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Advanced Herbal Medicine

Research Assignment

# Graves' disease



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## Graves Disease: Introduction

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Graves Disease is an autoimmune disorder which accounts for up to 85% of all cases of hyperthyroidism. It is much more prevalent in women than men, with a ratio of 8:1 and typically begins between the ages of 20 and 40 years. Non-painful, diffuse goiter with hyperthyroidism is the most common presentation of the disease. Other signs include exophthalmos, pretibial myxedema as well as other skin changes, acropachy, and less commonly paralysis. There is no single immunologic abnormality which explains the clinical features of the disease; however there is the presence of antibodies against thyroid stimulating hormone (TSH) receptors. Serum T3, T4, thyroid resin uptake, and free thyroxine are usually elevated. TSH receptor antibodies (TSH-R Ab) are present in 80% of cases. Other symptoms can be associated with Graves' disease including glucose intolerance, osteoporosis, dyspnea, polyuria, polydipsia, myopathy, and paralysis.

### *The typical clinical presentation of Graves's disease*

- Weakness, sweating, weight loss despite a good appetite, nervousness, loose stools, heat intolerance, irritability, insomnia and fatigue.
- Tachycardia, palpitations, and tremor.
- Increased T4, free T4, and free T4 index.
- Goiter and ophthalmopathy. (Pizzorno & Murray, 2006)

<i>Physical Signs</i>	<i>Other signs and Symptoms</i>
Smooth, diffuse, non-tender goiter	Muscular weakness and fatigue
Tachycardia (especially after exercise)	Anxiety
Loud heart sounds, often a systolic murmur	Heat Intolerance
Mild proptosis	Pretibial myxedema
Lid retraction	Vitiligo
Lid lag	Alopecia
Tremor	Onycholysis

Table1. Summary of the clinical presentation of Graves' disease. (Pizzorno & Murray, 2006)

Factors to be considered within case management of Graves' disease

<p><i>Gender</i></p>	<p>The disease is much more common in women than men, with a ratio of 8:1. Beirerwaltes (cited in Pizzorno &amp; Murray 2006, p.1771) suggests the female-to-male ratio is 7:1 To 10:1, however the ratio in those with ophthalmic complications is about 1:1. (Pizzorno &amp; Murray, 2006)</p>
<p><i>Genetics</i></p>	<p>There is a genetic susceptibility to Graves' disease and this is apparent in some populations. The disease is statistically more prevalent in some human leukocyte antigen (HLA) haplotypes such as HLA-B8 and HLA-DR3 in Caucasians, HLA-Bw35 in the Japanese, and HLA-Bw46 in the Chinese. HLA identical twins have a 50% chance of manifesting Graves' disease, and there is a 9% change for fraternal twins. (Pizzorno &amp; Murray, 2006)</p>
<p><i>Stress</i></p>	<p>Stress has been recognised as a precipitating factor since Graves' disease was first recognised. Sonino et al (cited in Pizzorno &amp; Murray 2006, p. 1772) suggest that Graves' disease often follows emotional shock such as some sort of loss including divorce, death, or difficult separations. (Pizzorno &amp; Murray, 2006)</p>
<p><i>Left-handedness</i></p>	<p>A study conducted by Wood &amp; Cooper (cited in Pizzorno &amp; Murray 2006, p. 1772) has showed a statistically significant trend for left-handed people to manifest Graves' disease. The trial included only male subjects, with 70% of subjects with Graves' disease being left-handed compared with 24% in the control group. (Pizzorno &amp; Murray, 2006)</p>

<p><i>Smoking</i></p>	<p>There is a statistically significant connection between Graves' disease and smoking, with smoking increasing ophthalmic complications. This risk is slightly lower than the hereditary link associated with the disease and negative life events. Bartalena et al (cited in Pizzorno &amp; Murray 2006, p. 1772) suggest that there is an increased risk for ophthalmopathy in those who already have an eye manifestation and who continue to smoke.</p> <p>(Pizzorno &amp; Murray, 2006)</p>
<p><i>Iodine Status</i></p>	<p>The mandatory consumption of iodized salt in Galicia, and the effects of this on thyroid function have been evaluated. The incidence of thyrotoxicosis as demonstrated by elevated T4 with suppressed TSH levels increased throughout the study, with 4.89 new cases per 100,000 population. Iodine supplementation in iodine sufficient areas can increase the incidence of hyperthyroidism in some individuals. (Pizzorno &amp; Murray, 2006)</p>
<p><i>Prescription Medication</i></p>	<p>In elderly patients with hyperthyroidism, there may be a toxic reaction to prescription medication. There is generally an iodine deficiency in the elderly and a higher use of the antihypertensive drug amiodarone. (Pizzorno &amp; Murray, 2006)</p>

