



3-10-2019

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Chakua, Dennis, "Management of subclinical hypothyroidism and its effects on cardiovascular endpoints" (2019). *Nursing Capstones*. 70.  
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Management of subclinical hypothyroidism and its effects on cardiovascular endpoints.

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## PERMISSION

Title Management of subclinical hypothyroidism and its effects on cardiovascular endpoints

Department Nursing

Degree Master of Science in Nursing

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**ABSTRACT**

The purpose of this care report was to synthesize evidence-based research related to the management of subclinical hypothyroidism among non-pregnant adults, and its effect of cardiovascular endpoints, at the five year follow up. Subclinical Hypothyroidism affects approximately 5-10 % of adults in the United states, with women greater than 60 years old accounting for 15% of these cases (Zhao et al., 2017). Inadequate management of these patients could result in progression to overt hypothyroidism, cardiovascular disease, neuropsychiatric symptoms and increased mortality. Today, we have Jane a 62-year-old female who presents to the clinic with complaints of increased fatigue and constipation with no other symptoms. Her diagnostic assessment reveals that her Thyroid stimulating hormone (TSH) concentration is elevated but her free thyroxine (T4) level is normal. Based on the clinical presentation and lab results would she be a candidate for levothyroxine replacement therapy or is close monitoring a reasonable option for this patient? There continues to be significant controversy regarding the role of thyroid replacement therapy for subclinical hypothyroidism. Recent observational studies evaluating cardiovascular endpoints and mortality among patient diagnosed with subclinical hypothyroidism; support the use of thyroid replacement therapy in most patients less than 65 years of age, with a TSH greater than 7.0mIU/L.

## BACKGROUND.

Subclinical hypothyroidism (SCH) is defined as an elevated serum thyrotropin level (TSH) in the presence of a normal (FT4) free thyroxine level (Stott, et al., 2017). This disorder is estimated to affect 5-10% of the general population with 15% of all cases affecting women 60 years of age and older (Zhao,2017). Most patients with this disorder are asymptomatic or they might present with vague symptoms suggestive of hypothyroidism. In most cases, the only way to diagnose SCH is through laboratory test to measure TSH. SCH and overt hypothyroidism share similar etiology, risk factors associated with SCH include Hashimoto's thyroiditis, prior ablative therapy for hyperthyroidism related to Graves' disease, external beam radiation to the brain, inadequate levothyroxine (L-T4) replacement for patients with hypothyroidism, and drugs that impair thyroid function (Suh & Kyu-kim,2015).

Since most patient with SCH are asymptomatic especially when TSH levels are  $<10\text{mU/L}$  it is difficult to identify these patients clinically based on symptoms alone. Approximately 30% of adults with this disorder will present with vague symptoms which include fatigue, constipation and dry skin. These symptoms could be misinterpreted by the clinician thus allowing the patient to progress to overt hypothyroidism. Consequences of failure to recognize and appropriately manage SCH include increased risk for cardiovascular disease, neuropsychiatric symptoms, Alzheimer's disease among women and all-cause mortality (Tng, 2016).

The rationale behind this case report is to synthesize the evidence-based recommendations pertaining to management of SCH and effects on cardiovascular endpoints. Various randomized trials have failed to show a difference in clinical outcomes pertaining to hypothyroid symptoms and quality of life among the treated and placebo groups. These findings were not reflected when evaluating certain

cardiovascular endpoints which include congestive heart failure, coronary vascular disease and hyperlipidemia. The purpose of this case study is to review current treatment recommendations associated with prevention of the previously mentioned cardiovascular endpoints among non-pregnant patients diagnosed with SCH.

### CASE REPORT

Jane is 62-year-old female who presents to your clinic for a routine physical exam. Her primary medical history includes obesity, dyslipidemia and depression. Today, she reports increased fatigue and constipation but denies any recent illness, change in weight, cold intolerance, dry skin or blood in the stool. Her symptoms have been present for the past few months. She has used over the counter stool softeners and laxatives for the constipation with notable relief. She denies any recent medication changes or travel outside the United States. She's concerned about the recent change in her activity level and wants further evaluation for this matter.

