

Elevated cardiovascular and renal risk factors in women with subclinical hypothyroidism are normalized by levothyroxine-replacement therapy

Adrees M, Gibney J, El-Saeity N, Boran G. Effects of 18 months of L-T₄ replacement in women with subclinical hypothyroidism. Clin Endocrinol (Oxf) 2009;71:298-303.

SUMMARY

BACKGROUND Overt hypothyroidism is associated with clinically apparent hemodynamic effects, including bradycardia and reduced cardiac output, and other serious effects on the heart such as reduced blood volume, increased systemic vascular resistance, diastolic hypertension, and reductions in renal blood flow. Hypothyroidism is also associated with dyslipidemia and carotid artery intima-media thickness, which may improve with short-term levothyroxine (L-T₄) replacement therapy. Cardiovascular and renal abnormalities that are seen in overt hypothyroidism also have been found in subclinical hypothyroidism (SCH). The aim of this study was to compare cardiovascular and renal variables in healthy women with those in women with SCH, and to assess the effects of L-T₄ replacement in women with SCH treated over 18 months.

METHODS This is a cross-sectional study of 64 patients from a cohort of 1895 patients with biochemical evidence of SCH. The inclusion criteria for the study were female sex and age 30 through 60 years with SCH, defined as persistent serum thyrotropin (TSH) elevation with normal serum free thyroxine (FT₄) for 6 months prior to commencement of the study. During the 6-month follow-up, a euthyroid status spontaneously developed in 4 individuals, who were thus excluded from the study, and 4 dropped out of the study because they could not follow the protocol. Four others were excluded from the

analysis because of celiac disease (n = 1), pernicious anemia (n = 1), and the need for antihypertensive therapy (n = 1). A total of 56 patients were assessed for cardiovascular risk factors before L-T₄ treatment and 52 were evaluated after 18 months of L-T₄ therapy. At the same time, 56 healthy women were also evaluated. All patients were assessed for carotid artery intima-media thickness, a surrogate marker for atherosclerosis, before and after L-T₄-replacement therapy for 18 months. Healthy women of similar age were also studied. Blood pressure (BP), plasma lipids, homocysteine, and estimated renal glomerular filtration rate (eGFR) were also evaluated during the study periods.

RESULTS

Patient Demographics (Figure 1)

The mean (±SD) age of women with SCH was 50±9 and 52±10 years during the pretreatment and posttreatment periods, respectively, and was 47±8 years in healthy women. Other demographic variables were as follows. The mean body-mass index (the height in meters divided by the square of the weight in kilograms) was 25.5±4.0, 24.9±4.2, and 25.7±4.0, in the pretreatment and posttreatment intervals in women with SCH and in healthy women, respectively. Mean FT₄ was 10.4±5.4, 18.0±2.3, and 15.8±2.2 pmol/L (P<0.001, as compared with FT₄ values in healthy women, and as compared with the pretreatment and posttreatment FT₄ values) (Figure 1).

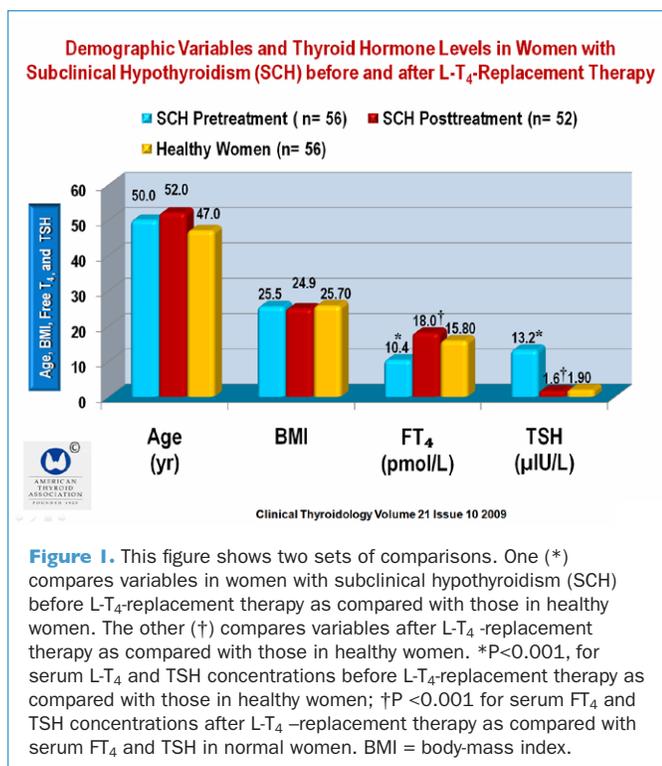
Mean serum TSH was 13.2±4.5, 1.6±1.8, and 1.9±1.0 μIU/ml during pretreatment and posttreatment periods and in healthy women, respectively (P<0.001, comparing paired pretreatment and posttreatment values in women with SCH; and P = 0.001, comparing the pretreatment TSH values in patients with SCH as compared with those in healthy women) (Figure 1).

