Stress and Fatigue

Naturopathic Nutrition 2
Learning Outcomes:

• On successful completion you will be able to:

• Evaluate the physiological effects of stress on all body systems
• Discuss the impact of stress on nutrient status and modulating the HPA axis using nutritional therapy
• Discuss the range of factors contributing to Chronic Fatigue Syndrome and the benefits of using nutritional therapy
Stress - coping with the modern lifestyle

• As CAM practitioners (not medical doctors) we can not claim to ‘treat stress’ as a medical condition per se when communicating with our clients

• When communicating with clients we can use phrases such as:
  – Helping to cope with a busy modern lifestyle
  – Supporting healthy coping mechanisms
  – Supporting a healthy nervous system
  – Helping regain inner calm
  – Promoting relaxation
What is Stress?

- Stress
  – the non-specific response of the body to any demand

- Stressor
  - that which produces stress
What is Stress?

Hans Selye developed valuable insights into the role of stress in disease

- According to Selye, stress in itself should not be viewed in a negative context
- It is not the stressor that determines the response; instead it is the individual's internal reaction, which then triggers the response
- This internal reaction is highly individualised. What one person may experience as stress, the next person may view entirely differently

“No one can live without experiencing some degree of stress all the time. You may think that only serious disease or intensive physical or mental injury can cause stress. This is false. Crossing a busy intersection, exposure to a draft, or even sheer joy are enough to activate the body's stress mechanisms to some extent. Stress is not even necessarily bad for you; it is also the spice of life, for any emotion, any activity causes stress. But, of course, your system must be prepared to take it. The same stress which makes one person sick can be an invigorating experience for another.”

Stress is both good and bad...

- **Acute Stress (Eustress)**
  - alarm reaction
  - recovery follows quickly
  - may save your life

- **Chronic Stress (Distress)**
  - constant/repeated stress
  - no recovery
  - impairs immune response/general health
‘Surviving’ the modern lifestyle

• The stress response is an extremely important one in protecting our life when our whole organism is threatened

• ‘Threat to life’ is subjective - your brain ‘decides’ what is dangerous – for some people it is war, pestilence, dangerous animals; for other people it might be loss of their status, their job, threats to their family – the physiological response is the same

• Some stressors are hard wired (all mammals elicit some measurable stress response to spiders and snakes!) where others are learned from our environment
The explosive development of the Internet and related communication technologies have brought into focus the problems of information overload – we are constantly exposed to information, communication and instant gratification.

Our modern lifestyle exposes us to less rest, more noise, more information, a greater influx of toxins, breaking down of family support systems and many ‘new’ threats to survival than previously.

Heylighen F (2002). Complexity and Information Overload in Society: why increasing efficiency leads to decreasing control. The Information Society. April 12
Overview of the nervous system

To review the players and hormones of the autonomic nervous system – please go back to your biomedicine slides and textbook!
• When our brains perceive that we are in a ‘life-threatening’ situation (perception here is the key) – we activate our stress response
• This results in an activation of the sympathetic nervous system (SNS) and the subsequent activation of hormonal release from the adrenal glands to prolong the response and help cope with the metabolic changes required
Two-System View of Stress Response
Activation of the sympathetic NS

• The stress response is characterised by the rapid activation of the sympathetic nervous system
• Results in the release of epinephrine and norepinephrine. These catecholamines promote enhanced vigilance, alertness, arousal and attention. They also feed back to increase the SNS response
• Blood concentrations of adrenal glucocorticoids also rise to peak levels after 15–30 min and are responsible for promoting longer-term adaptation and recovery

Hypothalamus–Pituitary–Adrenal Axis (HPA Axis)

### TABLE 1. Behavioral and physical adaptation during stress

**Behavioral Adaptation**
- Adaptive redirection of behavior
  - Increased arousal and alertness
  - Increased cognition, vigilance, and focused attention
  - Suppression of appetite and feeding behavior
  - Suppression of reproductive behavior
  - Inhibition of gastric motility; stimulation of colonic motility
  - Containment of the stress response

**Physical Adaptation**
- Adaptive redirection of energy
  - Oxygen and nutrients directed to the CNS and stressed body site(s)
  - Altered cardiovascular tone, increased blood pressure and heart rate
  - Increased respiratory rate
  - Increased gluconeogenesis and lipolysis
  - Detoxification from toxic products
  - Inhibition of growth and reproductive systems
  - Containment of the stress response
  - Containment of the inflammatory/immune response


Alarm phase -‘Fight or Flight’

• Increased arousal, cognition and vigilance
• Increased blood pressure, heart rate, respiratory rate
• Increased intermediate metabolism
  – gluconeogenesis and lipolysis
• Suppression of appetite and feeding behaviours
• Inhibition of digestion, stimulation of colonic motility
• Inhibition of growth and reproduction
• Inhibition of immune function

Alarm phase - ‘Fight or Flight’

Immediately upon activation of this pathway, the body begins an alarm reaction (cortisol is important here)

- Gluconeogenesis
- Decreased insulin sensitivity
- Amino acid mobilisation
- Protein catabolism
- Mobilisation of free fatty acids from adipose tissue
- Decreased phagocytosis and white blood cell migration
- Decreased lymphocyte production
- Disappearance of blood-born eosinophils and lymphocytes
- Increased red blood cell production

Glucocorticoids and mineralocorticoids

- Aldosterone:
  - increases water retention for increased BP

- Cortisol:
  - increases glucose production and mobilisation
  - increases protein catabolism
  - increases vessel sensitivity
  - reinforces the autonomic NS response
  - decreases inflammatory response
Physiological responses of cortisol

- Promotes gluconeogenesis
- Promotes breakdown of skeletal muscle protein
- Enhances fat breakdown (lipolysis)
- Suppresses immune system
- Breakdown of bone matrix (high doses)
Regulation of cortisol release

• Cortisol release is regulated by ACTH

• Release follows a daily pattern - circadian

• Negative feedback by cortisol inhibits the secretion of ACTH and CRH
Cortisol release can be increased by:

- physical trauma
- infection
- extreme heat and cold
- exercise to the point of exhaustion
- extreme mental anxiety
Hans Selye, considered the ‘father of stress research’, in the 1930s
1. During the **alarm reaction**, the body’s defences are reduced
2. When activation becomes chronic, the body transitions from alarm reactions to the **stage of resistance** in which defences are elevated
3. And finally to the **stage of exhaustion** in which defences are again reduced

Chronic stress

- Providing levels return to normal reasonably quickly, acute activation of the hypothalamic-pituitary-adrenal axis (HPA) presents minimal detrimental effect on the body.
- Long term activation - adrenal exhaustion and hypo-activation - have been associated with a myriad of disease processes.
- Elevated levels of circulating cortisol have a direct inhibitory effect on:
  - reproductive axis
  - growth hormone release
  - thyroid axis

Chronic stress

- As the body cycles through prolonged or repeated alarm reactions, receptors in the hippocampus become desensitised and damaged - it is unknown if the damage is permanent

- This leads to a feedforward overproduction of cortisol
A hyporeactive HPA axis might develop after prolonged periods of stress together with a hyperactivity of the HPA axis and excessive glucocorticoid release. Research suggests that chronic stress will eventually result in a hypoactive HPA axis.

Progression to hypoactivity

Representing a challenge for current concepts of stress research, a number of studies have now provided convincing evidence that the adrenal gland is hypoactive in some stress-related states. The phenomenon of hypocortisolism has mainly been described for patients, who experienced a traumatic event and subsequently developed post-traumatic stress disorder (PTSD). However, as presented in this review, hypocortisolism does not merely represent a specific correlate of PTSD, since similar findings have been reported for healthy individuals living under conditions of chronic stress as well as for patients with several bodily disorders. These include chronic fatigue syndrome, fibromyalgia, other somatoform disorders, rheumatoid arthritis, and asthma, and many of these disorders have been related to stress. Although hypocortisolism appears to be a frequent and widespread phenomenon, the nature of the underlying mechanisms and the homology of these mechanisms within and across clinical groups remain speculative. Potential mechanisms include dysregulations on several levels of the hypothalamic-pituitary adrenal axis. In addition, factors such as genetic vulnerability, previous stress experience, coping and personality styles may determine the manifestation of this neuroendocrine abnormality. Several authors proposed theoretical concepts on the development or physiological meaning of hypocortisolism. Based on the reviewed findings, we propose that a persistent lack of cortisol availability in traumatized or chronically stressed individuals may promote an increased vulnerability for the development of stress-related bodily disorders. This pathophysiological model may have important implications for the prevention, diagnosis and treatment of the classical psychosomatic disorders.