Her surgical history is positive for two C-sections, she takes Zoloft 25mg for depression, a multivitamin and fish oil tablets daily. She also takes Colace and senna as needed for constipation. She has no known allergies at this time. She is current on all her immunizations and health maintenance. Jane is a mother of two adult children; she resides at home with her husband and continues to work as a 5<sup>th</sup> grade school teacher. She denies a history of tobacco use but does use alcohol on social occasions. She denies illicit drug use; she is post-menopausal and remains sexually active.

Her physical examination reveals a well-nourished adult female. She has no signs of a goiter, lymphadenopathy or tremors. She has clear lung sounds to bilateral auscultation. Heart tones are normal without murmurs or jugular venous distention. Her Abdomen is soft with audible bowel sounds on all quadrants. Her diagnostic exam today was positive for normocytic anemia, without increase to the absolute reticulocyte count. Her TSH is elevated at 7.8 mU/L with normal FT4 level and antithyroid

peroxidase (anti TPO) antibodies are present. Her serum ferritin levels are normal at 100ng/ml. Her liver enzymes and kidney function test are all normal. Both CRP/ESR are within normal limits and her urinalysis is unremarkable. Her lipid panel is slightly elevated with LDL of 130mg/dl and a total cholesterol of 236 mg/dl.

Based on her symptoms and lab results, subclinical hypothyroidism is suspected. In patient with this disorder, normocytic anemic develops due to thyroid hormone deficiency. In some patients, anemia is the earliest and only manifestation of thyroid disease (Banday et al., 2018). In hypothyroid patients, a falsely elevated hemoglobin level could confuse the clinical picture due to the lower plasma level present in these patients (Banday et al., 2018). Hyperlipidemia can also be observed in the setting of undiagnosed SCH, a hypothyroid state decreases the expression of hepatic LDL receptors and results in reduced cholesterol clearance from the blood stream (Jabbar, et al., 2017). Among patient on optimum anti-lipid therapy with poor response, subclinical hypothyroidism should be ruled out prior to therapy escalation. Although (anti-TPO) measures are not indicated for management of subclinical hypothyroidism, this measure can be useful when there is uncertainly regarding course of management.

Considering her age/sex, presenting symptoms, positive (anti-TPO), elevated TSH and lipid panel this patient would benefit from thyroid hormone replacement to prevent progression to overt hypothyroidism. Current recommendation for thyroid replacement suggests starting with the lowest dose necessary for normalize TSH levels. For this patient, levothyroxine 25-50mcg daily would be appropriate and has been associated with decreased risk of overtreatment especially among older adults with underlying CVD. Follow up is recommended at six weeks after initiation of therapy to monitor serum TSH. Therapy can be titrated every six weeks until a therapeutic TSH level of 0.4-2.5 mU/L is achieved. Among patient older than 65 but less than 70 years old the target TSH level should be 1-5 mU/L (Pearse,et al., 2013)

SCH that is not appropriately managed has been associated with functional cardiovascular abnormalities which include left ventricular diastolic dysfunction and reduced ejection fraction especially among elderly women (Pearce, et al., 2017). A prolonged hypothyroid state promotes endothelial dysfunction, arterial stiffening, increased vascular resistance and atherosclerosis. There continues to be conflict related to who needs treatment while balancing the benefits and harms of offering thyroid replacement treatments. To answer this question, an extensive literature review was conducted evaluating the use of LT4 among non-pregnant adults diagnosed with SCH as it relates to three cardiovascular endpoint 1. Congestive Heart Failure (CHF) and 2. Coronary vascular disease (CVD). 3. Hyperlipidemia.