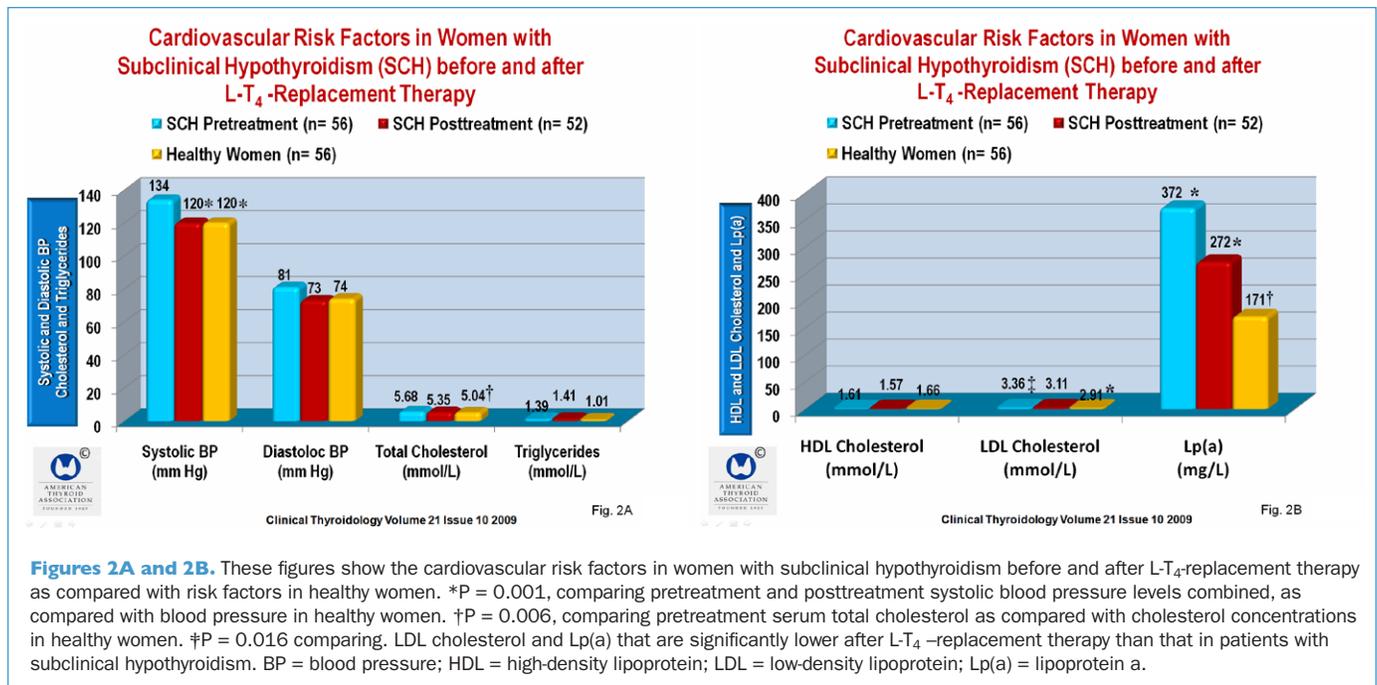
Thyroperoxidase antibodies were positive in 42 women with SCH (75%), negative in 48 healthy women, and equivocal in the others. All women with SCH tolerated L-T₄-replacement therapy. The mean dose of L-T₄ normalizing the serum TSH was 100±30 μg/day.

