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# Changes in Liver Function correlate with the Improvement of Lipid Profile after Restoration of Euthyroidism in Patients with Subclinical Hypothyroidism

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## ABSTRACT

Overt hypothyroidism frequently leads to liver dysfunction. Subclinical hypothyroidism (SCH) is linked to abnormalities of lipoprotein metabolism, however, data on liver function are lacking. We analyzed the effects of L-thyroxine (L-T4) therapy on liver function and their association with changes of serum lipoproteins in SCH as part of a prospective, double-blind study. 66 women with SCH were randomly assigned to receive either L-thyroxine or placebo for 48 weeks. Circulating liver and biliary enzymes as well as serum lipid levels were assessed at baseline and after 24 and 48 weeks. Alkaline phosphatase as parameter of hepato-biliary function increased after 48 weeks of L-T4 treatment ($p=0.004$). Circulating levels of alanine amino transferase (ALT) and serum aspartate transferase (AST) did not change during L-T4 treatment. However, there was a correlation between both, ΔAST and ΔALT with Δ-total cholesterol ($r=0.60$, $p<0.001$ and $r=0.52$, $p=0.002$, respectively). Similarly, both, ΔAST and ΔALT, correlated with ΔLDL cholesterol (LDL-C), respectively. Consecutively, patients with marked decrease of serum lipids during L-T4 therapy had a significantly higher decrease in AST and ALT, respectively, as compared to patients without amelioration of the lipid profile. Thyroid hormone replacement in SCH affects biliary tract function, yet, has no overall effect on hepatocellular enzymes. The relatively strong correlation between changes of serum AST and ALT with changes of LDL-C levels suggests that the mechanism of decreased LDL-C observed in restoration of euthyroidism in patients with SCH might be caused in part by changes of hepatic lipoprotein catabolism and a restored hepato-cellular function.

**Key words:** Hypothyroidism, thyroxine, liver

## INTRODUCTION

Normal circulating levels of thyroid hormones are required for both, normal hepatic function and normal bilirubin metabolism (Fagiuoli et al., 1993). Hence, overt thyroid dysfunctions are frequently associated with abnormalities of biochemical liver tests and in severe forms with histologically evident hepatocellular damage (Muller et al., 1994; Klion et al., 1971). In addition, bile flow and biliary output of bilirubin and bile salts are reduced in severe thyroid failure (Van Steenbergen et al., 1989).

In patients with overt hypothyroidism (OH), L-thyroxine (L-T4) treatment reduces elevated serum total and low density lipoprotein cholesterol (LDL-C) concentrations as well as circulating apolipoprotein A, B and E concentrations (O'Brien et al., 1997). The mechanisms accounting for these changes of serum lipid concentrations are complex. In OH alterations of hepatic function might play an important role since, for example, the activity of hepatic lipase is decreased (Tan et al., 1998; Packard et al., 1993).

Subclinical hypothyroidism (SCH) is characterized by the finding of elevated TSH levels in the presence of normal circulating thyroid hormones (Cooper, 2001). A significant decrease of total and LDL-C after physiological L-T4 therapy in SCH has been shown by our group and others (Meier et al., 2001; Danese et al., 2000). However, the mechanisms accounting for these changes have not been investigated and there are no data on liver function tests in SCH. Therefore, the aim of our study was to investigate the effect of L-T4 replacement on circulating levels of hepatic and biliary function using a double-blind placebo-controlled study design and to investigate a possible correlation between changes of liver function and changes of serum lipoproteins.

## MATERIALS AND METHODS

*Study Subjects and Design*

The present analysis was part of a prospective, double blind, placebo-controlled study, whose design and patient characteristics have been described previously (Meier et al., 2001). Briefly, between September 1993 and May 1997, 66 women with SCH were enrolled in the study. All patients were examined and followed-up in the Thyroid Research Unit of the Division of Endocrinology, Department of Medicine, University Hospital Basel, Switzerland. Patients aged 18 to 75 years, who had TSH levels higher than 5.0 mIU/L on two consecutive blood measurements, an exaggerated TSH response after TRH stimulation, free T4 concentration within the normal range, and were in good general health were included.