### **Literature Review**

As previously mentioned, there continues to be controversy as it relates to management of SCH. Experts in this field continue to debate what institutes an appropriate reference range and upper limit for serum TSH prior to initiation of treatment (Suh & Kyu kim, 2015). There is consensus among the various guidelines that patient who are pregnant, infertile, with hypothyroid symptoms and at risk of progression to over hypothyroidism should receive treatment (Suh & Kyu kim, 2015). Arguments against treatment of SCH center around overtreatment from excessive thyroid hormone replacement, exacerbation of cardiac symptoms, and the cost associated with life long treatment of this condition. Furthermore, various studies have demonstrated that spontaneous recovery is possible for most patients who present with SCH by the five year follow up. These results further complicate treatment decisions for these patients.

A literature review was conducted seeking current evidence related to the management of SCH and its effect of cardiovascular endpoint among non-pregnant adults. To accomplish this goal, an updated search was conducted on PubMed, CINAHL and Clinical-Key. Results were limited to published



research from 2013 to 2019. Studies included focused on SCH and cardiovascular endpoints, specifically cardiovascular disease, coronary vascular disease and hyperlipidemia. The results were restricted to English language articles only. Three systematic reviews were included in this case study, two of these reviews were clinical practice guidelines from the American association of clinical endocrinologist and American thyroid association task force (AACE/ATA). Guidelines from the European thyroid association (ETA) were also included in this review. Results from the thyroid hormone replacement for untreated older adults with subclinical hypothyroidism- a randomized placebo-controlled trial (TRUST) was also included in this review.

### **Congestive heart failure**

Overt hypothyroidism has been implicated with progression of cardiovascular disease but when considering SCH, cardiovascular effects are less clear. There is evidence to support the cardiovascular benefits associated with both T3 and T4. Myocardial relaxation and decreased peripheral vascular resistance are facilitated by T3 while T4 has been associated with improved hemodynamic effects (Hassan, Altamirano-Ufion, Zulfiqar & Boddu, 2017). Thyroid dysfunction can alter the contractility and relaxation of the ventricles leading to circulatory compromise. Based on the effect of thyroid function on the cardiovascular system we understand that managing thyroid dysfunction could potentially reverse the cause of heart failure in select populations.

A retrospective cohort study was conducted in the United Kingdom evaluating therapy for SCH among non-pregnant adults 40-70 years vs greater than 70 years old. The study included 4735 persons who has a TSH level between (5.01 to 10.0 mIU/L). Results were adjusted for age, sex, socioeconomic status, cholesterol, serum TSH and smoking history. Results showed subjects in the treatment group who received levothyroxine had lower risk for fatal or non-fatal ischemic heart disease 4.2% Vs 6.6% hazard ratio (Bruin-Rugge, Bougatsos, & Chou, 2015). The same study failed to show risk reduction

among patients older than 70 years old when comparing the treatment and placebo group. A recent randomized controlled trial (TRUST) evaluated the benefits of thyroid hormone replacement in managing hypothyroid symptoms. This study involved 737 adults who were at least 65 years of age with a serum TSH of 4.9-19.99. The results from this study failed to show a decline in cardiovascular event or mortality among patients treated with levothyroxine (Rodondi, et al., 2017). The investigators of this study conceded that this trial was underpowered to detect cardiovascular effects thus it's possible levothyroxine therapy may provide protection against cardiovascular disease or cause harm (Rodondi, et al., 2017).

Hassan (2017) found that controversy pertaining to SCH management were confounded by conflicting study results. Variations observed in these studies included an arbitrary TSH reference range to define SCH, varying study designs and a paucity of randomized controlled trials to support treatment recommendations. The ACC/AHA guidelines currently recommend that thyroid function be evaluated for patients with newly diagnosed heart failure based on evidence that thyroid replacement could be a reversible cause of cardiovascular disease (Hassan, Altamirano-Ufion, Zulfiqar & Bodddu,2017). In another prospective study evaluating TSH levels and harmful cardiovascular effects. The investigators concluded that among patients with a TSH level of 7 mIU/L and 10mIU/L a hazard ratio of 2.58 and 3.26 was observed respectively as it related to heart failure development (Hassan, Altamirano-Ufion, Zulfiqar & Bodddu,2017). Researchers have also observed an association between thyroid function and the New York heart association (NYHA) functional level. Lower T3 levels are associated with class III and IV NYHA classification and serves as a mortality risk predictor. Among patient with heart failure with preserved ejection fraction, 22% of these patients have some form of altered thyroid function and low T3 levels (Hassan, Altamirano-Ufion, Zulfiqar & Bodddu,2017).

