Turkish Journal of Endocrinology and Metabolism, (2004) 1 : 25-34 **ORIGINAL ARTICLE**

Twice Weekly L-T_4 for the Treatment of Primary Hypothyroidism

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This study was done to see whether levothyroxine (L-T_4) given twice a week is effective and safe in the management of primary hypothyroidism in 20 patients with primary hypothyroidism who were followed by the outpatient clinic, Ankara University Medical School Department of Endocrinology. The patients were euthyroid on their usual once daily L-T_4 treatment. They had neither coronary heart disease nor arrhythmia. Their ages were 20-50 and their mean daily L-T_4 dose was 123.75±29.77 μg (100-200). After the initial physical and biochemical evaluation, the patients were put on a twice daily L-T_4 regimen on which they took four times their usual daily dose of L-T_4 on Mondays, and three times that on Fridays. In the tenth week of that twice weekly L-T_4 regimen, the patients were reevaluated. On twice weekly L-T_4, serum mean free T_3 level, (3.78±0.49 vs 4.05±0.47 pmol/L; p=0.02), antithyroglobulin antibody titer (369±679 vs 984±2950 IU/ml; p=0.04), SGOT level (18.75±4.78 vs 22.45±6.42 U/L; p=0.007), creatine phosphokinase level (110.75±25.60 vs 125.94±32.71 U/L; p= 0.04), PEP (50.5±8.41 vs 70.7±16.59 msec; p= 0.03), PEP/LVET ratio (0.202±0.04 vs 0.288±0.09; p= 0.0031), and mean diastolic blood pressure (78.75±6.86 vs 83.25±10.55 mmHg; p= 0.03) were lower. Serum sensitive TSH (3.69±1.32 vs 2.75±0.68 mIU/ml; p= 0.02) and osteocalcin levels (8.03±6.85 vs 3.39±2.32 ng/ml; p= 0.008) and mean pulse rate were higher. Due to the observed effects on heart and bone reminiscing hyperthyroidism, it is hard to accept twice weekly L-T_4 regimen as a suitable form of treatment for hypothyroidism.

Key words: hypothyroidism, intermittent treatment, L-T_4

Introduction

The current approach to the treatment of primary hypothyroidism is to give the patient levothyroxine at daily intervals. However, the metabolic half life of L-T_4 in the body is longer than 24 hours, and it approaches 6-7 days (1-3). The metabolic effect of the drug lasts even longer (4,5). T_4 is actually a prohormone which is enzymatically converted, in extrathyroidal tissues, to the active hormone, triiodothyronine (T_3) (6,7). This peripheral conversion to T_3 increases when serum T_4 levels are lower and it decreases when serum T_4 levels are higher (8-11). So, in anticipation that treatment will be easier and patient compliance better if L-T_4 is given in wider spaced doses, this study was planned to observe the efficacy and safety of L-T_4 given in twice weekly doses to patients with primary hypothyroidism.

Materials and Method

The study was done in the outpatient unit of the department of endocrinology and metabolic diseases, Ankara University Medical School, İbn-i Sina Hospital, Ankara, Turkey, between March 1999 and July 1999 on 20 patients with primary hypothyroidism. Fourteen of the patients had autoimmune etiology. Primary hypothyroidism had developed, in four, secondary to subtotal thyroidectomy, and, in two, secondary to radioiodine ablation. The ages of our

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patients changed between 20 and 50, the mean age ± standard deviation being 38.9 ± 8.9 years. All were on daily L-T_4 treatment for at least three months with a mean ± standard deviation dose of 123.75 ± 29.77 (100-200) µg/day. All were euthyroid when they were taken into the study, and none of them had coronary heart disease or any cardiac rhythm abnormality. One of them was male, and 19 of them were female. An informed consent was taken from each patient.

The patients were evaluated with respect to the same parameters before (on daily L-T_4) and at two points on twice weekly L-T_4 treatment that lasted totally 10 weeks.

Twice weekly L-T_4 treatment

On this treatment each patient was given four times his usual daily L-T_4 on Mondays an three times his usual daily L-T_4 on Fridays with no thyroxine given on days between (Table 1). In the end of ten weeks of such therapy, each patient was evaluated on a Monday (three days after three times the usual daily dose of L-T_4) and on a Friday (four days after four times the usual daily dose of L-T_4) before taking L-T_4.

Table 1. LT-$_4$ doses patients received.