A total of 63 women (mean age 58.5 ± 1.3 yrs) completed the study according to the study protocol, with no serious adverse events reported. The underlying thyroid disorders leading to SCH consisted of autoimmune thyroiditis (n=32), Graves' disease (n=21; previously treated with radioiodine, surgery or carbimazole), toxic multinodular goiter (n=1, previously treated with radioiodine), surgically resected goiter (n=6) and idiopathic SCH (n=3). The frequencies of underlying thyroid disorders were equally distributed in the L-thyroxine and placebo groups. Lipid lowering agents were stopped at least 6 months before enrollment to the study.

Alcohol intake, assessed as daily intake of wine, beer and other spirits (glasses/d) was not significantly different between both groups. During the course of the study the use of other medications was registered. In summary, the following over the counter and prescribed drugs were taken: non-steroidal anti-inflammatory drugs (L-T4-Group: 5/31, Placebo-Group: 3/32), benzodiazepines (T4-Group: 4/31, Placebo: 3/32), barbiturates (T4-group: 0/31, Placebo-group: 1/32), diuretics (T4-group: 1/31, Placebo: 1/32), β-blockers (T4-group: 3/31, Placebo 3/32), bisphosphonates (T4-group 0/31, Placebo 2/32), magnesium (T4-group 2/31, Placebo 0/32), haloperidol (T4-group: 1/31, Placebo 0/32), nitroglycerin (T4-group: 1/31, Placebo 0/32) calcium antagonists (T4-group: 1/31, Placebo 0/32) and ACE-Inhibitors (T4-group: 2/31, Placebo 1/32 ). The intake of none of

these drugs was different in the T-4 treated group as compared to the placebo group.

*Assay methods*

Serum samples were collected in the fasting state, immediately put on ice and processed within 30 min. They were kept frozen at -70°C until assayed. Laboratory analyses were performed at the Department of Central Laboratories at the University Hospital Basel. Serum concentrations of hormones, lipids and liver enzymes were assessed at baseline and after 24 and 48 weeks. Serum TSH concentration (reference range, 0.3-4.0mU/L) was measured with an immunometric assay (Delfia, Wallac, Inc., Turku, Finland). Free T4 (8.0-23.0 pmol/L) and total T3 (1.2-3.1 nmol/L) were determined by microparticle enzyme immunoassays (IMx, Abbott Laboratories, Inc., Chicago, IL). Alanine amino transferase (ALT, reference range 10-37 U/L), serum aspartate transferase (AST, 11-36 U/L), gamma- glutamyl transpeptidase (gamma-GT, 8-66 U/L), total alkaline phosphatase (ALP, 31-108 U/L), bilirubin (5-26 μmol/L), globulin (18-34 g/L) and albumin (38-52 g/L) were measured by Hitachi 917 (Roche, Rotkreuz, Switzerland). Bone alkaline phosphatase (B-ALP, 8.0-16.6 μg/L) was determined using an immunometric assay (Tandem-MP Ostase, Beckman Coulter, Fullerton, USA).

Total cholesterol (reference range 3.0-5.2mmol/L) and high density lipoprotein cholesterol (HDL-C, 0.9-2.2 mmol/L) were assayed enzymatically by automated procedures (Roche, Rotkreuz, Switzerland). LDL-C levels (1.6-3.4mmol/L) were calculated using the formula of Friedewald. Apolipoprotein AI (0.95-2.0g/L) was measured using immunonephelometry (Beckman instruments, Inc./Hybritech, Palo Alto CA). For the original study, thyroid hormones and lipid values were both measured in duplicate at each time point within two weeks (Meier et al., 2001). In contrast, other parameters, e.g. liver function tests, were only measured once, at the first visit. For our analyses shown in this paper we therefore included only data of thyroid hormones and lipids of the first visit. The study was approved by the local ethical committee. All patients gave their written informed consent to participate in the trial.