The Cardiovascular Risk Factors before and after L-T₄ Therapy (Figures 2A and 2B)

The systolic BP was 134±120 and 120±15 mm Hg in the women with SCH (P = 0.0001, comparing pretreatment and posttreatment (paired) values and 120±13 mm Hg in healthy women (P = 0.0001, comparing pretreatment BP values in women with SCH with those in healthy women).

The diastolic BP was 81±10 and 73±8 mm Hg in the women with SCH (P = 0.005, comparing paired pretreatment and posttreatment values) and 74±3 mm Hg in the healthy women (P = 0.0001, comparing the pretreatment values in women with SCH with those in healthy women).





The mean total cholesterol was 5.68±1.07 and 5.35±1 mmol/L in women with SCH (P = 0.023, comparing paired pretreatment and posttreatment values) and 5.04±0.8 mmol/L in healthy women (P = 0.001, comparing pretreatment values in women with SCH with those in healthy women) (Figure 2A).

The mean serum triglycerides were 1.39±0.7 and 1.41±0.7 mmol/L in women with SCH (P = 0.14, comparing paired pretreatment and posttreatment values) and 1.01±0.43 mmol/L in the healthy women (P= 0.0001, comparing pretreatment values in women with SCH with those in healthy women).

The mean high-density lipoprotein (HDL) cholesterol levels were 1.61±0.7 and 1.57±0.4 mmol/L in women with SCH (P = 0.28, comparing paired pretreatment and posttreatment values) and 1.66±0.44 mmol/L in healthy women (P = 0.33, comparing the pretreatment values in women with SCH with those in healthy women).

The mean low-density lipoprotein (LDL) cholesterol levels were 3.36±0.9 and 3.11±0.85 mmol/L in women with SCH (P = 0.18, comparing paired pretreatment and posttreatment values) and 2.91±0.74 mmol/L in the healthy women (P = 0.016, comparing the pretreatment values in women with SCH with those in healthy women).

The lipoprotein a (Lp(a)) cholesterol levels were 372±53 and 272±38.7 mmol/L in women with SCH (P = 0.18, comparing paired pretreatment and posttreatment Lp(a)), and 1.71±25.5 mmol/L in the healthy women (P= 0.016, comparing the pretreatment values with those in healthy women).

The Renal Function Indexes before and after L-T₄-Replacement Therapy in Women with SCH (Figure 3)

Urea concentrations were 4.6±1.07 and 4.4±0.9 mmol/L in the women with SCH (P = 0.008, comparing paired pretreatment

and posttreatment values) and 4.6±1.5 mmol/L in healthy women (P = 0.25, comparing the pretreatment values with the urea values in healthy women).

Creatinine was 84±11 and 77±10 µmol/L in women with SCH (P = 0.008, comparing paired pretreatment and posttreatment values) and 0.78±7 µmol/L in healthy women (P = 0.001, comparing the pretreatment values with the creatinine values in healthy women).

The estimated glomerular filtration rate (eGFR) was 69±4 and 73±5 ml/min in women with SCH (P = 0.001, comparing paired pretreatment and posttreatment values) and 75±3 ml/min in healthy women (P= 0.001, comparing the pretreatment values in women with SCH with the eGFR values in healthy women).

Creatinine was 84±11 and 77±10 µmol/L in women with SCH, (P = 0.008, comparing paired pretreatment and posttreatment values) and 0.78±7 µmol/l in healthy women (P = 0.001, comparing the pretreatment values with the creatinine values in healthy women).

Cystatin C (cystatin C or cystatin 3 (formerly gamma trace, post-gamma-globulin or neuroendocrine basic polypeptide, which is a protein encoded by the CST3 gene, is mainly used as a biomarker of kidney function). Cystatin C was 0.91±0.2 and 0.78±0.1 mg/L in women with SCH (P = 0.001, comparing paired pretreatment and posttreatment levels) and 0.76±0.1 mg/L in healthy women (P = 0.001, comparing the pretreatment values in women with SCH with the cystatin C values in healthy women).