Patients	Daily L-T_4 dose (µg)	Twice weekly L-T_4 dose (µg)	
		Mon day	Friday
1	125	500	375
2	125	500	375
3	100	400	300
4	150	600	450
5	100	400	300
6	125	500	375
7	100	400	300
8	125	500	375
9	125	500	375
10	100	400	300
11	200	800	600
12	100	400	300
13	100	400	300
14	175	700	525
15	175	700	525
16	125	500	375
17	100	400	300
18	125	500	375
19	100	400	300
20	100	400	300

Evaluation parame ters

The patients were evaluated at each of the three points of evaluation mentioned above, with respect to systolic and diastolic blood pressure, pulse rate, and signs and symptoms related to thyroid. Blood samples were taken from them to measure serum free triiodothyronine (F T_3), free thyroxine (F T_4), and sensitive thyrotropin (sTSH) concentrations, thyroid microsomal (MAb) and thyroglobulin antibody (TGAb) titers, and aspartat amino transferase (AST), alkaline phosphatase (ALP), osteocalcin creatine phosphokinase (CPK), total cholesterol (C) low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and triglyceride (T) levels in the morning following a 12 hour fast. Their 12- lead electrocardiogram (ECG) tracings were obtained. Their systolic time intervals, mainly preejection periods (PEP) and left ventricular ejection times (LVET), were determined echocardiographically, and their PEP / LVET ratios were calculated.

F T_3, F T_4, and sTSH measurements were done by Automated Chemiluminescence system using the corresponding commertial kits, Chirion Diagnostik ASC 180 ® F T_3 + A, Fr T_4 + A, and TSH + B. Thyroid microsomal and thyroglobulin antibody titers were measured by IRMA using TMAb IRMA C. T (BC 1005) and TGAb IRMA C.T. (BC 1006), Liege, France, correspondingly. Osteocalcin in serum was measured by radioimmunoassay using Osteocalcin DSL - 6900 Radioimmunoassay, USA. ALP was measured using DMA, and AST, C, T, and CPK were measured using Biocon, and HDL was measured using Sigma on a Beckman CX $_7$ instrument. LDL was calculated automatically by the same instrument using the formula; LDL = C-[(T / 5) + HDL]. For the individual patient, measurements at different points of the study were done in different assays. The respective intra-and inter-assay coefficients of variation and the detectable minimum and maximum concentrations are 3.98%, 5.26%, 0.011 µIU/ml, and 150 µU/ml for the TSH assay, 2.1%, 5.6%, 0.8 pmol/L, and 30.8 pmol/L for the FT_3 assay, and 3.44%, 3.98%, 1.3 pmol/L, and 155 pmol/L for the FT_4 assay. The respective intra-and inter-assay coefficients of variations are 5.3% and 8.3% for the TgAb assay, 8.1% and 13.8% for the M Ab assay, and 7.4% and 6.7% for the osteocalcin assay. The normal values

of our laboratory for the various measurements done are indicated in Tables 1 and 2.

Echocardiography was done using a Hewlet - Packard Model sonos 1000 Ultrasound Imaging System instrument with a 2.5 MHz transducer by one of us who was not blinded as to the treatment regimens the patients were under. Patients were examined following a fasting period of minimum 3 hours duration. Parasternal M-mode images of the longitudinal section of the heart were obtained in the patient lying down on his back with a 45° tilt to the left. The preejection period was measured as the time elapsed from the beginning of the Q wave in the simultaneously obtained ECG tracing to the opening of the aortic valve. The left ventricle ejection time was measured as the time period between the opening and the closure of the aortic valve. This procedure was done all patients on daily L-T_4 treatment for at least three months and at two points (Monday and Friday) on twice weekly L-T $_4$ treatment in the end of ten weeks.

Statistical tests

Statistical analysis was performed using the Wilcoxon matched-pairs test. Statistical significance was assumed at $p<0.05$.

Results

The twice weekly L-T $_4$ treatment was well tolerated and no clinical sign or symptom that may be related to thyroid or an untoward effect was observed.

Table 2. Thyroid hormones, TSH, and autoantibodies to thyroid on daily and twice weekly L-T_4 (results given as mean ± standard deviation).

