management techniques were discussed in detail, and handouts were provided to the patient instructing on proper daily breathing techniques, such as progressive relaxation, imagery and visualization, and diaphragmatic breathing. Stress reduction exercises can be practiced in a group and/or in individual sessions. The patient was requested to conduct a simple breathing technique for 10 minutes twice per day in which he remained aware of his breath in a quiet environment while breathing slowly in through the nose and out through the mouth. Daily practice has been shown to have many positive long-term effects on health and mental well being.

For physiologic support of the stress axis, rhodiola 125 mg (standardized to 5% rosavins) twice daily and L-theanine 200 mg three times per day were recommended as well. Finally, testosterone replacement was initiated in the form of a 1% 5-g patch.

After 3 months, the patient successfully lost 25 pounds through dietary modifications, recommended dietary supplements, and exercise. He reported less daytime fatigue, particularly after meals, and improved sleep at night. His stress levels remained unchanged but he felt 'more even' and less susceptible to stressful events on the l-theanine. His repeat fasting blood sugar was 92 mg/dl that was decreased from 102 mg/dl. He had no adverse side effects from the medications or supplements and PSA levels remained unchanged. He was scheduled to return to our clinic in 3 months for re-evaluation.

Conflict of interest

The authors have no conflicts of interest to report.

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