*Statistical analyses*

All data are expressed as means ± standard deviation (SD) in text and tables and as means ± standard error of the mean (SEM) in figures. Unpaired t-test (two-sided) or Mann-Whitney U test in case of nonparametric distribution was used to show differences between both groups, as appropriate. We calculated delta (Δ)-values of all parameters by subtracting pretreatment values from posttreatment values. Treatment effects in the L-thyroxine or placebo group were analyzed by paired Student's t-test or by Wilcoxon signed rank test, respectively. Two-tailed P values $<0.05$ were considered statistically significant. Data were analyzed using Statistica for Windows (version 5.0, StatSoft, Inc., Tulsa, OK) and were analyzed by intention to treat.

## RESULTS

*Baseline characteristics*

At baseline the two groups of women with SCH (L-T4, n=31; placebo, n=32) were similar with respect to age, body mass index, alcohol consumption as well as medication intake. In both groups, basal TSH levels were elevated with an exaggerated TSH response of more than 35 mU/L after TRH administration. Peripheral thyroid hormone concentrations (fT4 and T3) were within the lower reference range. The patient groups were also well-balanced regarding baseline circulating liver enzymes, bilirubin, albumin and globulin as well as serum lipid levels **(Table 1)**.

**Table 1.** Baseline characteristics of the subjects

| Characteristics | **L-thyroxine group** (n=31) | **Placebo group** (n=32) |
|---|---|---|
| Age (yrs) | 57.3 ± 9.6 | 57.0 ± 10.9 |
| BMI (kg/m$^2$) | 24.5 ± 3.0 | 26.1±4.1 |
| Alcohol (glasses/d) | 0.3 ± 0.5 | 0.2 ± 0.4 |
| Thyrotropin (0.3-4 mIU/L) | 14.1 ± 9.8 | 11.4 ± 5.8 |
| Free thyroxine (8.0-23.0 pmol/L) | 11.8 ± 1.6 | 12.2 ± 1.4 |
| Triiodothyronine (1.2-3.1 nmol/l) | 2.0 ± 0.5 | 1.9 ± 0.3 |
| Gamma-GT (8-66 U/L) | 17.6 ± 10.4 | 20.8 ± 15.7 |
| Total ALP (31-108 U/L) | 63.3 ± 20.8 | 69.7 ± 28.1 |
| Bone specific ALP (8.0-16.6 μg/L) | 9.6 ± 4.1 | 10.2 ± 4.8 |
| Bilirubin (5-26 μmol/L) | 10.5 ± 4.0 | 12.5 ± 7.9 |
| Albumin (38-52 g/L) | 42.7 ± 3.7 | 42.8 ± 4.0 |
| Globulin (18-34 g/L) | 29.7 ± 4.6 | 30.5 ± 5.2 |
| AST (11-36 U/L) | 19.8 ± 7.3 | 19.4 ± 5.5 |
| ALT (10-37 U/L) | 18.2 ± 9.4 | 21.3 ± 15.1 |
| Total cholesterol (3.0-5.2 mmol/L) | 6.3 ± 0.9 | 6.1 ± 1.3 |
| LDL-C (1.6-3.4 mmol/L) | 4.0 ± 1.0 | 3.8 ± 1.3 |
| HDL-C (0.9-2.2 mmol/L) | 1.7 ± 0.4 | 1.6 ± 0.4 |
| Triglycerides (0.5-2.3 mmol/L) | 1.3±0.5 | 1.5 ± 0.9 |
| Apolipoprotein B-100 (0.65-1.35 g/L) | 1.3 ± 0.6 | 1.2 ± 0.3 |

Statistical significance was assessed by unpaired t-test (two-sided) or by Mann-Whitney U test in nonparametrically distributed data. All characteristics at baseline were similar between both treatment groups.

*Effect of treatment on thyroid hormone concentrations*

In L-T4-treated patients, TSH concentration decreased and remained within the reference range at least for the last 24 weeks. Mean serum TSH level at the end of the study was 3.1 ± 1.6 mU/L. No patient had a blunted or absent TSH response to thyrotropin-releasing hormone, thereby excluding over-treatment. Peripheral thyroid hormone concentrations (fT4 and T3) remained within the reference range. As expected, no change in any variable of thyroid function could be seen in patients treated with placebo **(Table 2)**.