	Normal range	Daily L-T4	Twice weekly L-T_4	
			Monday	Friday
FT_3 (pmol/L)	3.4 - 7.2	4.05 ± 0.47	4.0 ± 0.44	*3.78 ± 0.49
FT_4 (pmol/L)	9.5 - 26.0	16.81 ± 2.71	15.45 ± 3.36	17.12 ± 2.90
STSH (µIU/mL)	0.4 - 4.5	2.75 ± 0.68	*3.65 ± 1.37	*3.69 ± 1.32
TGAb (IU/mL)	0 - 50	894 ± 2950	699.77 ± 1168	*369 ± 679
MAb (IU/mL)	0 - 50	253.82 ± 420.80	105.87 ± 110.86	136.30 ± 249.74

*$p< 0.05$, FT_3=free triiodothyronine, FT_4=free thyroxine, sTSH=sensitive thyrotropin, TGAb= thyroglobulin antibody, MAb= thyroid microsomal antibody.

Table 3. Parameters with the potential of reflecting thyroid hormone action in tissues (results given as mean ± standard deviation).

	Normal range	On daily L-T_4	On twice weekly L-T_4	
			Monday	Friday
Osteocalcin (ng/mL)	3-35	3.39 ± 2.32	5.33 ± 3.58	*8.03 ± 6.85
Alkaline phosphatase (U/L)	38-155	66.0 ± 18.22	71.80 ± 17.71	68.65 ± 13.40
AST (U/L)	10-37	22.45 ± 6.42	*18.35 ± 3.42	*18.75 ± 4.78
Total cholesterol (mg/dL)	120-200	198.05 ± 35.9	199.9 ± 36.56	198.8 ± 34.50
LDL (mg/dL)	130	124.55 ± 32.19	127.5 ± 28.69	124.80 ± 25.92
HDL (mg/dL)	30-80	44.70 ± 8.35	41.4 ± 10.0	44.0 ± 8.15
Triglyceride (mg/dL)	40-120	142 ± 73.56	143.5 ± 56.97	142.55 ± 53.09
CPK (U/L)	0-172	124.95 ± 32.71	119.9 ± 47.21	*110.75 ± 25.60
PEP (msec)	105	70.7 ± 16.59	*51.05 ± 9.06	*50.5 ± 8.41
LVET (msec)	306	252.40 ± 37.15	264.70 ± 53.18	256.40 ± 41.21
PEP/LVET	0.35	0.288 ± 0.09	*0.202 ± 0.04	*0.202 ± 0.04
Diastolic BP (mmHg)	90	83.25 ± 10.55	79.75 ± 6.97	*78.75 ± 6.86
Systolic BP (mmHg)	140	131.50 ± 15.31	130.75 ± 10.67	130.50 ± 12.34
Pulse pressure (mm Hg)	40	48.75 ± 10.24	51.0 ± 9.81	51.75 ± 10.42
Heart rate (beat/min)	60-100	71.4 ± 6.39	*74.4 ± 7.75	*76.9 ± 7.91

*$p<0.05$, AST= aspartate aminotransferase, LDL= Low density lipoprotein cholesterol, HDL= High-density lipoprotein cholesterol, CPK= Creatine phosphokinase, PEP= preejection period, LVET= Left ventricular ejection time, BP=Blood pressure.

Serums mean hormone levels and antibody titers are shown in Table 2. As deduced from that table, Monday and Friday values reflect more or less the same trend in change. The mean FT_3, FT_4 levels and TgAb and MAb titers are all lower under twice weekly treatment, but statistically significant deviations from the respective means on daily L-T_4 have been observed only in the mean F T_3 level and the mean TgAb titer on Friday. Although still within the normal range, the mean sTSH level is significantly higher both in Monday and Friday measurements compared to daily L-T_4.

As for the tests with the capacity of reflecting thyroid hormone action on tissues, deviations from the respective means on daily L-T_4 are in the same direction both in Monday and Friday measurements (Table 3 and Figure 1-7). However, significant changes were observed only in osteocalcin, AST, CPK, PEP, PEP / LVET, diastolic blood pressure, and pulse rate means. The mean serum osteocalcin level and the pulse rate were higher on twice weekly L-T_4. The mean AST and CPK levels and the mean PEP, PEP/LVET, and the mean diastolic blood pressure values were lower on twice weekly L-T_4. Although there were those statistically significant differences of means as mentioned above, all means were in their generally accepted normal ranges both on daily and twice weekly L-T_4 treatment.