Hypersecretion to hyposecretion of cortisol
The physiological consequences of stress
Symptoms of adrenal dysfunction

Afternoon low between 3-4 PM
Anhedonia
Anxiety
Cognitive dysfunction
Confusion
Craving salt or sugar
Dark circles under eyes
Decreased ability to handle stress
Decreased libido
Decreased memory recall
Decreased productivity
Decreased tolerance
Depressed mood
Difficulty concentrating

Difficulty getting up in the morning
Fatigue not relieved by rest
Feeling better after eating
Increased effort to do everyday tasks
Increased fears
Increased recovery time
Increased symptoms with skipped meals
Insomnia
Lethargy
Orthostatic hypotension
Pain
Pre-menstrual tension

# Physiological consequences of stress

<table>
<thead>
<tr>
<th>BODY SYSTEM</th>
<th>PHYSIOLOGICAL EFFECTS OF STRESS</th>
</tr>
</thead>
</table>
| Central Nervous System (CNS)| • Increased mental arousal  
                             | • Increased cognitive function  
                             | • Increased vigilance  
                             | • Altered neurotransmitter synthesis and/or metabolism               |
| Cardiopulmonary Systems    | • Increased blood pressure  
                             | • Increased heart rate  
                             | • Increased respiratory rate                                        |
| Gastrointestinal Tract     | • Suppression of appetite  
                             | • Inhibition of digestion  
                             | • Stimulation of colonic motility                                    |
| Immune System              | • Inhibition of innate immunity  
                             | • Inhibition of T helper 1 immunity  
                             | • Stimulation of T helper 2 related immune function                  |
| Reproductive System        | • Inhibition of growth  
                             | • Inhibition of general reproductive function - the HPG reproductive axis is inhibited by HPA activation |
| Endocrine System           | • Reduces thyroid activity - CRH reduces TSH production and cortisol inhibits conversion of thyroxine to triiodothyronine |
## Disorders associated with HPA dysfunction

<table>
<thead>
<tr>
<th>Increased Stress System Activity</th>
<th>Decreased Stress System Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia nervosa</td>
<td>Atypical depression</td>
</tr>
<tr>
<td>Chronic active alcoholism</td>
<td>Chronic fatigue syndrome</td>
</tr>
<tr>
<td>Chronic excessive exercise</td>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Nicotine withdrawal</td>
</tr>
<tr>
<td>Melancholic depression</td>
<td>Obesity</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>Post-traumatic stress disorder</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>Seasonal depression</td>
</tr>
<tr>
<td>Pre-menstrual tension</td>
<td>Vulnerability to inflammatory diseases</td>
</tr>
<tr>
<td>Severe chronic disease</td>
<td></td>
</tr>
<tr>
<td>Vulnerability to addiction</td>
<td></td>
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</tbody>
</table>
Stress suppresses thyroid function

Activation of the HPA axis with resultant increased CRH and cortisol is associated with **decreased** production of thyroid-stimulating hormone (TSH).

Glucocorticoids also **inhibit** the activity of the enzyme **5-deiodinase**, which converts the relatively inactive thyroxine to the biologically active triiodothyronine.

Stress suppresses thyroid function

Stress suppresses reproductive function

The reproductive axis is inhibited at all levels by various components of the HPA axis.

CRH suppresses the secretion of gonadotropin-releasing hormone (GnRH).

Glucocorticoids, on the other hand, exert an inhibitory effect on the GnRH neuron, the pituitary gonadotroph and the gonads, and render target tissues of gonadal steroids resistant to these hormones.

Stress suppresses reproductive function

Stress compromises immunity

Stress hormones inhibit the function of neutrophils, macrophages, antigen-presenting cells, natural killer (NK) cells and T and B lymphocytes, and suppress the production of cytokines needed for pro-inflammatory and adaptive immune responses.

Stress diminishes vaccine responses, exacerbates viral and bacterial pathogenesis, slows wound healing and alters autoimmune diseases.

Stress increases the risk of cancer and infections

The combined effects of glucocorticoids and catecholamines are to inhibit innate immunity and T helper 1 related cytokines, and to stimulate T helper 2 related cytokines.

Stress-related immunosuppression therefore facilitates diseases related to deficiency of innate and cellular immune responses, such as common cold, tuberculosis and certain tumours.

Stress increases the risk of autoimmunity

A defective HPA axis response to stress or inflammation (hypoactivation) would produce a glucocorticoid-deficient state and would lead to relative resistance to infections and neoplastic disease, but increased susceptibility to autoimmune inflammatory disease.
The idea that psychological stress may give rise to oxidative stress is a relatively new one.

A number of studies have shown changes in the production of reactive oxygen species, including lipid peroxides, during periods of psychological stress.

Stressors have been shown to increase activity of neutrophils, causing release of oxidative metabolites and proteolytic enzymes into the surrounding tissue.

Cortisol causes oxidative stress

Glucocorticoids, the primary adrenal hormones secreted during stress, increase oxidative stress damage to neurons, in part by increasing glutamate and calcium and decreasing antioxidant enzymes.

Stress causes premature ageing

Psychological stress - both perceived stress (subjective) and chronicity of stress (objective) - is significantly associated with higher oxidative stress, lower telomerase activity, and shorter telomere length, which are known determinants of cell senescence and longevity. Women with the highest levels of perceived stress have telomeres shorter on average by the equivalent of at least one decade of additional ageing compared to low stress women.

Physiological Stress
Figure 1: Factors that may influence a person’s capacity to cope with stress.
Inflammation is stress

Major causes of inflammation:
• Allergens – environmental and food
• Dysglycaemia and insulin resistance
• Exogenous and endogenous ‘toxins’
• Nutritional deficiencies
• Malabsorption
• Oxidative stress
• Physical trauma
• Psychological stress
Inflammation stimulates the HPA axis

Cell products from an activated immune system, predominately the cytokines TNF-alpha, IL-1 and IL-6, stimulate CRF secretion and, hence, activate both the HPA axis and the SNS during inflammatory stress.

Chronic stress is associated with a hypersecretion of CRF and a decreased sensitivity to feedback inhibition by cortisol.

The rise in proinflammatory cytokines (IL-6, TNF-alpha and IFN-alpha) that frequently occur in major depression further increase the secretion of glucocorticoids.
Inflammation stimulates the HPA axis

The rise in proinflammatory cytokines that usually accompanies the chronic stress response results in a further stimulation of the HPA axis thereby adding to the stress response. While CRF would appear to play a pivotal role, evidence is provided that simultaneous changes in the serotonergic and noradrenergic systems, combined with the activation of peripheral and central macrophages that increase the proinflammatory cytokine concentrations in the brain and blood, also play a critical role in predisposing to anxiety and depression.

Obesity increases stress

Stress, primarily through hyperactivation of the HPA axis, appears to contribute to the accumulation of fat tissue, and *vice versa*.

Obesity itself seems to **constitute a chronic stressful state** and may cause HPA axis dysfunction.


Fig. 6. Model of a link between dietary intake and sympathetic outflow. During fasting, the small fall in glucose and the larger fall in insulin levels decrease insulin-mediated glucose uptake and metabolism in ventro-medial hypothalamic (VMH) neurons sensitive to glucose and insulin. This fall in glucose utilization stimulates an inhibitory pathway between the hypothalamus and the brainstem, thereby suppressing tonically active brainstem sympathetic centers and decreasing central sympathetic activity. In response to carbohydrate (CHO) intake, or in the face of insulin resistance where glucose and insulin are elevated, the opposite takes place: the small increase in glucose coupled with the larger increase in insulin stimulates glucose metabolism in these cells of the VMH, thereby suppressing the inhibitory pathway. The decrease in inhibition results in an increase of central sympathetic activity (Landsberg and Young, 1985).
Insulin resistance and stress

The insulin resistance of obesity, and consequent hyperinsulinaemia, drives *sympathetically mediated thermogenesis*, restoring energy balance at the expense of SNS overactivity.