**Table 2.** Parameters before and 48 weeks after treatment with L-T4 or placebo

| | Treatment with L-thyroxine (n=31) | | | Treatment with Placebo (n=32) | | |
|---|---|---|---|---|---|---|
| Variable | Before treatment | After 48 weeks | p | Before treatment | After 48 weeks | p |
| Thyrotropin (0.3-4 mIU/L) | 14.1 ± 9.8 | 3.1± 1.6 | <0.001 | 11.4 ± 5.8 | 9.9 ± 3.3 | ns |
| Free thyroxine (8.0-23.0 pmol/L) | 11.8 ± 1.6 | 18.2 ± 3.4 | <0.001 | 12.2 ± 1.4 | 12.5 ± 2.5 | ns |
| Triiodothyronine (1.2-3.1 nmol/l) | 2.0 ± 0.5 | 1.7 ± 0.1 | <0.001 | 1.9 ± 0.3 | 1.9 ± 0.1 | ns |
| Gamma-GT (8-66 U/L) | 17.6 ± 10.4 | 19.8 ±16.1 | ns | 20.8 ± 15.7 | 17.6 ± 10.3 | 0.03 |
| Total ALP (31-108 U/L) | 63.3 ± 20.8 | 68.0 ± 25.6 | 0.004 | 69.7 ± 28.1 | 68.0 ± 28.3 | ns |
| Bone specific ALP (8.0-16.6 μg/L) | 9.6 ± 4.1 | 10.2 ± 4.5 | ns | 10.2 ± 4.8 | 9.8 ± 4.7 | ns |
| Bilirubin (5-26 μmol/L) | 10.5 ± 4.0 | 11.5 ±5.1 | ns | 12.5 ± 7.9 | 11.9 ± 6.1 | ns |
| Albumin (38-52 g/L) | 42.7 ± 3.7 | 40.6 ± 4.6 | 0.04 | 42.8 ± 4.0 | 41.7 ± 4.3 | ns |
| Globulin (18-34 g/L) | 29.7 ± 4.6 | 32.6 ± 5.4 | 0.01 | 30.5 ± 5.2 | 32.5 ± 5.1 | ns |
| AST (11-36 U/L) | 19.8 ± 7.3 | 20.4 ± 5.1 | ns | 19.4 ± 5.5 | 19.8 ± 6.4 | ns |
| ALT (10-37 U/L) | 18.2 ± 9.4 | 18.3 ± 7.8 | ns | 21.3 ± 15.1 | 18.5 ± 11.2 | ns |
| Total cholesterol (3.0-5.2 mmol/L) | 6.3 ± 0.9 | 6.1 ± 1.1 | 0.02 | 6.1 ± 1.3 | 6.0 ± 1.1 | ns |
| LDL-C (1.6-3.4 mmol/L) | 4.0 ± 1.0 | 3.7 ± 0.9 | 0.004 | 3.8 ± 1.3 | 3.7 ± 0.9 | ns |
| HDL-C (0.9-2.2 mmol/L) | 1.7 ± 0.4 | 1.7 ± 0.4 | ns | 1.6 ± 0.4 | 1.6 ± 0.4 | ns |
| Triglycerides (0.5-2.3 mmol/L) | 1.3 ± 0.6 | 1.3 ± 0.5 | ns | 1.5 ± 0.9 | 1.5 ± 0.9 | ns |
| Apolipoprotein B-100(0.65-1.35 | 1.3 ± 0.3 | 1.2 ± 0.3 | 0.04 | 1.2 ± 0.3 | 1.2 ± 0.3 | ns |

Significance was determined by paired t test (two-sided) or by Wilcoxon matched pair test in case of nonparametric distribution.