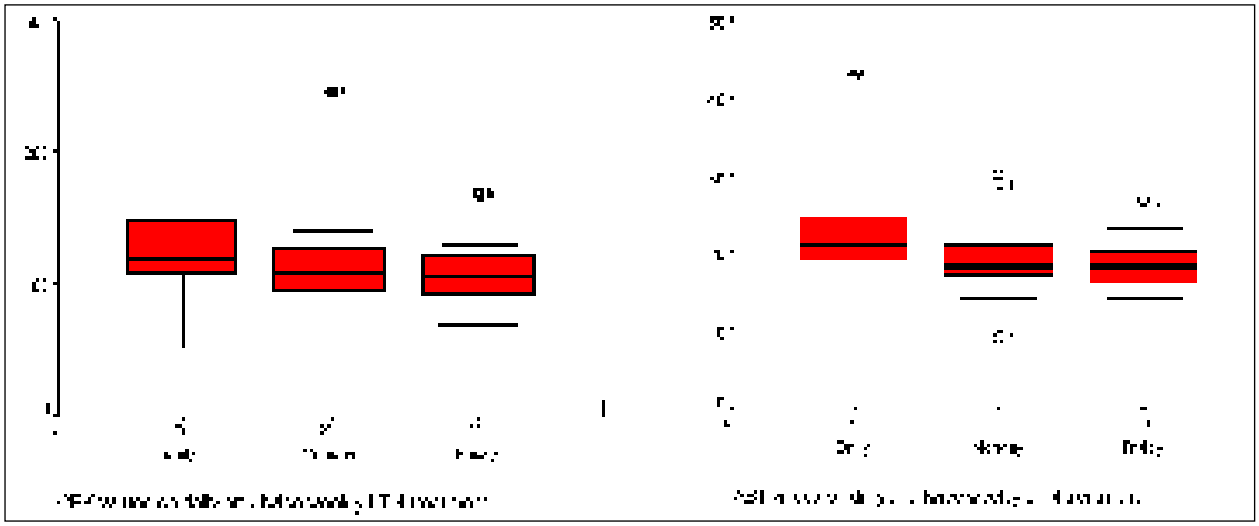

Figure 1. CPK and AST values on Daily and twice weekly LT-4 treatment.

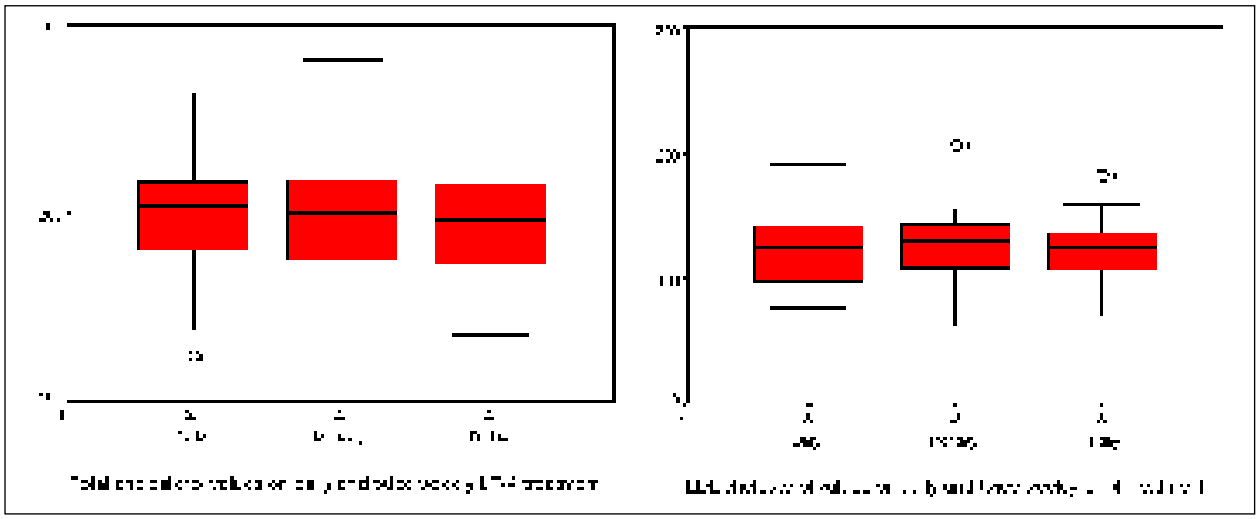

Figure 2. Total cholesterol and LDL cholesterol values on daily and twice weekly LT-4 treatment.