Evidence is accumulating that sympathetic nervous system activity is *increased* in insulin resistant, hyperinsulinaemic individuals.

Oestrogen and stress

Oestradiol may contribute to the normal functioning of the HPA response. High physiological levels of oestradiol among women increase basal concentrations of cortisol and ACTH.

Following the precipitous decline in the high, sustained levels of oestradiol and progestins during pregnancy, postpartum women experience greater HPA axis response to stressors.

Anxiety and thyroid dysfunction

Manifest hypothyroidism and hyperthyroidism, as causes of mental and neurological dysfunction, have been known for a long time.

We have also found that subclinical thyroid dysfunction increases the anxiety of patients whether hyperthyroid or hypothyroid.

Symptoms of anxiety frequently occur concomitant to the development and persistence of inflammatory bowel disease in patients. In the present study, we utilised an animal model of IBD, infection with Citrobacter rodentium, to determine whether the infection per se can drive anxiety-like behaviour.

The results of the present study demonstrate that infection with *C. rodentium* can induce anxiety-like symptoms that are likely mediated via vagal sensory neurons.

Lyte M. et al. *Induction of anxiety-like behavior in mice during the initial stages of infection with the agent of murine colonic hyperplasia Citrobacter rodentium*. Physiol Behav. 2006 Oct 30;89(3):350-7
‘Stress’ – such a loaded word

- People don’t want to admit they are stressed

- Many people who are "stressed out" may not be able to identify exactly what is causing them to feel stressed

- Typical presenting symptoms are insomnia, depression, fatigue, headache, upset stomach, digestive disturbances, and irritability
Adrenal Function Assessment
Diurnal Cortisol rhythm

Figure 2. Diurnal Cortisol Concentration

Cortisol and DHEA relationship

Figure 3. DHEA-S and Cortisol Competition

HPA assessment

Serum and urine

- Blood and urine tests are used to help diagnose Cushing’s syndrome and Addison’s disease, two serious disorders affecting the production of cortisol.
- If Addison's disease is suspected
  - measure the response of the adrenal glands to a stimulus such as injection of Synacthen - a synthetic form of ACTH, the hormone that stimulates the adrenal glands to produce cortisol.
- If Cushing's syndrome is suspected
  - dexamethasone - a drug that acts like cortisol and switches off the normal stimulus for cortisol production to make it easier to determine if you are making too much cortisol.

http://www.labtestsonline.org.uk/understanding/analytes/cortisol/test.html
HPA assessment

Serum

• Venous sampling can induce cortisol secretion simply by the process of sample collection

• Serum cortisol is 90 to 94 per cent bound by plasma proteins and its level can be affected by certain medication use or disease states

Adrenal Stress Index - Salivary

- Measures both saliva cortisol and DHEA levels and their ratios throughout the day
  - Salivary-cortisol testing negates the necessity of the patient making multiple visits for venous sampling since the sample can be taken by the patient and is a cost-effective method of determining diurnal cortisol patterns
- A simple, non-invasive test
- Uses four saliva samples
- Measures the free unbound fraction of the hormone that is available to exert its effect on the target tissue

## Adrenal Stress Index - Salivary

### Salivary Cortisol and DHEA - Age Group 14 - 40

<table>
<thead>
<tr>
<th>Cortisol Levels</th>
<th>Inside Range</th>
<th>Outside Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample 1 Post Awakening</td>
<td></td>
<td>5.8 L</td>
</tr>
<tr>
<td>Sample 2 (+ 4 - 5 Hours)</td>
<td></td>
<td>4.0 L</td>
</tr>
<tr>
<td>Sample 3 (+ 4 - 5 Hours)</td>
<td></td>
<td>2.3 L</td>
</tr>
<tr>
<td>Sample 4 (Prior to Sleep)</td>
<td>1.5 L</td>
<td></td>
</tr>
<tr>
<td><strong>Total Daily Cortisol</strong></td>
<td></td>
<td>13.6 L</td>
</tr>
</tbody>
</table>

Range: 21 - 41 nmol/L

<table>
<thead>
<tr>
<th>DHEA Levels</th>
<th>Inside Range</th>
<th>Outside Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample 2 (am)</td>
<td></td>
<td>0.26 L</td>
</tr>
<tr>
<td>Sample 3 (pm)</td>
<td></td>
<td>0.25 L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DHEA : Cortisol Ratio</th>
<th>Inside Range</th>
<th>Outside Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1.88 L</td>
</tr>
</tbody>
</table>

### Sample 1
- **Hormone**: Cortisol Mean
- **Reference Range**: 12 - 22 nmol/L

### Sample 2
- **Hormone**: DHEA Mean
- **Reference Range**: 0.26 - 0.40 - 1.47 nmol/L

### Sample 3
- **Hormone**: DHEA; Cortisol Ratio
- **Reference Range**: 1.88 - 2.0 - 6.0 nmol/L

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Genova diagnostics sample Adrenal Stress Index
<table>
<thead>
<tr>
<th>CORTISOL</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>High morning</td>
<td>Morning cortisol is a good indicator of peak adrenal gland function, since it represents peak cyclic activity. High cortisol reflects HPAA imbalance and morning hypoglycaemia or stress.</td>
</tr>
<tr>
<td>Low morning</td>
<td>This suggests a degree of adrenal hypofunction, maladaptation/ abnormal pacing with abnormal HPAA. If all four readings are also low, suspect adrenal fatigue.</td>
</tr>
<tr>
<td>High midday</td>
<td>Noon cortisol is an indicator of adrenal adaptive function as it reflects the response to the demands of the first few hours of the day. Elevated levels indicate HPAA imbalance and morning and noon hypoglycaemia or stress.</td>
</tr>
<tr>
<td>Low midday</td>
<td>Degree of adrenal hypofunction, with decreased adaptive response. If accompanied by low morning cortisol and total of the two reading is less than 7 with normal afternoon and evening and a low DHEA, suspect adrenal fatigue.</td>
</tr>
<tr>
<td>High afternoon</td>
<td>Daytime blood sugar imbalance</td>
</tr>
<tr>
<td>Low afternoon</td>
<td>This suggests suboptimal adrenal functioning, and if accompanied by low evening cortisol and low DHEA, suspect adrenal fatigue.</td>
</tr>
<tr>
<td>High evening</td>
<td>Hypoglycaemia and imbalance HPAA suggesting maladaptation.</td>
</tr>
<tr>
<td>Low evening</td>
<td>Cortisol levels should lower in evening. If all four readings low, suspect adrenal fatigue, otherwise maladaptation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DHEA</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>High total</td>
<td>Hyper response, inappropriate ACTH with imbalanced response from adrenals. May also reflect supplementary DHEA levels.</td>
</tr>
<tr>
<td>Low total</td>
<td>Maladaptation if consistently elevated cortisol. Adrenal fatigue if morning and evening cortisol only elevation, or if all markers low.</td>
</tr>
</tbody>
</table>
Progression of adrenal exhaustion

Adrenal Stress Index - interpretation

**Figure 1: Patterns of Cortisol and DHEA** secreted by the adrenals in response to stress

- **Normal hormone levels**: Optimal hormonal balance
- **Alarm Stage**: (short term)
  - Cortisol: ↑
  - DHEA: ↓
- **Resistance Stage 1**: (mid to long term)
  - Cortisol: ↑
  - DHEA: ↑
- **Resistance Stage 2**: (longer term)
  - Cortisol: ↓
  - DHEA: ↑
- **Resistance Stage 3**: (long term)
  - Cortisol: ↓
  - DHEA: ↓
- **Exhaustion Stage**
  - Cortisol: ↓
  - DHEA: ↓

Stages are established via total hormone secretions.
Adrenal Stress Index - Cortisol