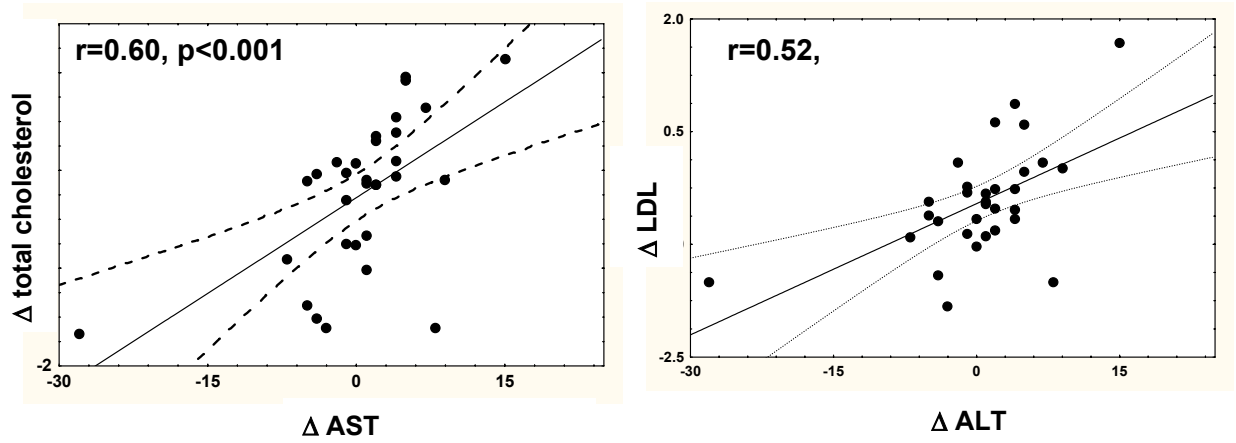
*Effect of treatment on serum lipid concentrations and liver function*

After 48 weeks of L-T4 treatment, total cholesterol, LDL-C and Apolipoprotein B-100 levels were significantly reduced, whereas HDL-C, triglycerides and apolipoprotein AI levels as well as lipoprotein(a) remained unchanged **(Table 2)**.

Total ALP levels increased after 24 and 48 weeks, respectively (p = 0.05 and 0.004). B-ALP did not alter significantly after 48 weeks of treatment. Gamma-GT tended to increase after 24 weeks of L-T4 treatment (p=0.06), however, remained unchanged after 48 weeks. After 48 weeks, circulating globulin levels increased (p=0.01), whereas serum albumin concentrations decreased significantly (p=0.04). Serum bilirubin levels were transiently increased after 24 weeks (p=0.04) without a significant treatment effect after 48 weeks. In the placebo group, there was no treatment effect, with the exception of a significant decrease of gamma-GT after 48 weeks **(Table 2)**.

There was no overall significant treatment effect on the hepatic enzymes AST and ALT in the L-T4-treated group. However, there was a positive correlation between the changes of circulating total cholesterol (Δ-total-cholesterol) and Δ-LDL-C and both the Δ-AST levels (r=0.60, p<0.001 and r=0.52, p=0.002, respectively) **(Figure 1)** as well as the Δ-ALT level (r=0.51, p=0.004 and r=0.38, p=0.03).