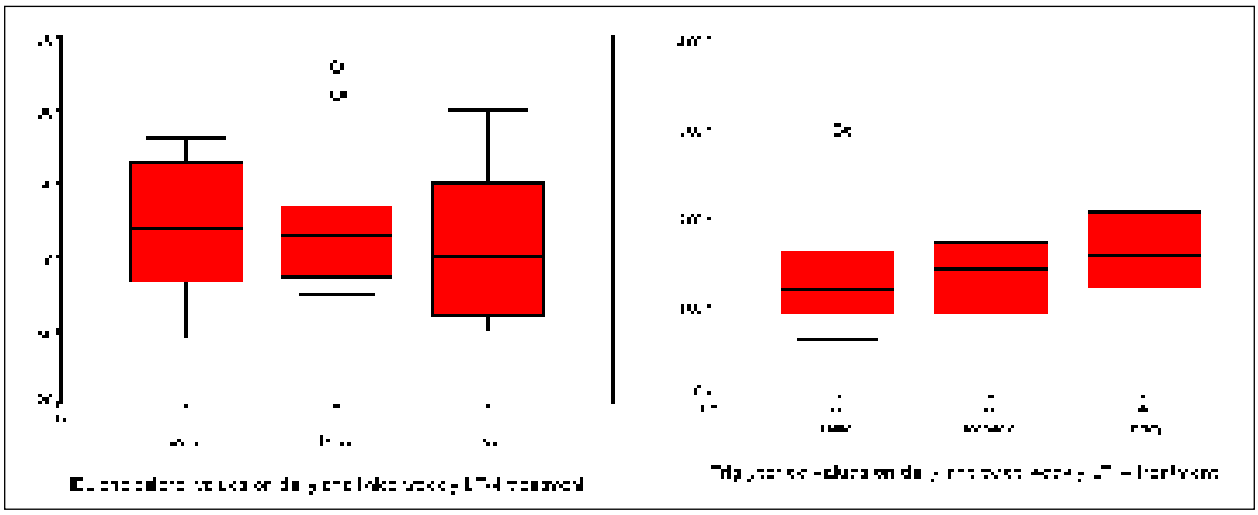

Figure 3. LDL cholesterol and triglyceride values on daily and twice weekly LT-4 treatment.

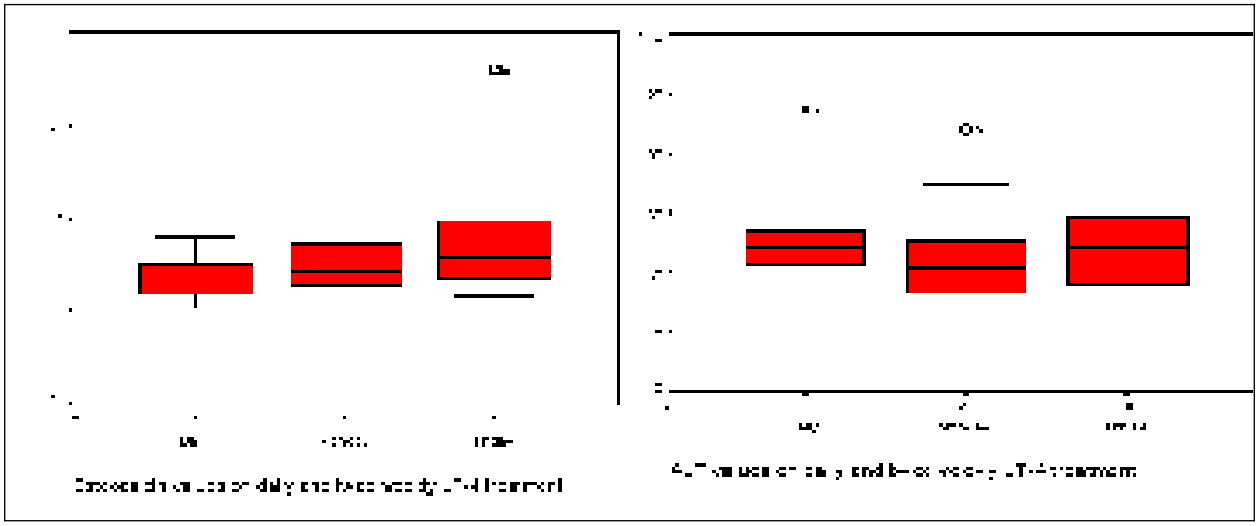

Figure 4. Osteocalcin and ALP values on daily and twice weekly LT-4 treatment.

