SUBCLINICAL HYPOTHYROIDISM

SUBCLINICAL HYPOTHYROIDISM AND POTENTIAL CONSEQUENCES

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Abstract

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Subclinical hypothyroidism (SH) is a mild form of hypothyroid disorder that does not present with specific clinical signs or symptoms. At diagnosis, the level of serum thyroid stimulation (TSH) is elevated while the free thyroxin (FT4) and triiodothyronine (T3) concentrations remain normal. Thyroid hormone is an essential element in cell growth during the development of the fetus and in the metabolic activity in adults. Overt hypothyroidism and its associated adverse consequences are well studied and documented. However, the long-term effect of SH and the resultant effects on structure and functional proteins prior to overt signs and symptoms remain to be answered. The potential consequences of untreated SH and management are presented in this article.
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**Introduction**

Sub-clinical hypothyroidism (SH) is defined as an elevation in serum thyroid stimulating hormone (TSH) above 4.5 mIU/L (normal range 0.45-4.5mIU/L) with normal serum free thyroxin (FT4) and triiodothyronine (T3) concentrations. The diagnosis is based on laboratory evaluation with few if any clinical signs or symptoms (Biondi & Cooper, 2008). Thyroid hormone in the form of T3 has multiple effects in the function of virtually every organ by modifying gene transcription in all tissues and alteration of the rate of protein synthesis and substrate turnover (Brent, 1994). Due to vague signs and symptoms, SH is not likely to be detected unless thyroid function screening is completed particularly for populations who have risk factors to develop SH. However, undetected and untreated SH can develop to overt hypothyroidism, cardiovascular disorders, heart failure, neuro-psychiatric symptoms and adverse impacts in pregnancy. Although a wide spectrum of abnormalities has long been recognized in patients with overt hypothyroidism, in sub-clinical hypothyroidism the diagnosis is not determined and treatment for SH is not current practice due to the controversy in benefits of the treatment (Biondi & Cooper, 2008).

**Literature Search Strategies**

A literature search was conducted using the key words, subclinical thyroid disorder, subclinical hypothyroidism, mild thyroid disorder and/with cardiovascular disease, heart failure, and thyroid dysfunction in pregnancy and neuro-psychiatric disorder in CINAHL, MEDLINE and a textbook. The search was limited to adult subjects, journal articles and a textbook in English. A search was conducted using the date range from 1990 to 2010. Articles identified (N=396) were screened by title, then by abstract to extract irrelevant articles. Thirty-two articles meeting the inclusion criteria were identified, and were grouped
in three sections, instrument development to measure subclinical hypothyroidism and adverse clinical outcomes, descriptions of the attributes, and theory development.

**Epidemiology of Subclinical Hypothyroidism**

In The National Health and Examination Survey (NHANES III), the prevalence of SH was 4.3% in the general population. This study also found a higher prevalence in older, European and Mexican descendants, and also in women who were also positive for the presence of anti-thyroid antibodies. (Hollowell et al., 2002). Research from 2008 describes the prevalence of subclinical hypothyroidism ranging from 4 to 10% of the adult population and is increased markedly in females after the age of 45 years (Biondi & Cooper, 2008). In a longitudinal 20-year study in which women with both high serum TSH and high thyroid antibody concentrations were followed, overt hypothyroidism developed at a rate of 4.3 percent per year (Vanderpump et al., 1995). Screening for early detection is recommended given that a large proportion of the U.S. population unknowingly has laboratory evidence of thyroid disease (Hollowell et al., 2002).

**Pathophysiology of Thyroid Hormone Synthesis**

The thyroid hormones are essential in cell growth and development. These hormones affect the body’s metabolism, growth of nails and hair, weight, temperature and energy level. To maintain cell growth, development and function, thyroid hormones availability is present constantly in the circulation and in the thyroid gland. Iodine is essential for thyroid hormone production. The two biologically active thyroid hormones: thyroxine (T4) and triiodothyronine (T3) are synthesized with iodine and thyroglobuline; T4 is solely a product of the thyroid gland, whereas T3 is a product of the thyroid and of other tissues. T4 and T3 are incorporated with thyroglobuline in the blood and in the thyroid gland. In response to low concentrations of
thyroid hormones, Thyroid-releasing hormone (TRH) is metabolized in the hypothalamus, which stimulates the pituitary gland to secrete TSH. With a stimulation of TSH, the thyroid gland synthesizes and secretes triiodothyronine (T3) and thyroxine (T4). The hypothalamic–pituitary–thyroid axis has a set point in regulating TSH and T4, T3, which are maintained within narrow margins by a regulatory feedback system (Copstead & Banasik, 2005).