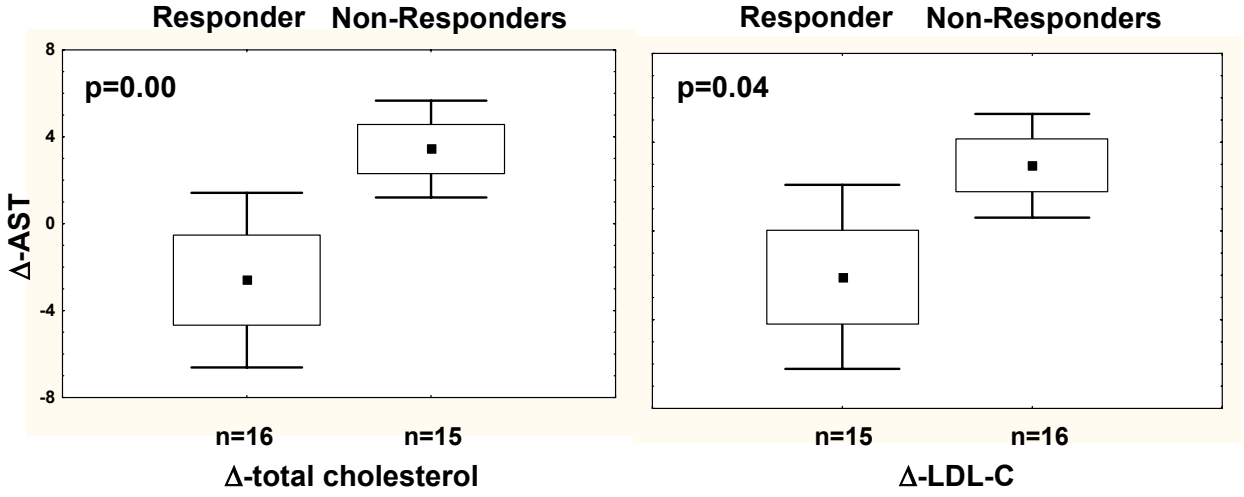
**Figure 1** Correlations between the changes of circulating total cholesterol (delta (Δ) cholesterol) and LDL-cholesterol (delta (Δ) LDL-cholesterol), respectively and Δ-aspartate transferase (Δ-AST) in the L-T4 group.




Similarly, we found a significant correlation between Δ-Apolipoprotein B and Δ-AST (r=0.35, p=0.05) and Δ-ALT (r=0.47, p=0.007). In contrast, there was no significant correlation between these parameters in the placebo group. Consequently, in the patients group with best treatment effect on L-T4 therapy (Δ-total cholesterol levels above the median and Δ-LDL-C above the median, i.e. "responders"), Δ-AST levels were significantly higher than in the group with Δ-total cholesterol and Δ-LDL-C levels below the median (i.e. "non-responders") **(Figure 2)**. Correlations for Δ-cholesterol levels with Δ-ALT levels showed similar results.

In contrast, correlations between Δ-lipid levels and the Δ-values of biliary parameters gamma-GT, ALP and bilirubin were not significant. Similarly, we found no influence of alcohol intake, menopausal state, intake of drugs other than L-T4 or placebo, respectively, or body mass index on different parameters of liver function.

**Figure 2** Comparison of changes of liver enzymes (Δ-AST) in patients with good treatment effect on L-T4 (Δ-total cholesterol levels and Δ-LDL-cholesterol levels, respectively, above the median, e.g. responders) and in patients without treatment effect on L-T4 (Δ-total cholesterol levels and Δ-LDL-cholesterol levels, respectively, below the median, e.g. non-responders). Diamonds represent means, boxes SEM and whiskers 1.96. SEM of the combined data.




## DISCUSSION

The principal finding of this study is that in female patients with SCH restoration of euthyroidism resulted in a significant increase of total ALP levels, whereas we found no significant changes of hepato-cellular enzymes (i.e. AST, ALT). However, the correlation of changes of hepatocellular enzymes with improvements in LDL-C was relatively strong.

According to the literature, thyroid function affects bile flow and composition: bilirubin excretion decreases in hypothyroid and increases in hyperthyroid rats (Gartner et al., 1972; Layden et al., 1976). In addition, gamma-GT levels are decreased in OH (Azizi, 1982). Mechanisms accounting for these changes in experimental hypothyroidism are a decreased biliary function, i.e., of enzyme activity, bile flow and output of bilirubins and salts (Van Steenbergen et al., 1989). Our findings suggest a slightly decreased excretion of bilirubin and ALP into the bile in SCH, resulting in transiently higher serum levels.