The American Association of Clinical Endocrinologist and American Thyroid Association (AACE/ATA) developed guidelines for the management of SCH. The guidelines were based on a

systematic review of various studies pertaining to SCH management. The AACE/ATA conducted a meta-analysis of 10 longitudinal studies pertaining to subclinical hypothyroidism. Their results showed that the risk of atherosclerotic cardiovascular disease was 1.51 among patient younger than 65 with a diagnosis of SCH, compared to 1.05 in patients older than 65 (Garber, et al., 2012). The same study also failed to show a causal relationship between L-thyroxine and decreased risk of cardiovascular disease. This was evidenced by lack of increased morbidity and mortality among patients who were not treated with L-thyroxine over 20 years of follow up. The results questioned the efficacy of L-thyroxine to prevent progression to ASCVD and suggested other factors including age could be the critical factor associated with cardiac morbidity.

The European Thyroid Association (ETA) reached similar conclusion regarding age as an independent risk factor for increasing heart failure events among patients diagnosed with SCH with a serum TSH > 10 mU/L (Pearce, et al., 2012). The ETA based their guidelines of various meta- analyses with the largest including 50,000 participants from eleven prospective cohort studies. This meta-analysis demonstrated an increase risk of CHD mortality when serum TSH levels were > 7.0 and significant risk if TSH >10 mU/L (Pearce, et al., 2012). The authors of these studies conceded that treatment recommendations are not supported by data from large randomized controlled trials. Even so, data from an observational analysis of 4500 SCH patient in the UK has demonstrated that L-thyroxine replacement for patient younger than 70 years was associated with lower CHD risk over 8 years of follow up (Pearce, et al., 2012). Based on these findings, it appears that L-thyroxine replacement has low risk of harm and might decrease risk of ASCVD among patients who are less than 70 years old with a diagnosis of SCH.

#### **Coronary vascular disease.**

Patient's diagnosed with SCH have an increased risk of developing CVD. Thyroid hormone receptors are present in both myocardial and vascular endothelium (Jabbar, 2017). SCH impairs the

relaxation of vascular smooth muscles cells resulting in increased systemic vascular resistance, arterial stiffening and altered endothelial function due to reduced nitric oxide levels (Jabbar,2017). Most patient with SCH will develop diastolic heart dysfunction related to impaired ventricular filling and relaxation (Jabbar, 2017).

A recent meta-analysis by Zhao (2017) evaluating the effect of levothyroxine therapy on the progression of carotid intima-media thickness among patients with SCH produced encouraging results. Three RCT's with 117 patients were included in this study. The results of the study showed L-T4 therapy significantly decreased the development of carotid intima-media thickness (C-IMT). The same study also demonstrated a decrease in C-IMT among mixed genders and female patients within the treatment group. These results were observed after long term therapy with L-T4 for > 6 months. The investigators concluded the decrease in C-IMT was related to L-T4 ability to decrease total cholesterol, triglycerides, low density lipoprotein and blood pressure (Zhao, et al., 2017). The significance of reducing C-IMT is due to its association with the development of atherosclerosis and related diseases. Among post-menopausal women, physiologic changes places them at greater risk for developing CVD; thus L-T4 therapy for patients who present with SCH would be a reasonable treatment option for women < 70 years of age.