**Etiology of Subclinical Hypothyroidism**

The causes of SH are the same as those of overt hypothyroidism. The potential triggers of SH include thyroid autoimmune (Hashimoto’s) thyroiditis with high serum concentrations of antithyroid peroxidase (AntiTPO antibodies), persistent elevation of TSH in subacute thyroiditis, postpartum thyroiditis, and painless thyroiditis. Thyroid injury due to radiation and surgery can cause SH. Medications such as amiodarone, lithium and iodine-contrast agents may also contribute to SH. Brain tumors, inadequate T4 replacement therapy for overt hypothyroidism, toxic substances and TSH receptor gene mutation can be the culprits of SH (Bioni & Cooper, 2008).

**Differential Diagnosis**

Since SH is diagnosed with elevated serum TSH alone, other causes of an elevated TSH should be considered before diagnosing of SH. Only persistent or progressive SH should be considered as an early stage of thyroid disease. It may be difficult to distinguish symptoms between thyroid gland transient dysfunction and SH (Bioni & Cooper, 2008). Diagnosis requires frequent follow-up to distinguish between transient dysfunction or permanent and progressive disease in the thyroid gland. Possible causes of transient dysfunction include recovery from non-thyroidal illness, subacute phase of hyperthyroidism, central
hypothyroidism with biologically inactive TSH and thyroid hormone resistance with the presence of heterophile antibodies interfering with the TSH assay. Additionally, clinicians should be aware that any previous radioiodine therapy, thyroid surgery or radiation therapy could cause a mild thyroid failure (Fatourechi, 2009). Table 1 presents the differential diagnoses of SH.

**Potential Clinical Outcomes from Untreated SH**

**Progression to Overt Hypothyroidism**

Studies indicate that SH tends to progress to overt hypothyroidism, at a rate of 2.6% each year if thyroid peroxidase (TPO) antibodies are absent and at a rate of 4.3% if they are present. However, in some subjects TSH levels become normalized over time. Further studies are required to determine why elevated TSH in some individuals becomes normalized. The risk factors for developing overt thyroid failure appear to depend on the initial measurement of the TSH level. Those individuals with higher levels of TSH (higher risk >6.0 mIU/L) and presence of thyroid peroxidase (TPO) antibodies (Bioni & Cooper, 2008) are at higher risk for developing overt hypothyroidism. During the 20-year follow-up of the Whickham cohort study, an increased serum TSH level was predictive of the progression to overt hypothyroidism (Vanderpump, 1995). It is important to identify and screen populations with risk factors for development of SH, such as family history of thyroid dysfunction, presence of TPO antibodies and the population of women older than 60.
Cardiovascular Disease (CVD) and its Related Morbidity and Mortality

Thyroid hormones cross the cell membrane, bind with intracellular receptors and act as transcription factors to modulate DNA transcription. These hormones are also important regulators of cardiac function and cardiovascular hemodynamics. Danzi and Klein (2004) summarized the effect of thyroid hormone on the cardiovascular system. The physiologically active form of thyroid hormone, triiodothyronine (T3) binds to nuclear receptor proteins and mediates the expression of several important cardiac genes in the heart and vascular system. In the vascular system, T3 mediates the relaxation of vascular smooth muscle resulting in decreased arterial resistance and diastolic blood pressure (Danzi & Klein, 2004). The effects of T3 deficiency are increased systemic vascular resistance (SVR), diastolic dysfunction, reduced systolic function and decreased cardiac preload. These abnormalities regress with thyroid hormone replacement therapy (Biondi & Klein, 2004). In addition, SH has been associated with an increase in a number of other cardiovascular risk factors that include markers of inflammation, vascular reactivity, endothelial function, and carotid media thickness (Kvetny, Heldgaard, Bladbjerg, & Gram, 2004).

Patients with sub-clinical hypothyroidism manifest many of the same changes in the cardiovascular system (CVS), but to a lesser degree than that which occurs in overt hypothyroidism (Danzi & Klein, 2004). Thyroid dysfunction, however mild, can significantly affect the CVS (Cini et al., 2009). Subclinical hypothyroidism is a strong indicator of risk for atherosclerosis and myocardial infarction in elderly women (Hak, Pols, Visser, Drexhage, Hofman & Witteman, 2000).