Some publications evaluating patients with OH found elevated concentrations of AST and ALT (Fagiuoli et al., 1993; Gow et al., 1989; Tajiri et al., 1984; Burnett et al., 1994) with normalization after adequate thyroid hormone replacement therapy. However, these studies were uncontrolled, and the number of patients was small. Serum AST and ALT are markers of hepato-cellular function. Increases in circulating liver enzymes may either be due to their increased synthesis and secretion, or to diminished catabolism. Since hypothyroidism is associated with a decreased metabolic rate, the observed decreases of hepatic enzymes during T4 replacement during those studies might rather be due to increases in catabolism. In addition, elevated AST and ALT levels in OH may also be caused by increased extracellular leakage of injured hepatocytes. Accordingly, hepato-cellular damages (reflected by elevated AST and ALT) caused by alcohol, drugs or viruses is typically accompanied by hypercholesterolemia (Vergani et al., 1978). Hypothyroidism can manifest itself with elevated serum concentrations of hepatocellular enzymes and is also characterized by dyslipidemia, suggesting an underlying unifying mechanism

for both changes. Interestingly, we observed a highly significant correlation between changes of hepatocellular enzymes (i.e. AST, ALT) and improvements in LDL-C. Accordingly, patients with the best treatment response of LDL-C on L-T4 therapy (i.e. a maximal lowering of total cholesterol and LDL-C levels based on median values), demonstrated a significantly higher decrease of liver enzyme levels than patients without a significant decrease in cholesterol in response to L-thyroxine. This finding is noteworthy, however, a causal relationship cannot be drawn from a correlation analysis alone. Pretreatment values were not predictive for these changes.

Thyroid hormone replacement in hypothyroidism has been observed to result in increased LDL-clearance, presumably due to increased LDL-receptor activity in the liver, which has been reported both in vitro (Salter et al., 1991) and in vivo (Thompson et al., 1978). In addition, restoration of euthyroidism increases the activity of hepatic lipase, which enhances the conversion of intermediate density lipoprotein cholesterol (IDL-C) to LDL-C and influences LDL composition. Restoration of euthyroidism improves LDL-C disappearance further which contributes to hepatic lipase activity as well as LDL receptor activities (Packard et al., 1993). We speculate that the elevated LDL-C and total cholesterol concentrations in SCH could result mainly from a decreased synthesis of the hepatic LDL- receptor. Conversely, the observed association of beneficial changes of lipoproteins with decreased serum concentrations of liver enzymes is probably due to a general increase in catabolic activity of the liver during L-T4 therapy or possibly due to a diminished leakage of intracellular hepatic enzymes upon restoration of the euthyroid state.

The observed changes of hepato-biliary- and cellular function could be explained by reversible non alcoholic hepatic steatosis (NASH) occurring in mild thyroid failure. However, hepatocellular tissue in primary thyroid failure has never been investigated. Structural changes of the hepatocyte with intracellular fat deposition could potentially explain the distinct findings in hepato-biliary and hepato-cellular function in our study.

Our study has some limitations. Circulating ALP levels originate not only from the liver but also from bone. However, we calculated the concentration of liver specific ALP level by subtracting the B-ALP level from total ALP. B-ALP did not change significantly after 48 weeks of L-T4 therapy. Accordingly, results for serum liver-specific ALP levels were comparable to circulating total ALP concentrations (data not shown). Since serum ALP and other changes remained in the normal reference range throughout the study period, the clinical relevance of our findings could be questioned. However, normal reference ranges are a measure of inter-individual variance and the ‘normal range’ for a specific individual is much less wide. Accordingly, individual changes observed in this double blind study can be relevant for an affected patient, despite being within the so-called ‘normal range’. One might also argue that the TSH levels at the end of the study were still in the high-normal range in L-T4 treated patients indicating that some patients were metabolically still hypothyroid. Indeed, of the 31 L-T4 treated patients 7 had a TSH level above 4mU/L and 3 above 5mU/L. Hence, further lowering of TSH levels could have even increased the impact on lipid profile and changes of hepato-biliary function.

In conclusion, thyroid hormone replacement affects biliary function in patients with SCH, leading to mildly increased hepato-biliary enzymes. In contrast, L-T4 treatment overall has no significant effect on markers of hepatocellular-function. However, improvement in LDL-C levels in SCH is significantly associated with changes of AST and ALT, compatible with changes of hepatic lipoprotein catabolism and a restored hepato-cellular function.

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