Mean pretreatment common carotid artery (CCA) diameter was 6.13±0.05 mm in women with SCH, and mean posttreatment CCA was 6.57 (P = 0.003, comparing pretreatment and posttreatment CCA diameter) (Figure 4).

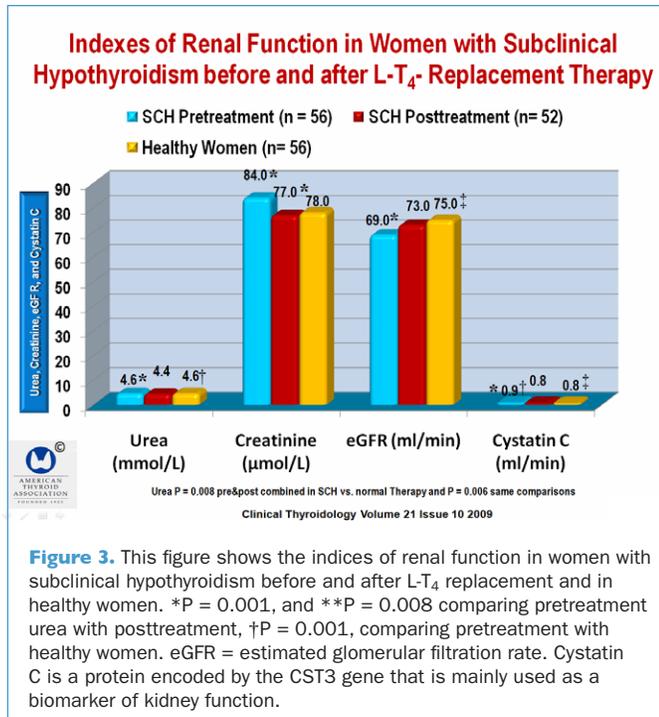


Figure 3. This figure shows the indices of renal function in women with subclinical hypothyroidism before and after L-T₄ replacement and in healthy women. *P = 0.001, and **P = 0.008 comparing pretreatment urea with posttreatment, †P = 0.001, comparing pretreatment with healthy women. eGFR = estimated glomerular filtration rate. Cystatin C is a protein encoded by the CST3 gene that is mainly used as a biomarker of kidney function.

Before and after L-T₄-replacement therapy, mean common carotid artery intima-media thickness was 0.82±0.2 and 0.71±0.2 mm (P = 0.046). Likewise, mean brachial artery diameter was 32±0.5 and 4.0±0.1 mm, before and after L-T₄-replacement therapy (P = 0.001). The percent change in brachial artery diameter before and after L-T₄-replacement therapy was 15.6±2.8 and 4.0±0.1%, respectively (P = 0.001). Sublingual glyceryl nitrate (GTN) increased the brachial artery diameter from 3.8±0.1 mm in the pretreatment assessment