The American Heart Association/American College of Cardiology guidelines consider both calcium score and C-IMT as a class IIa recommendation for evaluation of asymptomatic adults with cardiovascular risk (Zhao, et al., 2017). The previously mentioned study determined that a 0.1mm difference in C-IMT was associated with an increased prospective risk of CVD from 10% to 15 % while stroke risk increased from 13% to 18% (Zhao. et al., 2017). The use of levothyroxine among patients with SCH demonstrated a reversal of C-IMT thus decreasing risk associated ASCVD (Zhao, et al., 2017). The same study failed to demonstrate harm related to thyroid replacement for these patients. Furthermore,

the study failed to provide treatment recommendations; suggesting individualized therapy for these patients based on clinical judgement until the results from TRUST are published.

The European Thyroid Association also evaluated the effect of levothyroxine as it related to coronary heart disease. The guidelines included a meta-analysis of ten pooled studies with 14,449 participants. The Investigators found a pattern of moderate increased risk of coronary heart disease (CHD) and mortality among SCH patients (Pearce, et al., 2013). The study also acknowledged that the relationship between CHD and SCH could have been influenced by mean age of participants and the TSH elevation level. The same meta-analysis demonstrated conflicting results which showed no association between SCH and incidence of CHD and mortality after 10 years follow up in one prospective study (Pearce, et al., 2017). Additionally, the study also raised concerns regarding the upper level of serum TSH requiring treatment. Recent studies have demonstrated that TSH levels seem to increase with longevity (Pearce, 2017). It is unknown if the rise in TSH level as we age is a normal physiological response thus more research is needed to answer this question. Because of the expected rise in TSH as we age, L-T4 replacement among SCH patients should be individualized for patients older than 70 years of age. The reason being, L-T4 replacement has not demonstrated a decrease in CVD risk among these patients. Current research continues to show that young <65 and moderately older <70 with SCH could decrease their risk of developing CVD with L-T4 replacement.

### **Hyperlipidemia**

The association between thyroid function and serum cholesterol has been well documented in the literature. As previously mentioned, overt and SCH has been associated with altered lipid metabolism resulting in hypercholesterolemia and increase ASCVD risk (Duntas & Brenta, 2018). As the level of serum TSH increases, the number of LDL receptors in the liver diminish causing an imbalance in synthesis and degradation rate of cholesterol. The result is increased levels of total cholesterol (TC) and

Low-density lipoprotein (LDL). The combination of dyslipidemia and hypothyroidism facilitates the development of CHD, a leading cause of death in various parts of the world (Duntas & Brenta, 2018). Current research evaluating thyroid function and its effect on lipid metabolism suggest a multi-disciplinary approach could be beneficial in determining when and how hypothyroidism should be treated in a setting of dyslipidemia.

Various studies have demonstrated how dyslipidemia can be affected by hypothyroidism. In a cross-sectional study evaluating 2,799 individuals age 70-79 with a TSH > 5.5mIU/L, researchers observed a 9mg/dl increase in cholesterol level. These findings were reinforced in a larger cross-sectional study which included 30,656 participants that showed a direct correlation between TSH level and lipid values (Duntas & Brenta, 2018). These findings were not supported by a meta-analysis conducted by the U.S preventive service taskforce (USPSTF). When considering lipid values alone, the meta-analysis concluded that treatment of SCH may improve LDL and TC levels but the treatment effect was small (-28 to 0mg/dl) for cholesterol levels and (-22 to 2mg/dl) for LDL levels. Based on the minimal decline in lipids levels, they were hesitant to conclude that treatment resulted in clinically significant results (Bruin-Rugge, Bougatsos, & Chou, 2015)

Higher TSH values have been associated with metabolic syndrome (mets), this condition is characterized by abdominal obesity, insulin resistance, dyslipidemia and hypertension. Various studies have described the relationship between the incidence of Mets as it relates to hypothyroidism. One such study was the heart, aging and body composition study. The investigators included 3,075 community dwelling adults in this prospective cohort study. Results showed that SCH in the setting of TSH > 10mIU/L was associated with increased prevalence but not incidence of Mets (Duntas & Brenta, 2018). These findings were confirmed in another longitudinal aging study conducted in Amsterdam. Finding from this study concluded that subjects with a serum TSH level above 2.28mIU/L has an increased prevalence of Mets compared to subjects with a TSH of less than 1.04 mIU/L (Duntas & Brenta, 2018).