Diastolic Heart Failure

It appears that thyroid hormone affects cardiac function not only by modulating DNA
The presence of diastolic dysfunction in the presence of a normal ejection fraction (EF) but with exercise intolerance is a predictor for the development of heart failure (HF) and leads to a higher risk of mortality in the elderly (Deswal, 2005).

Research to evaluate left ventricular (LV) diastolic function with Doppler echocardiography and radionuclide ventriculography in young and middle-aged patients with Hashimoto thyroiditis and mild but persistent TSH increases were compared with euthyroid controls. This study demonstrated that subclinical hypothyroid patients had a more prolonged isovolumetric relaxation time and an impaired time-to-peak filling rate which are markers of altered LV diastolic function (Biondi, Palmieri, Lombardi & Fazio, 2002). Moreover, an increase in LV diastolic pressure will increase pulmonary capillary pressure, which can cause dyspnea, exercise limitation, and pulmonary congestion (Biondi et al., 2002). An MRI research study evaluating the cardiac function in a SH group was completed with matching of euthyroid controls. This study demonstrated in SH, there was significantly decreased cardiac preload and increased afterload that resulted in reduced stroke volume and cardiac output (Ripoli et al., 2005), which is an important negative predictor in cardiac morbidity and mortality.
Neuropsychiatric Syndrome

Some studies support that SH is associated with neuropsychiatric diseases including neurotic depression, anxiety, or cognitive dysfunction. A cognitive function study was reported comparing SH patients treated with Levothyroxine (LT4) treatment and a control group without treatment. The treatment group showed a significant improvement in memory performance but no improvement in affective functions (Baldini et al., 1997). However, another study suggested the lifetime frequency of depression was significantly higher in the subjects who met the criteria for SH (56%) than in those who did not (20%) suggesting that SH might lower the threshold for the occurrence of depression (Haggerty, Stern, Mason, Beckwith, Morey, & Prange, 1993).

Potential Impact in Pregnancy

Physiologic changes associated with pregnancy require an increased availability of thyroid hormones by 40% to 100% in order to meet the needs of mother and fetus during pregnancy. For the maternal thyroid gland to meet the demands of pregnancy it must be present, disease-free and capable of responding with adequate stores of iodine (Smallridge et al., 2005). Therefore, it is essential to have adequate stores of iodine for thyroid hormone production when pregnancy demands a higher output.

The prevalence of SH during pregnancy is 2.3% in those with TSH levels above 6.0 mIU/liter and 0.3% in those with TSH levels above 12 mIU/liter. Seventy percent of women with abnormal TSH values had TPO antibodies (Klein et al., 1991). It is well documented that clinical thyroid dysfunction has been associated with pregnancy complications such as hypertension, preterm birth, low birth weight, placental abruption, and fetal death. However,
the relationship between sub-clinical hypothyroidism and pregnancy outcomes has not been well studied. Casey and colleagues (2005) reported that women with sub-clinical hypothyroidism were 3 times more likely to have a pregnancy complicated by placental abruption and preterm birth (Casey, Dashe, Wells, McIntire, Byre, Leveno & Cunningham, 2005). One report linking IQ scores and high levels of serum TSH during the second trimester demonstrated, 62 out of 186, age seven to nine year olds, had a lower IQ score correlating with mother’s higher than normal TSH during pregnancy (Haddow & Group, 2005).

Case Study

Kathy is a very pleasant 62 year-year-old woman with a history of sub-clinical hypothyroidism who presented to the emergency room with progressive shortness of breath. She complained of fatigue and intermittent dyspnea with exertion over a couple of months. She was hospitalized for several days for an evaluation to evaluate the etiology of her symptoms inclusive of a coronary angiogram that showed normal coronary arteries. She was diagnosed with idiopathic diastolic heart failure with an ejection fraction of 65 %, etiology unknown. She had no medical history other than mild hypertension that has been controlled with low dose of hydrochlorothiazide and otherwise was active and healthy. Two years prior to this event, her serum thyroid panel revealed sub-clinical hypothyroidism with an elevated TSH level of 7.7mlU/L with normal T4, T3. At this time, no further evaluation or treatment was initiated. At this hospitalization, her serum thyroid panel showed an elevated TSH level of 16mlU/L with low FT4 and T3, indicating her sub-clinical hypothyroidism had progressed to overt hypothyroidism. In this patient cardiomyocyte and resultant cardiac dysfunction was a plausible explanation for the cause of her diastolic heart failure. After a week, her condition was sufficiently stabilized to return home with a long journey of heart failure management.
SH and its managements

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treatment for hypothyroidism.