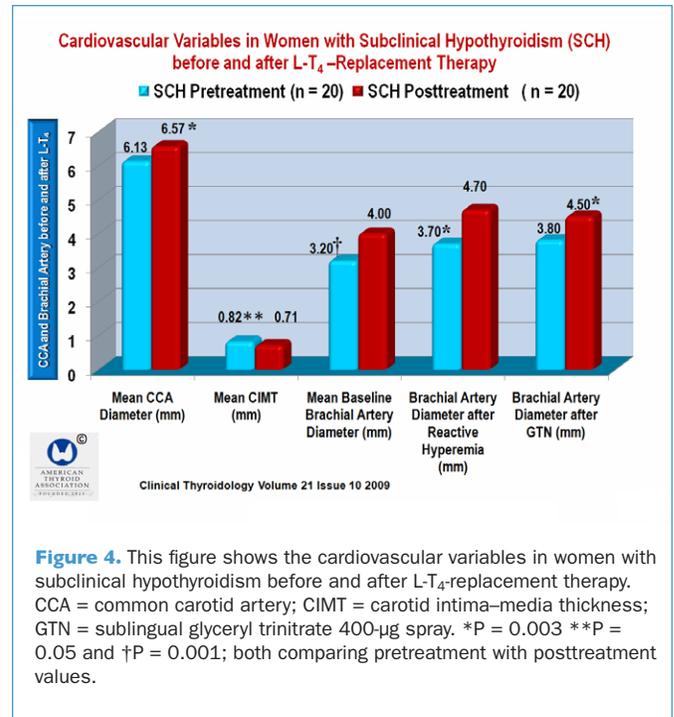


Figure 4. This figure shows the cardiovascular variables in women with subclinical hypothyroidism before and after L-T₄-replacement therapy. CCA = common carotid artery; CIMT = carotid intima-media thickness; GTN = sublingual glyceryl trinitrate 400-μg spray. *P = 0.003 **P = 0.05 and †P = 0.001; both comparing pretreatment with posttreatment values.

and 4.5±0.5 mm in the posttreatment assessment (P = 0.046); the percent increases were 15.6±2.8% and 17.5±1.2% before and after GTN, respectively.

CONCLUSION Cardiovascular risk factors increase and renal function declines in women with subclinical hypothyroidism. However, treatment with levothyroxine-replacement therapy also improves cardiac risk factors and renal function.

COMMENTARY

The study by Adrees et al. is a cross-sectional retrospective study of 64 patients with biochemical evidence of SCH. The study group, which comprised women ages 30 through 60 years with SCH, had persistent elevation of serum TSH with FT₄ for 6 months prior to commencement of the study. After L-T₄-replacement therapy for 18 months, there was significant improvement in blood pressure, plasma lipids and homocysteine, and significantly reduced carotid intima-media thickness, a surrogate for reduced progression of atherosclerosis.

Although there is evidence that cholesterol and lipoprotein metabolism is altered with SCH, controversy remains concerning the risk of cardiovascular disease (CVD) that is associated with SCH. A meta-analysis by Danese et al. (1), found that all of the 1786 published studies reported changes in serum total cholesterol concentrations during L-T₄-replacement therapy in patients with SCH. Twelve studies reported triglyceride changes, 10 HDL cholesterol changes, and 9 LDL cholesterol changes, and the decline in serum total cholesterol was directly proportional to baseline concentrations. In contrast, patients with hypothyroidism who received suboptimal doses of L-T₄ had significantly larger declines in serum total cholesterol after TSH was normalized than did untreated individuals with SCH.

However, serum HDL cholesterol and triglyceride concentrations showed no change. The authors concluded that the results suggested that L-T₄-replacement therapy for individuals with SCH lowers mean serum total cholesterol and LDL cholesterol concentrations and that the reduction in serum total cholesterol may be larger in individuals with higher pretreatment cholesterol levels and in hypothyroid individuals taking suboptimal doses of L-T₄. The authors found no significant effects of L-T₄ on serum HDL or triglyceride concentrations.

A 2006 study by Cappola et al. (2) of 3233 U.S. community-dwelling individuals aged 65 years or older found no differences between SCH or overt hypothyroidism and euthyroidism for cardiovascular outcomes or mortality. Subclinical hypothyroidism had an adjusted hazard ratio of 1.07 (95% confidence interval, 0.90 to 1.28) for coronary heart disease. In short, the data did not support the hypothesis that unrecognized SCH is associated with other cardiovascular disorders or mortality.

Others find an effect of L-T₄ on cardiac function and structure in patients with SCH. A double-blind, placebo-controlled study by Monzani et al. (3) found that L-T₄-treated patients had a significant reduction of the cardiac preejection/ejection time (PEP/ET) ratio (P<0.05) and an increase in isovolumic relaxation time (P<0.05)