***Lycopus europaeus* (Gypsywort)**

Bugleweed decreases T3 levels due to reducing peripheral T4 levels. The herb also decreases TSH levels, as well as luteinizing hormone and testosterone. Bugleweed inhibits the effects of exogenous TSH on the thyroid gland, blocks the effects of TSH and TSH receptor sites located on the thyroid membranes, inhibit the peripheral deiodination of T4 to T3, and block the effects of antithyroid immunoglobulins on TSH receptors. Isolated compounds from the oxidation of 3,4-dihydroxycinnamic acid are found to be responsible for these effects. (Pizzorno & Murray, 2006)

A prospective two-armed open study has been conducted to assess the effect of *Lycopus europaeus* on thyroid function and associated symptoms during a three month follow-up phase. The study population consisted of patients with a basal TSH <1.0m U/l and hyperthyroidism-associated symptoms. A total of 62 patients were included in the study. A total of 33 subjects were given a *Lycopus europaeus* preparation which contained 20 mg of the herb in tablet form. The T3 and T4 excretion in 24 hour urine was measured as a primary objective parameter. Hormones, the general condition, and the symptoms associated with hyperthyroidism were registered as secondary parameters. Urinary T4 excretion was significantly increased in the *Lycopus europaeus* treated patients. Symptoms specific to the thyroid gland were also diminished including reduced heart rate in the morning. Findings from this trial suggest that *Lycopus europaeus* is an effective treatment in slight forms of hyperthyroidism. (Beer et al, 2007)

### ***Melissa officinalis* (Lemon balm)**

Therapeutic considerations involved in the management of Grave's disease involve reducing the symptoms associated with the condition. Stress control is essential to assist in normalising the function of the thyroid. The common clinical presentation of the disease includes nervousness, irritability, sweating, palpitations, and insomnia. *Melissa officinalis* also impacts directly on thyroid hormones. Like Bugleweed, *Melissa officinalis* inhibits the exogenous effects of TSH on the thyroid gland, and blocks the effects of TSH on the TSH receptor sites. *Melissa officinalis* also has been shown to be effective in reducing stress. (Pizzorno & Murray, 2006)

*Melissa officinalis* is contemporaneously used as a mild sedative and calming agent. A double-blind, placebo-controlled, randomised trial has been conducted to assess the efficacy of *Melissa officinalis* on induced stress. A total of 18 subjects received two separate single doses of a standardised extract (300 mg and 600 mg) and a placebo, on separate days separated by a 7-day washout period. The results showed that the 600 mg dose of *Melissa officinalis* ameliorated the negative effects of stress. There were significant increased self-ratings of calmness, with a significant increase in the speed of processing, with no reducing in accuracy. Results from this study suggest *Melissa officinalis* is an effective treatment to mitigate the effects of stress. (Kennedy et al, 2004)



### ***Leonurus cardiaca* (Motherwort)**

*Leonurus cardiaca* is considered as having antithyroid activity. This herb is used for mild thyroid hyperfunction and can be used for long term treatment. *Leonurus cardiaca* is particularly beneficial in the treatment of hyperthyroidism due to its antiarrhythmic effects. Heart palpitations are commonly experienced by those with Graves' disease, and therefore this herb may be beneficial in reducing this symptom caused by the condition. *Leonurus cardiaca* has been used in China for the treatment of coronary heart disease with favourable results. The Commission E in Germany supports the use of this herb as an adjuvant therapy for hyperthyroidism. (Bone 2003, Yarnell & Abascal, 2003)

A trial has been conducted to assess the effects of chronic administration of melatonin (0.75 mg at night for 10 days) and motherwort tincture in decreasing retinal brightness sensitivity and improving the emotional state in anxious young subjects. Analogous changes were less pronounced after the treatment with *Leonurus cardiaca*. The trial suggests there is a relationship between the limitation of anxiety and the improvement of visual function. (Ovanesov et al, 2006)

### ***Hypericum perforatum* (St Johns Wort)**

*Hypericum perforatum* is indicated where Graves' disease is suspected to be caused by a viral infection. Key constituents of this herb include thodianthrones hypericin and pseudohypericin, flavonoids, and phenolic compounds. Hypericin and pseudohypericin have demonstrated activity against several enveloped viruses and against several retroviruses. *Hypericum perforatum* is also a commonly used treatment for depression, anxiety, nervousness, and restlessness. Therefore this herb may be warranted for the treatment of Graves' disease due to its effects on the immune and nervous system. Graves' disease typically presents with nervousness, insomnia, and irritability.