• The major glucocorticoid
  – glucose + cortex + steroid

• Best known and studied effects of glucocorticoids are on carbohydrate metabolism and immune function

• Glucocorticoids are among the most frequently used drugs, and often prescribed for their anti-inflammatory and immunosuppressive properties
Cortisol functions

• Stimulation of gluconeogenesis, particularly in the liver
  – This pathway results in the synthesis of glucose from non-hexose substrates such as amino acids and lipids and is particularly important in carnivores and certain herbivores. Enhancing the expression of enzymes involved in gluconeogenesis is probably the best known metabolic function of glucocorticoids

• Mobilisation of amino acids from extrahepatic tissues
  – These serve as substrates for gluconeogenesis

• Inhibition of glucose uptake in muscle and adipose tissue
  – A mechanism to conserve glucose

• Stimulation of fat breakdown in adipose tissue
  – The fatty acids released by lipolysis are used for production of energy in tissues like muscle, and the released glycerol provide another substrate for gluconeogenesis


Adrenal Stress Index - DHEA

- Dehydroepiandrosterone (DHEA)/Sulphate (DHEA-S)
- DHEA possesses significant anti-glucocorticoid activity
- Preliminary results suggest DHEA may retard the ageing process
  - In a study of 75 healthy subjects aged 90 to 106 years, men with the highest DHEA-S levels had the highest level of functioning
  - Inverse correlation between DHEA levels and the degree of dependence in activities of daily living and mobility
  - In one study, plasma DHEA level was low in 80% of the male nursing home residents who required total care compared with 40% low in other nursing home residents and 6% in independently living men of comparable age

Adrenal Stress Index - DHEA

Low levels are also linked with:

- Depression and dysthymia
- Impaired learning and memory
- An increased risk for Alzheimer's disease
- Osteoporosis
- Low sexual thoughts, sexual interest, and satisfaction for both the mental and physical aspects of sexuality
- Erectile dysfunction
- Cancer
- Inflammation
  - inverse relationship between DHEA and IL-6
  - SLE, IBD, RA

Nutritional Therapy
• Cortisol and **blood glucose** levels have an intimate relationship

• During times of stress, cortisol mobilises glucose into the bloodstream by gluconeogenesis, decreased insulin sensitivity, amino acid mobilisation, and protein catabolism

• **Hypoglycaemia** causes the release of cortisol

• Skipping meals or eating meals or snacks rich in simple carbohydrates can create a hypoglycaemic state, which induces the stress mechanism and release of cortisol
Food intake

- Avoid intake of chemical stressors, including drugs and alcohol

- Caffeine amplifying cortisol production many hours after ingestion
  – this amplification effect persists with regular use of caffeine

- Caffeine should be avoided by individuals who are under chronic stress, as well as by those who wish to avoid adrenal dysfunction
Food intake

• One of the key dietary recommendations to support the adrenal glands is to ensure adequate potassium levels within the body
  – consuming foods rich in potassium and avoiding foods high in sodium

• Most have a dietary potassium-to-sodium (K:Na) ratio of less than 1:2. In contrast, most researchers recommend a dietary K:Na ratio higher than > 5:1 for health
  – A natural diet rich in fruits and vegetables can produce a K:Na ratio higher than 50:1, as most fruits and vegetables have a K:Na ratio of more than 100:1
Food allergy

- As far back as 1930, pioneering allergist Albert Rowe began noticing that anxiety and fatigue were key features of food allergies.
- Rowe described a syndrome known as "allergic toxaemia"
  - included the symptoms anxiety, fatigue, muscle and joint aches, drowsiness, difficulty with concentration, and depression
- Around the 1950s, this syndrome began to be referred to as the "allergic tension-fatigue syndrome"
- With the popularity of chronic fatigue syndrome, many physicians and other people are forgetting that food allergies can lead to anxiety as well as chronic fatigue.
Magnesium

- Reduces the activity of the HPA-axis in both acute and chronic administration
  - NMDA antagonistic and GABA agonistic properties

- Recommended dosage
  - 200–500 mg per day
Magnesium

- Magnesium and oxidative status were investigated in young volunteers exposed to chronic stress (political intolerance, awareness of potential military attacks, permanent stand-by duty and reduced holidays more than ten years) or subchronic stress consisting of everyday mortal danger in military actions lasting more than three months.
- **Significant decreases** in plasma ionised Mg2+, total Mg and ionised Ca2+ concentrations were found in both groups. Similarly, both study groups exhibited oxidative stress as assessed by increased plasma superoxide anions and malondialdehyde and modified antioxidant defence. There were no significant differences between the two stress groups.
- A negative correlation between magnesium balance and oxidative stress was observed suggesting that the same aetiological factor *(chronic stress)* initiate decreases in both free and total magnesium concentrations and simultaneously increase oxidative stress intensity. These findings support the need for magnesium supplementation with antioxidant vitamins for people living in conditions of chronic stress.

Magnesium

Stress intensifies release of catecholamines and corticosteroids that increase survival of normal animals when their lives are threatened. When magnesium (Mg) deficiency exists, stress paradoxically increases risk of cardiovascular damage including hypertension, cerebrovascular and coronary constriction and occlusion, arrhythmias and sudden cardiac death (SCD). In affluent societies, severe dietary Mg deficiency is uncommon, but dietary imbalances such as high intakes of fat and/or calcium (Ca) can intensify Mg inadequacy, especially under conditions of stress. Adrenergic stimulation of lipolysis can intensify its deficiency by complexing Mg with liberated fatty acids (FA). A low Mg/Ca ratio increases release of catecholamines, which lowers tissue (i.e. myocardial) Mg levels. It also favors excess release or formation of factors (derived both from FA metabolism and the endothelium), that are vasoconstrictive and platelet aggregating; a high Ca/Mg ratio also directly favors blood coagulation, which is also favored by excess fat and its mobilization during adrenergic lipolysis. Auto-oxidation of catecholamines yields free radicals, which explains the enhancement of the protective effect of Mg by anti-oxidant nutrients against cardiac damage caused by beta-catecholamines. Thus, stress, whether physical (i.e. exertion, heat, cold, trauma--accidental or surgical, burns), or emotional (i.e. pain, anxiety, excitement or depression) and dyspnea as in asthma increases need for Mg. Genetic differences in Mg utilization may account for differences in vulnerability to Mg deficiency and differences in body responses to stress.

Docosahexaenoic acid (DHA)

• Reduce aggressiveness in Japanese students during examination periods
• Also blunts the sympathetic activity elicited by mental stress in healthy volunteers
  – Seven human volunteers were studied on two occasions, before and after three weeks of supplementation with 7.2 g/day fish oil. On each occasion, the concentrations of plasma cortisol, and catecholamines, energy expenditure (indirect calorimetry), and adipose tissue lipolysis (plasma non esterified fatty acid concentrations) were monitored in basal conditions followed by a 30 min mental stress (mental arithmetic and Stroop test) and a 30 min recovery period.

Medical students underwent a double-blind, placebo-controlled trial of DHA (1.5g/day) during a nine week period of final exams. At the start and end of the study, plasma catecholamines (adrenaline, noradrenaline and dopamine) and cortisol were measured.

B5 – Pantothenic acid

• An important part of coenzyme A, and is necessary for fatty acid synthesis and degradation, steroid synthesis and metabolism of carbohydrates and protein

• Coenzyme A is essential for the formation of cortisol in the adrenal cortex

• Has been effective in treating fatigue and anxiety

• Pantothenic acid deficiency results in adrenal atrophy, characterised by fatigue, headache, sleep disturbances, nausea, and abdominal discomfort

• Pyridoxine deficiency has been identified as a significant predictor of increased overall psychological stress
• Pyridoxine deficiency is significantly associated with increases in
  – Depression
  – Fatigue
  – Confused mood level
  – But not with anxiety, anger or vigour

Amino Acids

• Phenylalanine / Tyrosine
  – Precursors to catecholamine neurotransmitters
  – Folate, B3, B6, B12, C, Fe, Cu are required to metabolise tyrosine to the catecholamines
  – Dosage: one to two grams per day

• Taurine
  – Improves mood for patients who are very anxious
  – Directly reduce excess SNS activity by acting as an antagonist to vasopressin and noradrenaline

Phosphatidylserine (PS)

- Often used for improved cognitive function, PS has been shown to have potent inhibitory effects on the HPA axis.