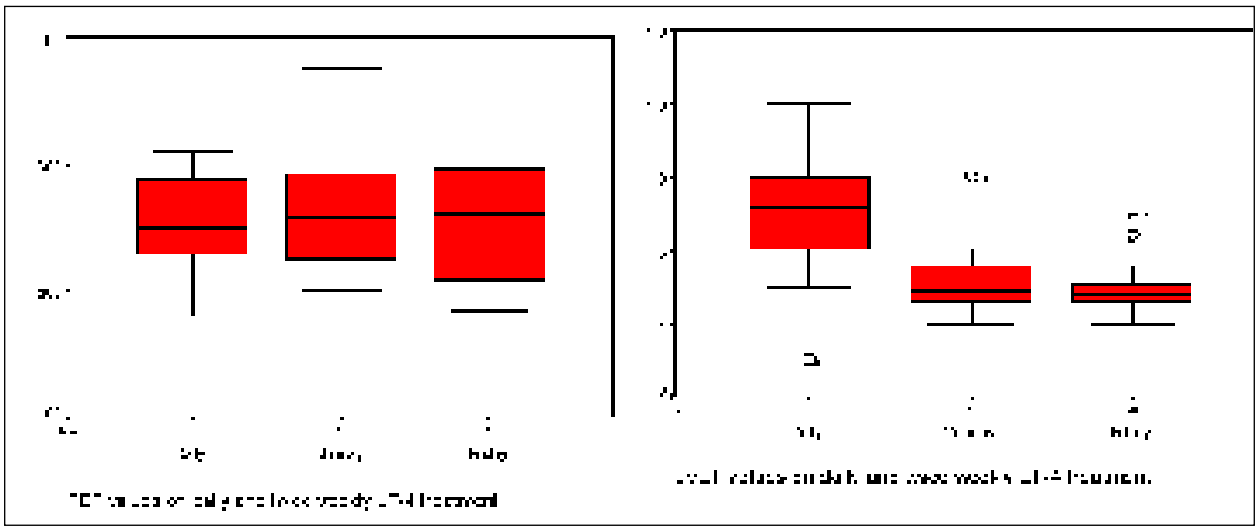

Figure 5. PEP and LVET values on daily and twice weekly LT-4 treatment.

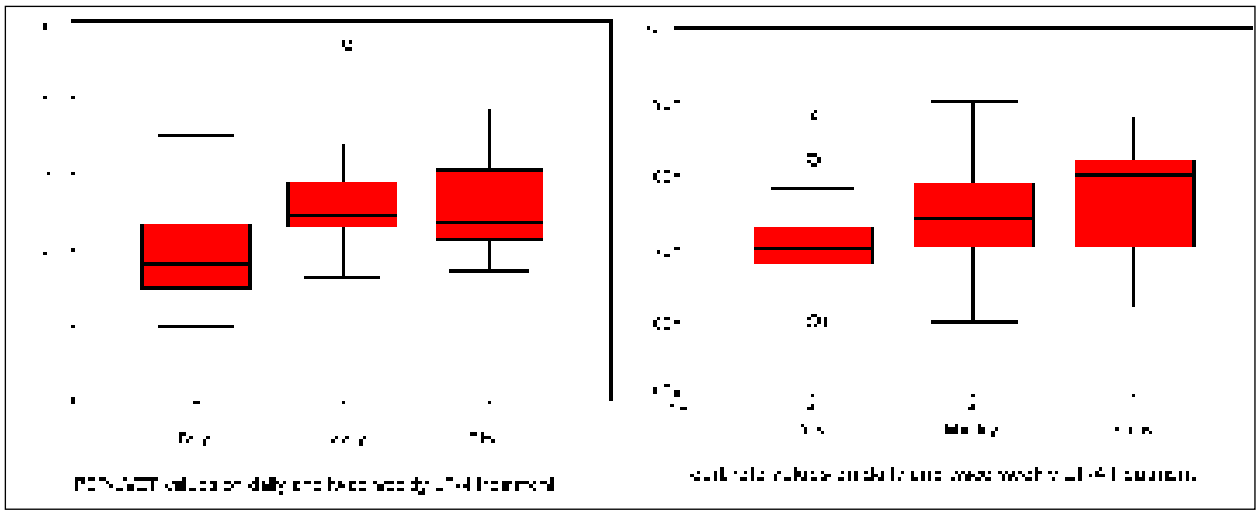

Figure 6. PEP/LVET and Heart rate values on daily and twice weekly LT-4 treatment.