(Bone, 2003)

Mischoulon & Rosenbaum (cited in Gahlsdorf et al, 2007) have shown that hyperforin, the active constituent of St. John's Wort (SJW), increases the amount of available extracellular serotonin, dopamine, and norepinephrine into the central nervous system synapses. This constituent has also been shown to increase the amount of glutamate in the synaptic cleft, with glutamate playing an important role in unipolar depression. Hypericin, another active constituent of SJW, may also impact on the hypothalamic-pituitary-adrenal axis, therefore decreasing cortisol production. Hypericin is also thought to inhibit serotonin, dopamine, and norepinephrine, which is the same mechanism of action to many of the newer pharmaceutical antidepressant medications. (Gahlsdorf et al, 2007)

A study has been conducted to compare the efficacy and tolerability of St John's Wort with imipramine in individuals with mild to moderate depression. The study consisted of 324 subjects diagnosed with mild to moderate depression. Subjects were randomised to receive 75 mg of imipramine twice daily or 250 mg of St John's Wort extract twice daily over a period of 6 weeks.

Scores decreased from 22.4 at the baseline to 12.00 at the end point among subjects given hypericum. Scores fell from 22.1 to 12.75 in the subjects taking imipramine. The anxiety-somatisation subscale was decreased significantly in the hypericum group compared with the imipramine group. The study suggests *Hypericum perforatum* extract is therapeutically equivalent to imipramine in treating depression. Hypericum had a significant advantage over imipramine in reducing anxiety. (Woelk. 2000)

### ***Curcuma longa* (Turmeric)**

Body tissues exposed to high levels of thyroid hormone are known to be susceptible to free radical-mediated injury. This concern is warranted for thyrotoxic myopathy and cardiomyopathy, which are two major complications of hyperthyroidism. A low status of antioxidants is clearly prevalent in hyperthyroid patients. This makes it pragmatic to treat hyperthyroid patients with antioxidant therapy. Where patients are given conventional therapy and antioxidants, there is a simultaneous return to the euthyroid state at a quicker rate. (Pizzorno & Murray, 2006)

*Curcuma longa* includes the key constituents essential oil (containing sesquiterpene ketones) and yellow pigments known as diarylheptanoids, including curcumin. *Curcuma longa* has demonstrated anti-inflammatory, antioxidant, and antimicrobial properties. (Bone, 2003)

The antioxidant activity of *Curcuma longa* was initially demonstrated in 1976 and it has been shown to be a potent free radical scavenger. The herb is also an inhibitor of NFκB which leads to the down regulation and inhibition of proinflammatory genes and cytokines. Turmeric also contains polyphenols, which have been shown to be immunomodulating, which is essential in the treatment of this condition. (Clarke & Mullin, 2008)

Choudhuri et al (cited in Bengmark 2006, p. 48) states the average consumption of curcumin is 100 mg/day in Asian countries. Curcumin has powerful anti-inflammatory actions. Curcumin inhibits both COX and lipoxygenase (LOX) pathways which reduces the synthesis of prostaglandins. (Wallace, 2002)

## Conclusion

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The main objective of the natural treatment of Graves' disease is to reduce the symptoms caused by the condition, whilst trying to promote normal thyroid function by inhibiting the effects of TSH, and the deiodination of T4 to T3. Although there is little evidence supporting the role of herbal therapy for the treatment of Graves' disease, the already available evidence is somewhat promising.

Unfortunately a natural approach in the treatment of the condition has not received much attention.

Herbs that have antioxidant, anti-inflammatory, nervine, anxiolytic, and antiarrhythmic properties

may be beneficial in reducing the clinical symptoms associated with the condition. *Lycopus*

*europaeus* seems to be the most promising herb identified to date in re-establishing normal thyroid

status; however additional clinical trials are required as this herb has not been adequately evaluated

in clinical studies. There is much evidence supporting the role of herbal therapy in reducing risk

factors such as stress that may contribute to the condition. The current available evidence is a

promising starting point in determining further natural approaches for the treatment of Graves'

disease. (Pizzorno & Murray, 2006)

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