- Monteleone, et al., showed positive inhibitory effects of PS to physical stress on both ACTH and cortisol following a single bolus injection and ten days of oral administration.

- Monteleone, et al., found oral dosages of 400 mg/day displayed no statistical difference from placebo, while administration of 800 mg/day had significant inhibitory effects on the HPA axis.

Ascorbate

- Ascorbate is necessary for conversion of cholesterol into pregnenolone, one of the initial steps in cortisol, DHEA-S, and sex hormone production
- During chemical, emotional, psychological, or physiologic stress, the urinary excretion of vitamin C is increased
- A deficiency of ascorbate may create hypofunction of the adrenal cortex
- Ascorbate is best used buffered in combination with bioflavonoids
  - Dosage - 1000 mg bid

Vitamin E

- Acute or chronic exposure to stress increases free radical formation throughout the body but specifically in the adrenal cortex.
- In response to stress, Vitamin E has been shown to protect the adrenal cortex from free radical damage and reduce cortisol production.
- Dosage – 400 IU bid
  - use as a mixed tocopherol preparation.

Other Nutrients

- Micro-minerals, specifically zinc, copper, manganese, selenium, molybdenum, chromium, and iodine, are also important cofactors for adrenal cortex function

<table>
<thead>
<tr>
<th>Table 3. Suggested Nutritional Protocol for Adrenal Stress*</th>
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<tbody>
<tr>
<td>Ascorbic acid</td>
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<tr>
<td>Balanced B-complex including:</td>
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<td>Bioflavonoids</td>
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<td>Biotin</td>
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<td>Calcium</td>
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<td>Pantothenic acid</td>
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<tr>
<td>Pyridoxine</td>
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<tr>
<td>Vitamin A (retinol)</td>
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<td>Vitamin E w/mixed tocopherols</td>
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<td>Zinc</td>
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*All dosages are oral, twice daily (BID)
Herbal adaptogens

• Adaptogens are natural herbs that have non-specific, normalising effects on physiology; they influence normal body functions only enough to encourage non-specific resistance to stressors

• Adaptogen herbs include:
  – *Eleutherococcus senticosus*
  – *Panax ginseng*
  – *Rhodiola rosea*
  – *Withania somnifera*
  – *Shisandra chinesis*
  – *Cordyceps sinensis*
  – *Ginkgo biloba*
  – *Ocimum sanctum*
Rhodiola rosea

- Found and used traditionally in the Arctic regions including Alaska, north-eastern Siberia, Russia and northern parts of Europe
- Contains phenylpropanoids such as rosarín, rosavin and rosin
- Works on hypothalamus to increase resistance to toxins and stress
- Improves oxygen-carrying capacity of the blood
- Helps increase stamina and endurance
- Mood elevating through increased levels of serotonin and dopamine
- Reduces frequency of migraine headaches
- Increases physical work capacity
- Helps in some areas of male sexual dysfunction

Clinical studies in the administration of Rhodiola

- Increased physical and mental efficiency
- Produced significant improvement in physical fitness, mental fatigue and neuro-motoric tests
- Produced significant improvement in mental performance and reduced general fatigue in young healthy doctors during night
- Produced a significant anti-fatigue effect (improved mental work quantity and quality per unit time) in young cadets
- Relieved symptoms of asthenia (fatigue, decline in work capacity, sleeplessness, poor appetite, irritability, headache)
- Improved the amount and quality of intellectual work and decreased the error rate in proofreading tests
- Increased physical work capacity, coordination, general wellbeing and decreased mental fatigue and situational anxiety
- Increased physical work capacity and reduced recovery time between periods of high-intensity exercise in healthy volunteers and athletes
- Improved coordination, strength, endurance and cardiovascular measures in athletes
- Inhibited exercise-induced inflammatory markers in the blood of healthy volunteers undergoing exhausting physical exercise

The objective of this study was to study the impact of liquorice and grapefruit juice on the absorption and metabolism of cortisone acetate (CA)

Conclusion: Liquorice and in particular GFJ increased cortisol available to tissues in the hours following oral CA administration

Both patients and physicians should be aware of these interactions, and we recommend that circulating levels of cortisol should be monitored in habitual users

Glucocorticoid action is modulated by 11beta-hydroxysteroid dehydrogenases (11beta-HSDs):

Licorice is a competitive inhibitor of 11beta-HSD2

Keep lifestyle changes simple

Many of your stressed and anxious patients may not welcome or succeed with extensive lifestyle change at first.

- “I’ve got no time to exercise/eat healthily”
- “I’m too tired to cook/exercise”
- “Eating healthily is expensive”
- “I can’t cope with any changes right now”
- “Coffee and chocolate are the only things holding me together”

No matter what the excuse, you will achieve greater compliance and success with dietary changes if you can first relieve the patient’s stress, anxiety and fatigue.
Finding purpose

Having a firm purpose in life was associated with the tendency to have less anxiety and a lower incidence of psychiatric/somatic symptoms. Persons scoring low in the purpose in life area showed excessive response of the sympathetic nervous system to emotional stress.

Fatigue

- Fatigue is one of the most common reasons for people to seek consultation and treatment.
- It is estimated that up to 50% of patients consider fatigue an issue, and the prevalence of fatigue lasting longer than six months is as high as 20% in our patients.
- Underlying causes and drivers of fatigue are many, and may seem complicated and difficult to address.
- Fatigue may also be a driver of secondary health problems which will be difficult to resolve unless the underlying fatigue is also resolved.

Drivers of Fatigue

- Obesity / Insulin Resistance
- Emotional / Mental Stress (HPA Dysfunction: Hyper / Hypo)
- Sleep Deprivation (Sleep Apnoea)
- High Fat / High Sugar Diet
- High Free Fatty Acids
- Cytokines (IL-1, IL-8, TNF)
- Immune Activation (Gut / Liver)
- Fat Oxidation, Glucose Oxidation
- iNOS / Oxidant Stress
- Mitochondrial Dysfunction / Damage
- ATP Deficiency / Fatigue
- Ageing (Low Thyroid / Low Gonadal Function)
Mitochondria

- The mitochondria are responsible for 90% of the energy produced in the cell
- They are responsible for generating energy in the form of adenosine triphosphate (ATP) and heat, and are involved in the apoptosis signalling pathway
- The number of mitochondria that a cell contains varies depending on the cell type and its energy needs
  - Typically each cell has between 200 and 2000 mitochondria
  - Cells that require large amounts of energy have the most mitochondria, such as cardiac cells
    - 75% of the content of cardiac cells is mitochondria!

Mitochondria

• Energy production is the result of two closely coordinated metabolic processes—
  – the tricarboxylic acid (TCA) cycle / Krebs / citric acid cycle
  – the electron transport chain (ETC)

• The TCA cycle converts carbohydrates and fats into some ATP, but its major job is to produce the coenzymes NADH and FADH so that they, too, are entered into the ETC

Mitochondrial energy production

Mitochondria

• Damage to mitochondria is caused primarily by reactive oxygen species (ROS) generated by the mitochondria themselves
  – primarily the superoxide (O2–) radical
  • superoxide is transformed to hydrogen peroxide (H2O2) by manganese superoxide dismutase (MnSOD) or copper/zinc superoxide dismutase (Cu/Zn SOD) and then to water by glutathione peroxidase (GPX) or peroxiredoxin III (PRX III). However, when these enzymes cannot convert ROS such as the superoxide radical to H2O fast enough, oxidative damage occurs and accumulates in the mitochondria

Mitochondria

• The key areas susceptible to damage in mitochondria
  – lipids
  – proteins
    • decreases their affinity for substrates or coenzymes and thereby decrease their function
  – oxidative phosphorylation enzymes
  – mtDNA lipid membranes

• Once a mitochondria is damaged, mitochondrial function can be further compromised by increased cellular requirements for energy repair processes