Screening and Diagnosis

Routine screening for thyroid function is controversial, not currently practiced and is not recommended by the United States Preventive Services Task Force (Helfand, 2004). However, universal screening compares favorably with other preventive medical practices in cost-effective studies especially in pregnant and elderly woman. Populations older than 45 years of age especially women show a prevalence of SH that can progress to overt disease (Hollowell et al., 2002). In a cost effective comparison study, the cost of treatment for potential complications from untreated SH such as overt hypothyroidism, CVD, HF and neuropsychiatric syndrome is far greater than the cost of routine screening for thyroid function in the elderly (Danese, Powe, Sawin & Ladenson, 1996).

Moreover, studies indicate that placental abruption and preterm birth can be the source of neurodevelopment impairment in infants that can result in lower IQ scores (Casey et al., 2005). The population of pregnant women in general has a 2.5 percent risk of adverse clinical outcomes due to SH (Haddow & Group, 2005). The American College of Obstetricians and Gynecologists and the National Guideline Clearinghouse (NCH, 2007) recommend testing only in symptomatic pregnant women or those with a family history of thyroid disease (Improvement, 2007). However, a study demonstrated that targeted thyroid function testing of only the high-risk group would miss about one third of the women that are pregnant with overt/subclinical hypothyroidism (Vaidya et al., 2007).

Given the potential complications from untreated SH, an acceptable approach to prevent adverse clinical symptoms and outcomes is routine screening of TSH serum level
in those patients that are symptomatic, have a family history of thyroid dysfunction, patients who are pregnant or considering pregnancy, women older than 60 and for those with cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus, and smokers.

**Treatment**

There are no guidelines for the treatment of patients with elevated serum TSH and normal FT4 and T3. Currently experts recommend treatment of patients with serum TSH concentration >10 mU/L. Treatment for those with TSH serum level between 5 to 10 remains controversial. Data pertaining to the prevention or progression to hypothyroidism with treatment at these levels has not proven to be a treatment benefit.

Arguments for not treating SH are the potential risks from thyroid replacement including cardiac arrhythmia and exacerbation of angina pectoris particularly in patients over age 65. In elderly patients, a higher TSH threshold is recommended for treatment since the upper limit of normal for serum TSH may be higher in this age group (Somwaru, Arnold, Joshi, Fried & Cappola, 2009).

Untreated SH is associated with progression to overt hypothyroidism and adverse clinical outcomes particularly with TSH levels greater than 10mU/L. Research supports aggressive case finding with routine screening and treatment in pregnant women, individuals older than 60 years, and those at high risk for thyroid dysfunction and cardiovascular dysfunction (Surks et al., 2004). Development of SH tends to increases with age as does potential adverse effects on the cardiovascular system risks for cardiovascular disease, quality of life and mortality. Identification of those to screen and when to initiate treatment should be considered (Burgio, Gruttadauria, Fulco, Lunetta & Vancheri, 2005). The influencing factors
that determine which patients to treat with TSH levels between 5-10 mIU/L are those that a positive TPO lab result, women who are pregnant or considering pregnancy, and those with cardiovascular risk factors (Biondi & Cooper, 2008).

The goal of treatment is the reduction of serum TSH concentration into the normal reference range. Initiation of treatment should begin with the lowest dose necessary to normalize the serum concentration starting with levothyroxine 25 to 50 mcg daily to avoid overtreatment. After the optimal thyroxine dose has been defined, long-term monitoring of patients with an annual clinical evaluation and serum TSH measurement is appropriate (Ayala, Danese, & Landson, 2000).

**Recommendations for Nurse Practitioners**

The role of nurse practitioners is of great importance with regard to subclinical hypothyroidism. SH does not present with signs or symptoms. Yet, there is great potential for organ damage without early detection and prompt treatment particularly in pregnancy, those with a family history of SH, women 60 and over and for those who have cardiovascular risk factors.