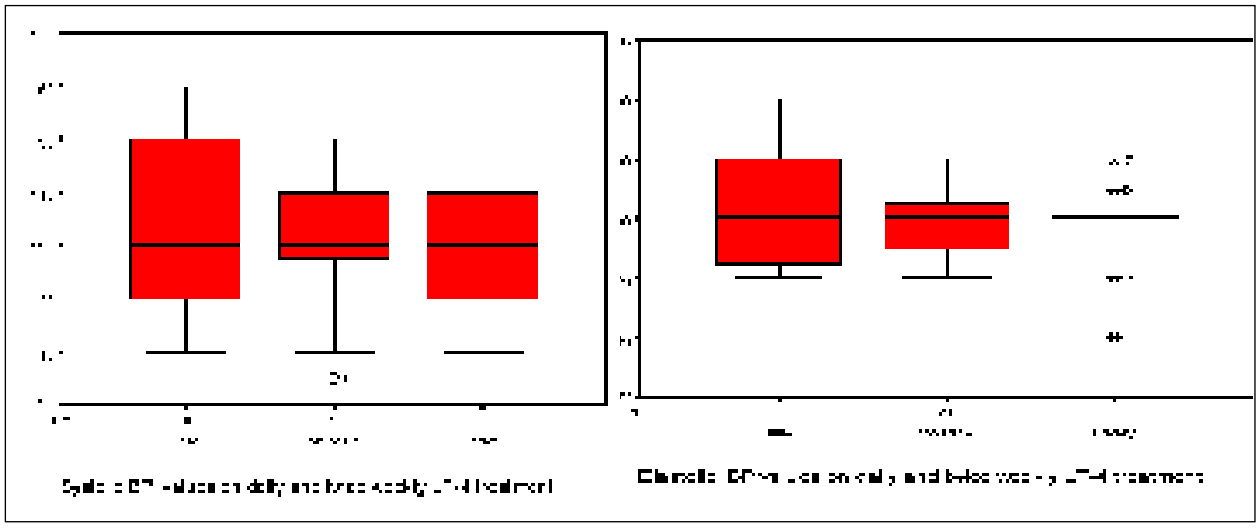

Figure 7. Systolic and Diastoloic BP values on daily and twice weekly LT-4 treatment.

Discussion

Similar to the previous experience of Grebe et al, who had administered L-T_4 on a once weekly basis, twice weekly L-T_4 was well tolerated by our patients, and no sign of acute toxicity was observed, but some of our findings suggest that giving larger doses of L-T_4 with intervals longer than 24 hours will not be free from problems. 12 Such longer interval L-T_4 treatment regimens may not be suitable for TSH suppression since we have observed an increase in sTSH levels and a decrease in F T_3 levels on twice weekly L-T_4. In some previous studies, increases in T_4 levels and small changes in T_3 levels on once weekly L-T_4 treatment have been observed (5,13,14). Grebe et al have reported low FT_3 and FT_4 values seven days following the L-T_4 dose on weekly L-T_4 treatment (12).

On the other hand, our results give a slight hint that higher than usual daily doses of L-T_4 given intermittently may effectively suppress thyroid antibody levels, since TGAb levels are lower on twice weekly L-T_4 in our patients. The delineation of how this occurs is beyond the scope of this study. We can only speculate that if the intermittent high dose of L-T_4 given to the patients in this study had affected an acute and severe suppression of TSH secretion during the three-or four-day period until the next dose, then this suppression of TSH could have an effect towards lowering TGAb levels. However, this we do not know since we have not closely monitored the TSH levels of our patients

during the interval between L-T_4 doses. We have done our sampling only at the end of the interval. TSH has been shown to stimulate the release of thyroid cell-surface components from thyroid-cell plasma membrane preparations, and Hashizume K et al have shown that the administration of thyroxine during thionamid treatment decrease the production of antibodies to TSH receptors and the frequency of recurrence of hyperthyroidism in cases of Graves' disease (15,16). However, the decrease in thyroid antibody titers observed in this study can simply be reflecting the natural course during replacement therapy since daily and twice weekly thyroxine treatment regimens were not compared in a cross-over study design.