Mitochondria

- Hyperglycaemia induces mitochondrial superoxide production by endothelial cells
  - An important mediator of diabetic complications such as cardiovascular disease and atherosclerosis, hypertension, heart failure, ageing, sepsis, ischaemia-reperfusion injury, and hypercholesterolaemia

- Inflammatory mediators such as TNF-α have been associated in vitro with mitochondrial dysfunction and increased ROS generation
ACQUIRED CONDITIONS IN WHICH MITOCHONDRIAL DYSFUNCTION HAS BEEN IMPLICATED

- Diabetes\textsuperscript{3,11,12}
- Huntington’s disease\textsuperscript{13}
- Cancer,\textsuperscript{3} including hepatitis C virus-associated hepatocarcinogenesis\textsuperscript{14}
- Alzheimer’s disease\textsuperscript{13}
- Parkinson’s disease\textsuperscript{13}
- Bipolar disorder\textsuperscript{15,16}
- Schizophrenia\textsuperscript{16}
- Aging and senescence\textsuperscript{3,17,20}
- Anxiety disorders\textsuperscript{21}
- Nonalcoholic steatohepatitis\textsuperscript{22}
- Cardiovascular disease,\textsuperscript{11} including atherosclerosis\textsuperscript{23}
- Sarcopenia\textsuperscript{24}
- Exercise intolerance\textsuperscript{25}
- Fatigue, including chronic fatigue syndrome,\textsuperscript{26,27} fibromyalgia,\textsuperscript{28,29} and myofascial pain\textsuperscript{2}
In addition to being a driver of the above conditions, fatigue may occur as a consequence of such conditions; the result being a self perpetuating vicious cycle that requires correct understanding to break.
Essential nutrients for mitochondrial function

Mitochondrial Basis of Fatigue

• Acetyl-L-Carnitine (N-Acetyl Carnitine)
• Alpha Lipoic Acid
• CoQ10
• Magnesium
• B vitamins
• Essential Fatty Acids
• Antioxidants
Essential nutrients for mitochondrial function

Key clinical concepts in stress management. Metagenics Australia
Carnitine

• N-acetyl carnitine / Acetyl-L-carnitine is one of the most critical nutrients for mitochondrial function
  – Red meat is the highest food source
  – Vegetarian sources are avocado and tempeh

• NAC serves several functions:
  – Assists in the transport of fat across cell membranes in muscle tissue for use as an energy source
  – Is essential for mitochondrial fatty acid oxidation – primary fuel source for heart and skeletal muscles and to maintain CoA levels
Carnitine

• NAC other functions:
  – Improves blood sugar control/insulin sensitivity
  – Involved in the protection of membrane structures and reduction of lactate production
  – Antioxidant – in the cell membrane preventing protein oxidation and pyruvate and lactate oxidative damage
  – Prevents apoptosis of skeletal muscle cells
  – Neuroprotective
  – Lipid lowering

• Total cholesterol, triglycerides, LDL, apoproteins A1 and B

Carnitine

Dosage:

• Two to four grams per day
  – in split doses

No advantage appears to exist in giving an oral dose greater than two grams at one time, with absorption studies indicating saturation at this dose

Alpha lipoic acid

- Lipoic acid is an important nutrient for the mitochondria, both structurally and functionally, with lipoic acid actually forming a component of complex V within the electron transport chain
  - Complex V is also known by a separate name - ATP synthase - as the name implies, this complex produces ATP
- Lipoic acid, therefore, is an essential and integral nutrient for ATP or energy production within the mitochondria and is fundamental in the treatment of fatigue
Lipoic acid improves mitochondrial energy production by several other means:
  • Facilitates citric acid cycle activity
  • Increases glucose uptake into the cells to be used as an energy source
  • Increases pyruvate and alpha-ketoglutarate availability
  • As an antioxidant, lipoic acid also protects mitochondrial structures

Dosage: 300 – 600 mg a day

Food sources - red meat, organ meats, spinach, broccoli, potatoes, yams, carrots, beets, and yeast
Ubiquinone

• Ubiquinone/Coenzyme Q10/CoQ10 is present in virtually all cells and in especially high concentrations in the heart, liver, kidney, and pancreas

• Within the cell, 25 to 30 per cent of total coenzyme Q10 is found in the nucleus, 40 to 50 per cent in the mitochondria, 15 to 20 per cent in the microsomes, and 5 to 10 per cent in the cytosol

• CoQ10 is essential for the shuttling of electrons along the electron transport chain
  – think of insulation on a wire, without adequate CoQ10 the highly reactive electrons fly off the electron transport chain – the ‘wire’ – causing oxidative damage and reducing energy production
Ubiquinone

- Ubiquinone shuttles electrons from complexes I and II to complex III
- Cytochrome c, an iron-containing haemprotein with a binuclear centre of a copper ion, transfers electrons from complex III to complex IV
In a study at the University of Bologna in Italy, administration of CoQ10 at a dosage of 150 mg/day for six months to ten patients with mitochondrial cytopathies (such as chronic progressive external ophthalmoplegia and Leber’s hereditary optic neuropathy) resulted in improved mitochondrial function, but no dose response trial has been conducted.
Ubiquinone

- In a double-blinded, placebo-controlled, 3 crossover design, 17 healthy volunteers were randomized to oral coenzyme Q10 (100 or 300 mg/d) or placebo administration for 8 d. As a fatigue-inducing physical task, subjects performed workload trials on a bicycle ergometer at fixed workloads twice for 2 h and then rested for 4 h. During the physical tasks, subjects performed non-workload trials with maximum velocity for 10 s at 30 min (30-min trial) after the start of physical tasks and 30 min before the end of the tasks (210-min trial).

- Results: The change in maximum velocity from the 30- to the 210-min trial in the 300-mg coenzyme Q10–administered group was higher than that in the placebo group. In addition, subjective fatigue sensation measured on a visual analogue scale in the 300-mg coenzyme Q10–administered group after the fatigue-inducing physical task and recovery period was alleviated when compared with that in the placebo group.

- Conclusion: Oral administration of coenzyme Q10 improved subjective fatigue sensation and physical performance during fatigue-inducing workload trials and might prevent unfavourable conditions as a result of physical fatigue.

Mizuno, K et al. Antifatigue effects of coenzyme Q10 during physical fatigue. Nutrition, Volume 24, Issue 4, Pages 293-299
Ubiquinone

Dosage:
We naturally make 10-30 mg of Coenzyme Q10 daily, however this production decreases around the age of 30.

In patients with fatigue, neurodegenerative conditions, those on statin drugs to lower cholesterol, and in the elderly this dose needs to be higher - 100-300 mg each day is recommended.

Coenzyme Q10 has been safely used in studies lasting up to 30 months.
Magnesium

- Magnesium has a crucial role in energy production where it transfers phosphates from ADP to ATP and back again. This transfer of phosphates is the most fundamental step of energy creation and release.

- An underlying magnesium deficiency, even if subclinical, can result in chronic fatigue and symptoms similar to CFS.
  - In addition, low red blood cell magnesium levels, a more accurate measure of magnesium status than routine blood analysis, have been found in many patients with chronic fatigue and CFS.

- Literature demonstrates that magnesium deficiency is not necessarily due to low dietary intake and several studies have shown good results with supplementation, with improvements in magnesium stores.

Magnesium

- Magnesium intake was assessed using six 24-h dietary records during a one-year period in 5,448 subjects (3,111 women 35-60 years old and 2,337 men 45-60 years old) in the SU.VI.MAX cohort, selected at a national level in France.
- The overall mean dietary intake was estimated at 369 +/- 106 mg/day in men and 280 +/- 84 mg/day in women.
- 77% of women and 72% of men had dietary magnesium intakes lower than recommended dietary allowances; 23 per cent of women and 18 per cent of men consumed less than 2/3 of the RDA.
- A strong positive correlation existed between energy and magnesium intake (r = 0.79; p < 10(-4)).