Nurse practitioners need to be aware of subclinical hypothyroidism and potential adverse clinical consequences from untreated SH. Recommendations for routine annual TSH level screening are for pregnant women, those with a family with a history of thyroid dysfunction, women 60 and older and for those who have cardiovascular risk factors.

Management of SH differs depending on TSH serum concentration and demographic group. Recommendations from American Association of Clinical Endocrinologists (AACE) for treatment include patients with a TSH that is greater than 10 mIU/liter or in patients with TSH levels between 5 and 10 mIU/L in pregnant women and those who show a presence of
TPO antibodies (Baskin et al., 2002). The Endocrine Society recommends thyroxine replacement in pregnant women with subclinical hypothyroidism given that the potential benefits outweigh the potential risks (Endocrine Society, 2007). Current practices are individualized with no consensus recommendations and guidelines to treat SH except in those individuals with a TSH level greater than 10 mIU/l starting with a low dose of levothyroxine (Fatourechi, 2009). Table 2 outlines the recommendations for treatment of SH.

Conclusion

Subclinical hypothyroidism is a mild form of hypothyroidism disorder with vague or non-specific clinical symptoms. Diagnosis relies on an elevated serum TSH and a normal serum free thyroxine (T4). Standard recommended screenings for this disorder are not currently recommended although a substantial proportion of patients with SH eventually develop overt hypothyroidism and secondary clinical symptoms and outcomes. Screening and treatment of the population of pregnant women, family history of thyroid dysfunction, women age over 60 and those with cardiovascular risk factors are recommended to prevent potential adverse progressive effects. Untreated SH can lead to cardiovascular disease, heart failure, neuropsychiatric symptoms, and complicated pregnancy due to untreated subclinical hypothyroidism. Further large scale randomized research is needed in the population of patients with SH evaluating the relationship of elevated TSH and normal T3, and T4 serum levels. Guideline development is needed for screening and treatment in this patient population. It is important for nurse practitioners to be aware of SH and the related potential serious clinical outcomes for untreated subclinical hypothyroidism.
References


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Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted

The incidence of thyroid disorders in the community: a twenty-year follow-up of the
Whickham Survey. *Clin Endocrinol (Oxf), 43*(1), 55-68.
Table 1
Differential Diagnosis of Subclinical Hypothyroidism: Other Causes that Increase TSH

<table>
<thead>
<tr>
<th>Other conditions elevating TSH</th>
<th>Possible causes increasing TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery from non-thyroidal illness</td>
<td>Transient elevated TSH following TSH suppression</td>
</tr>
<tr>
<td>Recovery from subacute, painless or postpartum thyroiditis</td>
<td>Transient elevated TSH, but not always, following the hyperthyroid phase</td>
</tr>
<tr>
<td>Subacute phase of hyperthyroidism</td>
<td>Transient elevated TSH</td>
</tr>
<tr>
<td>Laboratory analytical problem</td>
<td>Assay variability</td>
</tr>
<tr>
<td>Untreated adrenal insufficiency</td>
<td>Treat adrenal insufficiency</td>
</tr>
<tr>
<td>TSH - Secreting pituitary adenoma</td>
<td>Central hypothyroidism</td>
</tr>
<tr>
<td>Other possible causes for elevated TSH</td>
<td>Previous radioiodine therapy, thyroid surgery or radiation and impaired renal function and rare mutations of the TSH receptor</td>
</tr>
</tbody>
</table>

Source: "The clinical significance of subclinical thyroid dysfunction" (Biondi 2008).
Flow Chart 1
Recommendations for Treatment of Subclinical Hypothyroidism

For those who do not have potential transient elevated TSH such as recovery from non-thyroidal illness, thyroiditis or radiation/surgery of thyroid,

Start low dose of levothyroxine and regular monitoring of thyroid function with TSH serum concentration.

For those who had risk factors such as
1. Cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus, smoker
2. Positive TPO antibodies or evidence of autoimmune thyroditis
3. Pregnancy

Consider initiating with low dose of levothyroxine with regular monitoring of thyroid function with TSH serum concentration.

For those who have negative risk factors cardiovascular disorder, TPO antibodies, and non-pregnancy and women over 60:
6-12 months intervals of TSH monitor

Source: “The clinical significance of subclinical thyroid dysfunction” (Biondi 2008).