A case-control study by Nagasaki et al. (4) evaluated whether L-T₄ replacement might cause regression of the intima-media thickness (IMT) in the common carotid artery (CCA). Thirty-five hypothyroid patients were examined for their CCA IMT before and 1 year after normalization of thyroid function by L-T₄ replacement. As compared with 35 healthy controls, mean (\pm SE) basal CCA IMT was significantly higher in patients with hypothyroidism (0.635 ± 0.018 mm) as compared with control subjects (0.559 ± 0.021 mm, $P<0.005$). After 1 year of L-T₄ therapy that achieved euthyroidism in 34 of 35 patients, there was a significant decrease of CCA IMT (0.552 ± 0.015 mm, $P<0.0001$) that was comparable to that among the healthy controls. The CCA IMT change was closely associated with basal levels of total cholesterol ($r = -0.472$, $P = 0.0031$), LDL cholesterol ($r = -0.441$, $P = 0.0076$) and the HDL/total cholesterol ratio ($r = -0.435$, $P = 0.0057$). The authors concluded that L-T₄ therapy might have the potential to reverse the progression of atherosclerosis in hypothyroid patients. They further suggested that increased levels of LDL cholesterol and the total/HDL cholesterol ratio may have an important role in the increased in CCA IMT of patients with hypothyroidism.

The study by Adrees et al. confirmed the above findings, including increased levels of Lp(a) and homocysteine levels in SCH that also improved after L-T₄-replacement therapy. The authors suggest that these effects are clinically significant, as supported by the observed reduction in CIMT—which is currently the most widely accepted surrogate marker of atherosclerosis and is independently predictive of stroke and myocardial

infarction—after L-T₄ replacement. Moreover, Monzani et al. also found reduced CIMT after L-T₄-replacement therapy in a 12-week study (3). Others also have observed a beneficial effect of L-T₄ on cardiovascular risk factors and endothelial function (5;6)

Adrees et al. suggest that increased arterial vasodilatation might explain the increase in eGFR that was found after L-T₄-replacement therapy. They argue that GFR is reduced in overt hypothyroidism. For example, den Hollander et al. (7) found a strong correlation between the change in thyroid status after L-T₄-replacement therapy and the change in renal function as a result of therapy expressed as serum creatinine ($r^2 = 0.81$, $P<0.0001$) and estimated GFR (0.69 , $P<0.0001$). Thus, the kidney seems to be an important target of thyroid hormone action in patients with SCH. There is one small cross-sectional study that found no difference in eGFR in subjects with SCH. Adrees et al. found that eGFR was normalized with L-T₄-replacement therapy in their patients with SCH. This was supported by the observation that cystatin C, a biomarker of renal function (8;9). Adrees suggest that the clinical implications of change in renal function are as yet unknown.

The final conclusion by Adrees et al. that normalization of cardiovascular risk factors following L-T₄-replacement therapy in SCH potentially explains reduced CIMT seems to be a reasonable conclusion from the data reported in this study.

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References

1. Danese MD, Ladenson PW, Meinert CL et al. Clinical review 115: effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. *J Clin Endocrinol Metab* 2000;85:2993-3001.
2. Cappola AR, Fried LP, Arnold AM et al. Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA* 2006;295:1033-41.
3. Monzani F, Di B, V, Caraccio N et al. Effect of levothyroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebo-controlled study. *J Clin Endocrinol Metab* 2001;86:1110-5.
4. Nagasaki T, Inaba M, Henmi Y et al. Decrease in carotid intima-media thickness in hypothyroid patients after normalization of thyroid function. *Clin Endocrinol (Oxf)* 2003;59:607-12.
5. Razvi S, Ingoe L, Keeka G et al. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. *J Clin Endocrinol Metab* 2007;92:1715-23.
6. Taddei S, Caraccio N, Virdis A et al. Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. *J Clin Endocrinol Metab* 2003;88:3731-7.
7. den Hollander JG, Wulkan RW, ManteI MJ et al. Correlation between severity of thyroid dysfunction and renal function. *Clin Endocrinol (Oxf)* 2005;62:423-7.
8. Perianayagam MC, Seabra VF, Tighiouart H et al. Serum Cystatin C for Prediction of Dialysis Requirement or Death in Acute Kidney Injury: A Comparative Study. *Am J Kidney Dis* 2009.
9. de Boer IH, Katz R, Cao JJ et al. Cystatin C, albuminuria, and mortality among older adults with diabetes. *Diabetes Care* 2009;32:1833-8.

www.thyroid.org/patients/ct/index.html