Magnesium

Magnesium is an essential mineral that is required for optimal biological function including energy metabolism. Although national nutritional surveys indicate that usual magnesium intakes do not meet recommendations, particularly among older women, diet-induced magnesium depletion is considered rare among humans without concurrent illness. The authors examined the effects of dietary magnesium restriction on biochemical measures of magnesium and physiologic responses during submaximal exercise in ten postmenopausal women, 45-71 years old, not receiving hormone replacement therapy. The women consumed diets containing conventional foods with varying magnesium content totalling 112 mg/8.4 MJ (2000 kcal) supplemented with 200 mg magnesium daily for 35d (control), then 112 mg/8.4 MJ for 93d (depletion) followed by 112 mg/8.4 MJ supplemented with 200 mg magnesium/d for 49d (repletion) in a depletion-repletion experiment. RBC magnesium concentration (P < 0.05), magnesium retention (P < 0.05) and skeletal muscle magnesium concentration (P < 0.05) decreased when dietary magnesium was restricted. Peak oxygen uptake, total and cumulative net oxygen uptake determined by using indirect calorimetry and peak heart rate increased (P < 0.05) during standardized submaximal work with restricted compared with adequate dietary magnesium. These findings indicate that dietary magnesium depletion can be induced in otherwise healthy women; it results in increased energy needs and adversely affects cardiovascular function during submaximal work. This may also explain previous observations of increased energy cost during standardized exercise in physically active men and women considered to have reduced magnesium.

Radical-mediated oxidative damage of skeletal muscle membranes has been implicated in the fatigue process. Vitamin E (VE) is a major chain breaking antioxidant that has been shown to reduce contraction-mediated oxidative damage. We hypothesised that VE deficiency would adversely affect muscle contractile function, resulting in a more rapid development of muscular fatigue during exercise. To test this postulate, rats were fed either a VE-deficient (EDEF) diet or a control (CON) diet containing VE. Following a 12-week feeding period, animals were anesthetized and mechanically ventilated. Muscle endurance (fatigue) and contractile properties were evaluated using an in situ preparation of the tibialis anterior (TA) muscle. Contractile properties of the TA muscle were determined before and after a fatigue protocol. The muscle fatigue protocol consisted of 60 min of repetitive contractions (250 ms trains at 15 Hz; duty cycle=11%) of the TA muscle. Prior to the fatigue protocol, no significant differences existed in the force-frequency curves between EDEF and CON animals. At the completion of the fatigue protocol, muscular force production was significantly ($P<0.05$) lower in the EDEF group (reduced by 69%) compared to CON group (reduced by 38%). Following the fatigue protocol, a right shift existed in the force-frequency curve at low stimulation frequencies ($\leq40$ Hz) in the EDEF animals compared to the CON animals ($P<0.05$). The stimulated and the contralateral TA muscle from the EDEF animals had significantly higher markers of lipid peroxidation compared to the same muscles in the CON animals ($P<0.05$). These data support the hypothesis that VE deficiency impairs muscular endurance and alters muscle contractile properties following a prolonged series of contractions.
Essential Fatty Acids

- Low levels of essential fatty acids (EFAs) appear to be a common finding in chronic fatigue syndrome.
- Lipid replacement therapy has been successfully used in clinical studies to reduce fatigue and protect cellular and mitochondrial membranes from damage by ROS.
- EPA component of fish oil induces mitochondrial growth, size and distribution.
- DHA component is essential for the structure of the electron transport chain complexes.

Omega 3 Fatty Acids

- Much of the energy production in the mitochondria involves the lipid membrane.
- An inadequate intake of essential omega 3 fatty acids, impairs the activity of the mitochondrial membrane.
- Subsequently the activity of the membrane-bound transporters, enzymes and channels is impeded, which has a detrimental effect on energy production resulting in cellular fatigue.
- Supplementing with fish oils regulates ion homeostasis, has an antioxidant benefit, improves oxygen usage and therefore improves ATP production.
FISH OILS IMPROVE CHRONIC FATIGUE SYNDROME

There is evidence that there is an association between chronic fatigue syndrome, a condition of unknown aetiology, and essential fatty acids. A series of patients with chronic fatigue syndrome were treated solely with a high-EPA-containing essential fatty acid supplement. All showed improvement in their symptomatology within 8 to 12 weeks. These results, which are consistent with a recent detailed report of cerebral and clinical changes associated with a high intake of EPA, suggest that this n-3 highly unsaturated fatty acid may offer the hope of effective treatment for at least some patients with chronic fatigue syndrome.

Monolaurin

- Lauric acid found predominantly in breast milk and coconut oil, may be useful in therapy for post-viral or infection related fatigue.
- Lauric acid is broken down to monolaurin, conversion rate is low (1-6%).
- Monolaurin disrupts the lipid coat or membrane of enveloped virus’s and other infectious agents which may prevent infection.
- Clinical trials in human subjects are lacking, however preliminary research is promising.
- Invitro studies show strong results as an antimicrobial against a wide range of pathogens – herpes virus and measles particularly.
- Supplemental range is between 60- 3000mg three times daily. A maintenance dose of 600-1200mg is suggested. Not for use during preganancy/breastfeeding.

Iron deficiency and anaemia are extremely common causes of fatigue and should be one of your first considerations when assessing a patient with fatigue.

Iron is essential for energy production and has the following functions which relate to energy and fatigue:

- oxygen carrier
- part of several mitochondrial electron transport proteins required for ATP production
- cofactor for an enzyme in the citric acid cycle
- cofactor in the synthesis of carnitine, which carries fatty acids across the mitochondrial membrane
- powers a step in gluconeogenesis
- plays a role in the function of certain neurotransmitter amines
Fatigue

And naturally ascertain and address the ‘drivers’

- Thyroid function
- Adrenal function
- Inflammation
- Sex hormone balance
- Obesity
- Poor assimilation of nutrients
Lifestyle

• Ensure adequate, regular, and consistent amounts of **sleep** each night
• Effective **relaxation** is essential
  – try techniques such as yoga, breathing exercises or meditation
• Maintaining a reasonable **work** and **personal** schedule is important
• Manage **stressful** circumstances if possible
• Address chronic **pain** and/or **depression**
• Increase **physical activity**
  – physical activity boosts energy levels, while a sedentary lifestyle is a known cause of fatigue
• Avoid **alcohol** and **drug** use
• Limit **caffeine**
  – too much caffeine, particularly in the evening, can cause insomnia. Limit caffeinated drinks to two or less per day, and avoid these types of drinks after dinner
• Avoid **sleeping pills**
  – sleeping pills don’t work in the long term because they don’t address the causes of insomnia
• Eliminate **cigarette** smoking
  – For the body to make energy it needs to combine glucose with oxygen, but the carbon monoxide in cigarette smoke reduces the amount of oxygen available in the blood
• Seek treatment for **substance abuse**
  – excessive alcohol consumption or recreational drug use contributes to fatigue, and is unhealthy and potentially dangerous
• Learning to **do nothing** is helpful
  – One of the drawbacks of modern life is the urge to drive ourselves to bigger and better heights. A hectic lifestyle is exhausting. Try to carve out a few more hours in your week to simply relax and hang out. If you can’t find a few more hours, it may be time to rethink your priorities and commitments
• Encourage having more **fun**!
  – Laughter is one of the best energy boosters around
Chronic fatigue

Causes of Chronic Fatigue

• Depression
• Stress/low adrenal function
• Impaired liver function or environmental illness, or both
• Impaired immune function
  – Chronic fatigue syndrome
  – Chronic *Candida* infection
  – Other chronic infections
• Food allergies
• Hypothyroidism
• Hypoglycaemia
• Anaemia and nutritional deficiencies
• Sleep disturbances
• Cause unknown

Chronic fatigue

- Pre-existing physical condition
  - Diabetes
  - Heart disease
  - Lung disease
  - Rheumatoid arthritis
  - Chronic inflammation
  - Chronic pain
  - Cancer
  - Liver disease
  - Multiple sclerosis

- Prescription drugs
  - Antihypertensive
  - Anti-inflammatory agents
  - Birth control pills
  - Antihistamines
  - Corticosteroids
  - Tranquilizers and sedatives
Chronic Fatigue Syndrome (CFS)

• Also referred to as Myalgic Encephalomyelitis (ME)