Considering these results, the risk of Mets should be considered among SCH patients. The appropriateness of therapy for these patients should consider their risk for progression to CHD in the presence of a persistent hypothyroid state.

In a separate study comparing the role of SCH as it relates to lipid profiles among the young and old. Researchers evaluated 17,046 middle ages and elderly patients across china between 2011 and 2012. Results from this study concurred with previous study conclusion showing a correlation between TSH levels and hyperlipidemia. This study demonstrated that each 1mU/L increase in TSH was related to an increase in both TC and LDL as age increased (Duntas & Brenta, 2018). The study also demonstrated a plateau in lipid levels among the elderly despite continued TSH elevation. It is hypothesized that among the very old, serum TSH elevation might be a physiologic response to increase survival. Even so, TSH level >10 mIU/L should be followed closely among this age group due to increased risk of dyslipidemia and detrimental effects of developing CHD

### **Discussion**

The relationship between hypothyroidism and cardiovascular function cannot be ignored based on the preceding literature review. When considering how to proceed with management of SCH patients, the clinician should understand the systemic effects associated with thyroid dysfunction. This review focused on cardiovascular endpoint specifically heart failure, coronary heart disease and hyperlipidemia. There continues to be conflicting research findings regarding SCH management; but most studies have demonstrated that treatment is appropriate if the patient is less than 65 years of age, with hypothyroid symptoms, and at risk for developing cardiovascular endpoint previously mentioned.

Untreated SCH could progress to diastolic heart failure without appropriate thyroid replacement. Evidence shows, adults < 65 years of age to be at increased risk for developing HF in a setting of prolonged hypothyroidism. The progression of HF is associated with multiple comorbidities

and could be avoided, and in some cases reversed if appropriate therapy is initiated early in the disease process. Various studies concur that TSH levels  $> 7$  mIU/l was associated with statistical significance for CHD while TSH levels  $> 10$  mIU/L were predictive of cardiovascular events (Pearse, et al., 2013). The implications of these findings suggest the benefits of thyroid replacement might outweigh the harms associated with overtreatment in select population.

CHD appears to be a risk factor of SCH especially among young adults. There appears to be a relationship between age and serum TSH elevation as it relates to CHD among SCH patients. Younger patient  $< 65$  with elevated serum TSH appear to have the highest risk of developing CHD. The landmark Wickham survey evaluating thyroid disorders in the community; had initially concluded that no association was apparent between hypothyroidism and CHD over 20 year of follow up. When investigators re-analyzed their data with an emphasis on SCH patients, they concluded these patients has increased CHD and mortality. Based on the strength of this longitudinal study, and multiple other randomized clinical studies, Thyroid replacement appears to be a viable treatment option to decrease CHD risk. The use of L-thyroxine therapy has been shown to be beneficial in restoring a euthyroid state and improving surrogate markers for cardiovascular function (Pearse, et al., 2013).