As for the effects of twice weekly L-T_4 treatment on tissues other than those comprising the hypothalamus-pituitary-thyroid axis, we have found that PEP and PEP/LVET values decreased on twice weekly L-T_4, suggesting a trend towards a hyperthyroid state. Thyroid hormones have more or less well established effects on cardiac function, and systolic time intervals have been used to define thyroid status for quite a long while. Of those, PEP and PEP/LVET ratio have emerged as the most reliable markers of the thyroid status. To our knowledge, the awakening interest in systolic time intervals as tools to determine thyroid function takes its roots from a study by Amidi et al. Those authors have shown, though in a rather invasive fashion, that the ejection rate of left ventricle increases in thyrotoxicosis (17). In multitude of studies done on patients with thyroid problems, shortening of PEP and decrease in the PEP/LVET ratio have been observed in hyperthyroidism, and shortening of systolic time intervals have been reported in subclinical hyperthyroidism (15,18-27). It has also been observed that systolic time intervals normalize following the return to normal ranges of thyroid hormone levels under suitable antithyroid treatment (15, 18, 20, 23, 29). PEP and the PEP/LVET ratio have been found to increase in hypothyroidism and in subclinical hypothyroidism, and they have been reported to normalize upon L-thyroxine replacement (15, 18, 19, 22, 25, 28-35). Hodges et al denote the PEP/LVET ratio as an important parameter in determining the suitable replacement dose of L-T_4 going on the results of their study in newborns (35). Although there is a general agreement on the PEP and the PEP/LVET ratio changes in relation to the thyroid status, conflicting results have been reported with LVET. 36-41 Most workers have not observed a meaningful change of LVET in hyperthyroidism (18,19,21, 27, 42). However, some have reported an increase and others reported a decrease in values (20,28).

Although the increase in pulse rate and the decrease in diastolic blood pressure paralleling PEP and the PEP/LVET ratio which is found to decrease, in our present study, on twice weekly L-T_4 are just markers of thyroid hormone action, this action on heart can lead, also, to arrhythmia since the incidence of arrhythmia have been reported to have increased on L-T_4 therapy (12,43). Furthermore, we have measured systolic time intervals only three and four days after the L-T_4 dose. If we had measured them in earlier periods and employed 24 hours cardiac rhythm monitorization, we could have observed more prominent changes, or detected arrhythmias. However, that is only speculation for the time being. Cardiac rhythm monitorization gives results in the parallel of systolic time intervals under long term thyroxine suppression therapy (44).

Predisposition to osteoporosis is another concern associated with L-T_4 treatment especially when this treatment is given in larger doses for TSH suppression and after menopause. In hyperthyroidism, both the osteoclastic resorption of bone and osteoblastic activity increase, the trabecular bone volume and cortical thickness decrease and, according to some authors, osteoporosis and associated fractures develop (45-49). As opposed to these, in hypothyroidism, the osteoblastic activity and the rate of bone turnover are decreased, and the trabecular bone volume and cortical bone thickness are reported to increase (45,50-53). Serum alkaline phosphatase and osteocalcin concentrations that are markers of the rate of bone turnover are increased in hyperthyroidism and decreased in hypothyroidism (45, 54). Although we have not observed any significant change in serum alkaline phosphatase levels, the serum osteocalcin levels of our patients are higher on twice weekly L-T_4 implying an increase in bone turnover.

Although our systolic time interval and osteocalcin results imply increased thyroid hormone action on tissues under twice weekly L-T_4, we have found

that F T_3 levels are conflictingly lower under that treatment. However, tissue effects have not always been in good correlation with serum thyroid hormone levels also in previous studies (33). A possible explanation for the discrepancy between serum T_3 levels and observed tissue effects derives from the evidence indicating the presence of pools of T_3 generated by tissue conversion from T_4. These tissue pools are not exchangeable with the circulating T_3 pool (55,56). Our PEP and LVET results have not been corrected for heart rate since there are previous studies suggesting that there are no significant correlations between heart rate and PEP or LVET (37,57-60).

In conclusion, the results of this present study have led us to think that twice weekly treatment may accentuate the disadvantageous effects of L-T_4 on heart and bone. We do not think that treatment regimens on which L-T_4 is given with intervals of three days or longer, are not safe alternatives to once a day L-T_4 treatment in the management of primary hypothyroidism. Furthermore, our results also suggest that twice weekly L-T_4 is less potent than daily L-T_4 treatment in affecting a suppression of TSH levels. It can be speculated that long-term twice weekly L-T_4 treatment may have adverse effects on the heart and bones and these effects may be hazardous depending on their morbidity.

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Abbreviations:

L-T4 : levothyroxine
PEP : preejection periods
LVET : left ventricular ejection times
FT4 : free thyroxine
FT3 : free triiodothyronine
S TSH : sensitive thyrotropin
TMAb : thyroid microsomal antibody
TGAb : thyroglobulin antibody
AST : aspartat amino transferase
ALP : alkaline phosphatase
CPK : creatine phosphokinase
LDL : low density lipoprotein cholesterol
HDL : high density lipoprotein cholesterol (HDL)
C : total cholesterol
T : triglyceride
ECG : electrocardiogram