• Chronic fatigue syndrome (CFS):
  – is a disorder of unknown aetiology
  • it is likely that multiple factors promote its development, sometimes with the same factors both causing and being caused by the syndrome
  – is characterised by a state of chronic fatigue that persists for more than six months
  – is accompanied by cognitive difficulties

Chronic Fatigue Syndrome (CFS)

Proposed aetiologies

- Elevated levels of antibody to Epstein-Barr virus in people with CFS-like symptoms, most of whom had had a history of infectious mononucleosis a few years earlier
- Other organisms proposed as causative agents in CFS
  - Human herpes virus-6
  - Inoue-Melnick virus
  - Brucella
  - Borrelia burgdorferi
  - Giardia lamblia
  - Cytomegalovirus
  - Enterovirus
  - Retrovirus

Chronic Fatigue Syndrome (CFS)

Immunologic abnormalities reported for CFS

• Elevated levels of antibodies to viral proteins
• Decreased natural killer cell activity
• Low or elevated antibody levels
• Increased or decreased levels of circulating immune complexes
• Increased cytokine (e.g. interleukin 2) levels
• Increased or decreased interferon levels
• Altered T helper cell to T suppressor cell ratio

Chronic Fatigue Syndrome (CFS)

Table 1: International CFS Study Group Definition of Chronic Fatigue Syndrome

I. Clinically evaluated, unexplained persistent or relapsing chronic fatigue that:
   • is of new or definite onset (has not been lifelong).
   • is not the result of ongoing exertion.
   • is not substantially alleviated by rest.
   • results in substantial reduction in previous levels of occupational, educational, social, or personal activities.

II. The concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue:
   • self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities
   • sore throat
   • tender cervical or axillary lymph nodes
   • muscle pain
   • multi-joint pain without joint swelling or redness
   • headaches of a new type, pattern, or severity
   • unrefreshing sleep
   • postexertional malaise lasting more than 24 hours

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Chronic Fatigue Syndrome (CFS)

- Hypothalamic dysfunction has been implicated as a common denominator in these syndromes

- This may occur secondary to mitochondrial dysfunction

- Dysfunction of hormonal, sleep, and autonomic control (all centred in the hypothalamus) and energy-production centres may explain the large number of symptoms and why most patients have a similar set of complaints

Kindling - a theory of CFS development

- Kindling might represent a heuristic model for understanding the etiology of Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS).
- Kindling occurs when an organism is exposed repeatedly to an initially sub-threshold stimulus resulting in hypersensitivity and spontaneous seizure-like activity.
- Among patients with ME/CFS, chronically repeated low-intensity stimulation due to an infectious illness might cause kindling of the limbic-hypothalamic-pituitary axis. Kindling might also occur by high-intensity stimulation (e.g., brain trauma) of the limbic-hypothalamic-pituitary axis. Once this system is charged or kindled, it can sustain a high level of arousal with little or no external stimulus and eventually this could lead to hypocortisolism.
- Seizure activity may spread to adjacent structures of the limbic-hypothalamic-pituitary axis in the brain, which might be responsible for the varied symptoms that occur among patients with ME/CFS. In addition, kindling may also be responsible for high levels of oxidative stress, which has been found in patients with ME/CFS.
CNS sensitisation

• The observation of central sensitisation in CFS is in line with our current understanding of CFS
• The presence of central sensitisation in CFS corroborates with the presence of several psychological influences on the illness, the presence of infectious agents and immune dysfunctions and the dysfunctional hypothalamus-pituitary-adrenal axis as seen in these severely debilitated patients

Chronic Fatigue Syndrome (CFS)

• Analogy used for patients

  *If the energy demands on your body are more than it can meet, your body “blows a fuse.” The ensuing fatigue forces you to use less energy, protecting you from harm. On the other hand, although a circuit breaker may protect the circuitry in the home, it does little good if you do not know how to turn it back on, or that it even exists*

• Research in genetic mitochondrial diseases shows not simply myopathic changes, but also marked hypothalamic disruption. As energy stores are depleted, hypothalamic dysfunction occurs early on

Chronic Fatigue Syndrome (CFS)

Nutritional therapy treatment options:

- **SHIN** stands for:
  - Sleep
  - Hormonal support – thyroid, adrenal, DHEA, testosterone, oestrogen
  - Infections/Immune dysfunction
  - Nutritional support

Chronic Fatigue Syndrome (CFS) - SHIN

Chronic fatigue syndrome (CFS) is an illness characterized by persistent and relapsing fatigue, often accompanied by numerous symptoms involving various body systems. The etiology of CFS remains unclear; however, a number of recent studies have shown oxidative stress may be involved in its pathogenesis. The role of oxidative stress in CFS is an important area for current and future research as it suggests the use of antioxidants in the management of CFS. Specifically, the dietary supplements glutathione, N-acetylcysteine, alpha-lipoic acid, oligomeric proanthocyanidins, Ginkgo biloba, and Vaccinium myrtillus (bilberry) may be beneficial. In addition, research on food intolerance is discussed, since food intolerance may be involved in CFS symptom presentation and in oxidation via cytokine induction. Finally, recent evidence suggests celiac disease can present with neurological symptoms in the absence of gastrointestinal symptoms; therefore, celiac disease should be included in the differential diagnosis of CFS.

Despite considerable worldwide efforts, no single etiology has been identified to explain the development of chronic fatigue syndrome (CFS). It is likely that multiple factors promote its development, sometimes with the same factors both causing and being caused by the syndrome. A detailed review of the literature suggests a number of marginal nutritional deficiencies may have etiologic relevance. These include deficiencies of various B vitamins, vitamin C, magnesium, sodium, zinc, L-tryptophan, L-carnitine, coenzyme Q10, and essential fatty acids. Any of these nutrients could be marginally deficient in CFS patients, a finding that appears to be primarily due to the illness process rather than to inadequate diets. It is likely that marginal deficiencies not only contribute to the clinical manifestations of the syndrome, but also are detrimental to the healing processes. Therefore, when feasible, objective testing should identify them and their resolution should be assured by repeat testing following initiation of treatment. Moreover, because of the rarity of serious adverse reactions, the difficulty in ruling out marginal deficiencies, and because some of the therapeutic benefits of nutritional supplements appear to be due to pharmacologic effects, it seems rational to consider supplementing CFS patients with the nutrients discussed above, along with a general high-potency vitamin/mineral supplement, at least for a trial period.
In 21 patients with chronic fatigue syndrome (CFS) versus 20 normal subjects, we investigated the oxidant/antioxidant balance and its correlation with muscle symptoms. Patients versus controls showed significantly: lower Lag Phase and Vitamin E (Vit E) concentrations in plasma and low-density lipoproteins (LDL), higher LDL thiobarbituric acid reactive substances (TBARS), higher fatigue and lower muscle pain thresholds to electrical stimulation. A significant direct linear correlation was found between fatigue and TBARS, thresholds and Lag Phase, thresholds and Vit E in plasma and LDL. A significant inverse linear correlation was found between fatigue and Lag Phase, fatigue and Vit E, thresholds and TBARS. Increased oxidative stress and decreased antioxidant defenses are related to the extent of symptomatology in CFS, suggesting that antioxidant supplementation might relieve muscle symptoms in the syndrome.

Carnitine is essential for mitochondrial energy production. Disturbance in mitochondrial function may contribute to or cause the fatigue seen in chronic fatigue syndrome (CFS) patients. One previous investigation has reported decreased acylcarnitine levels in 38 CFS patients. We investigated 35 CFS patients (27 females and 8 males); our results indicate that CFS patients have statistically significantly lower serum total carnitine, free carnitine and acylcarnitine levels, not only lower acylcarnitine levels as previously reported. We also found a statistically significant correlation between serum levels of total and free carnitine and clinical symptomatology. Higher serum carnitine levels correlated with better functional capacity. These findings may be indicative of mitochondrial dysfunction, which may contribute to or cause symptoms of fatigue in CFS patients.
EGCG

• The use of Epigallocatechin gallate in CFS was investigated in a mouse model
• The treatment group with long term use of EGCG restored all the behavioral and biochemical alterations associated with chronic fatigue syndrome