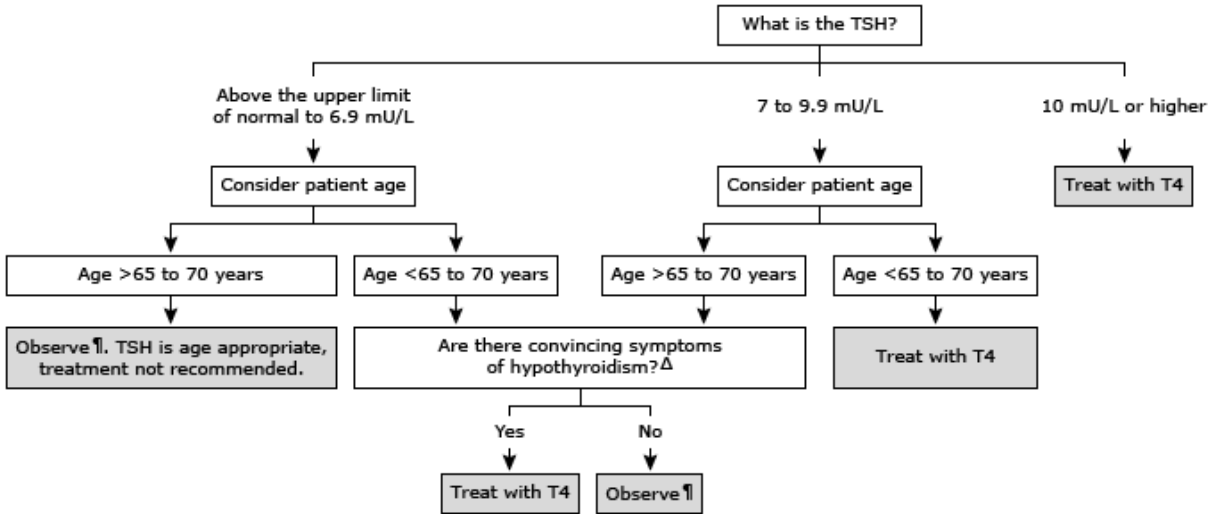
Metabolic syndrome is a consequence of a prolonged hypothyroid state with manifestation of dyslipidemia, abdominal obesity, glucose intolerance and hypertension. Numerous studies have documented the positive relationship between serum TSH and dyslipidemia. Interestingly, gender differences were observed in recent studies showing the effect of serum TSH level on lipid profiles. It appears the difference in lipid profiles increase with age and is more pronounced among women. Results from two large meta-analysis demonstrated an improvement in lipid profiles among SCH patient treated with L-T4. The findings were confirmed by numerous small randomized controlled trials which reported a decrease in serum TC and LDL levels among SCH patients treated with L-thyroxine (Pearse, et al., 2013)



Based on the prevalence of undiagnosed SCH and the risk of disease progression culminating in the development of the previously mentioned cardiovascular endpoints, leading organizations have developed screening criteria for the detection of hypothyroidism in asymptomatic patients. The AACE/ATA recommend measures of TSH in individuals at risk of hypothyroidism and in patients older than 60 years of age. The American academy of family physicians (AAFP) recommends periodic assessment of thyroid function in older women, while the American college of physicians specify screening for women older than 50 years. The USPSTF differs in their recommendation, citing insufficient evidence to assess for benefits and harms associated with screening. Thus far, screening for hypothyroidism and early treatment for hypothyroidism has failed to show improvement in clinical outcomes especially when measuring quality of life indicators.

The findings from this case study appear to support the treatment for SCH with L-T4 based on the following clinical features. Treatment is recommended for patients less than 65 years old. Women above 50 years old are at increased risk for SCH and thus would benefit from periodic screening and early treatments. The presence of anti-thyroid peroxidase (Anti-TPO) is predictive for overt hypothyroidism and thus L-T4 is suggested for these patients. A serum TSH > 7mIU/L is associated with increased incidence of cardiovascular disease, while a level >10mIU/L correlates with cardiovascular events among the young and middle-aged adults. Serum TSH levels appear to increase with age, but this increase is not associated with increase mortality among adults > 70 years of age. Current studies show the risk of harm associated with L-T4 therapy to be small compared to the severe cardiovascular endpoints associated with non-treatment. When considering the documented reversal effects of levothyroxine as it related to heart failure, coronary vascular disease and hyperlipidemia, replacement therapy should receive serious consideration especially among adult females less than 65 years of age with a diagnosis of SCH.

*Treatment algorithm for levothyroxine replacement among non-pregnant adults with subclinical hypothyroidism.*



(Ross, 2018)

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