Original Article

Effect of Levothyroxine Replacement on Lipid Profile and Renal Function of Primary and Subclinical Hypothyroid Patients

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Abstract

Background: *Hypothyroidism is an important endocrine disorder associated with deleterious effects on multiple systems including cardiovascular, musculoskeletal, renal and nervous system. It is established that thyroxine replacement shows improvement in many clinical and biochemical parameters of overt hypothyroidism, but there is scarce data about these disorders in this sub-continent. The present study intends to find out the effect of thyroxine replacement on lipid profile and renal function in hypothyroid patients.*

Methods: *This was an observational cohort study, done in endocrine inpatient and outpatient departments of BIRDEM General Hospital from August 2013 to July 2014. Patients with newly detected hypothyroidism, both primary and subclinical, were selected by convenient sampling. A semi-structured questionnaire was used to collect the clinical and laboratory informations from the patients. Baseline clinical and laboratory informations including lipid profile and serum creatinine were collected and e-GFR was calculated. Then tablet levothyroxine was started at a dose of 25 micrograms/day and adjusted by 12.5-25 micrograms/day dose increments 4-6 weekly till FT_4 and TSH were normalized. After 6 months, clinical and biochemical data were collected and e-GFR calculated.*

Results: *Seventy four hypothyroid patients were followed up for 6 months. All the patients became euthyroid during this time with thyroxine replacement (mean daily dose of thyroxine 96.61 ±25.62 micrograms). There was significant improvement in hypothyroid symptoms and significant reduction in weight and systolic and diastolic blood pressure in the patients after thyroxine replacement. There was reduction in total cholesterol (187.66 ±19.90 mg/dl to 164.37±17.49 mg/dl, P<0.001), LDL (P<0.001) and triglycerides (P<0.001) but HDL did not increase significantly (31.93 ±2.99 mg/dl to 31.98 ±2.75 mg/dl, P=0.46). Renal function improved significantly in terms of eGFR (74.78±13.70 ml/min/1.73m^2 to 89.23±18.24 ml/min/1.73m^2, P<0.001).*

Conclusion: *The present study concludes that there is increased prevalence of dyslipidaemia and renal dysfunction in hypothyroid patients in this cross-sectional population. Adequate replacement of thyroxine can, at least in part, reverse these problems. It also shows significant improvement of the patients with subclinical hypothyroidism, which is regarded by many authors as mild thyroid failure.*

Key words: *Hypothyroidism, Subclinical hypothyroidism, Lipid profile, eGFR*

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Introduction

Hypothyroidism is a common endocrine disorder. It is defined as a clinical syndrome resulting from a deficiency of thyroid hormones, which in turn results in a generalized slowing down of metabolic processes.[1] In community surveys, the prevalence of overt hypothyroidism varies from 0.1 to 2 percent in different countries.[2] The prevalence of subclinical hypothyroidism is higher, ranging from 4 to 10 percent of adults, with possibly a higher frequency in elderly women.[3] There is limited data regarding prevalence of hypothyroidism in Bangladesh. In a community based study in 2006 in Khulna, prevalence of primary and

subclinical hypothyroidism were found to be 4.97% and 6.59% respectively.[4] In another study conducted in 2010, 18% of the patients attending the endocrine outpatient department of a tertiary level hospital were hypothyroid.[5]

It is well known that hypothyroidism is associated with dyslipidaemia. Despite the reduced activity of HMG-CoA reductase, there is an increase in the serum total cholesterol concentration, mainly due to raised levels of serum low density lipoprotein (LDL) cholesterol and intermediate density lipoprotein (IDL) cholesterol. Decreased activity of LDL-receptors' resulting in decreased receptor-mediated catabolism of LDL and IDL is the main cause of the hypercholesterolemia observed in hypothyroidism.[6] Impairment of renal function is also an important manifestation of hypothyroidism. Renal blood flow rate, glomerular filtration rate (GFR) and tubular reabsorptive and secretory capacities are all reduced. Although the blood urea nitrogen (BUN) level is usually normal, serum creatinine and uric acid levels may be increased.[7] Studies suggest that levothyroxine therapy in hypothyroid patients lowers mean serum total and LDL cholesterol concentrations[8] and preserves renal function.[9] But, there is scarce data regarding the effects of thyroxine replacement in Bangladeshi population.

In view of the above situation, the current study is designed to find out the effect of thyroxine replacement in primary and subclinical hypothyroidism in Bangladeshi population in terms of lipid profile and renal function.

Methods

This was an observational cohort study, carried out in the Department of Endocrinology, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General Hospital, Dhaka from August 2013 to July 2014.

Study population

Adult population aged ≥18 years with primary and subclinical hypothyroidism from all socioeconomic strata attending both out-patient and in-patient department of BIRDEM General Hospital, Dhaka.

Selection criteria

Inclusion criteria: The patients attending out-patient and in-patient departments of BIRDEM General Hospital newly diagnosed as primary and subclinical hypothyroidism and age ≥18 years.

Exclusion criteria: The patients having severe co-morbid conditions (End-stage renal disease, acute heart failure, decompensated chronic liver disease, acute stroke, known case of malignancy) and patients with secondary hypothyroidism were excluded.

After applying the selection criteria, 132 patients were enrolled in the study by purposive sampling. However, only 74 patients completed the study. Clinical and biochemical data were collected from the study subjects as follows-

- Face to face interview was conducted by using a semi structured questionnaire containing information (e.g. cold intolerance, constipation, menorrhagia in females, dry skin, hoarseness of voice, facial puffiness, physical activity, weight, BMI, hypertension).
- Serum free thyroxine (FT_4), thyroid stimulating hormone (TSH), anti-thyroglobulin and anti-thyroid peroxidase antibodies levels were done at first visit.
- Fasting lipid profile and serum creatinine levels were measured and e-GFR was calculated using Modification of Diet in Renal Diseases (MDRD) formula at first visit.
- All patients were treated with tablet levothyroxine (Open label from market) starting with 25 micrograms/day and dose was adjusted by 12.5-25 micrograms/day increments 4-6 weekly till patients were biochemically euthyroid.
- After 6 months, data was collected regarding clinical features of hypothyroidism, FT_4 and TSH levels, serum fasting lipid profile and serum creatinine. Calculation of e-GFR was performed.

Primary hypothyroidism was defined as FT_4 below normal reference range (<9.14 pmol/L) and TSH above >10 μIU/ml. Subclinical hypothyroidism was defined as FT_4 within normal reference range (9.14 to 23.18 pmol/L) and TSH above 5.01 to 10 μIU/ml.

Data were analyzed by computer with the help of SPSS (Statistical Package for Social Sciences) version 17.0. Statistical analyses were done by using appropriate statistical tool like 'Chi-square' test, student's 't' test, where applicable. Statistical significance was set at .05 level and confidence interval at 95% level.

Ethical approval from the ethical approval committee of Bangladesh Diabetes Association (BADAS) was obtained prior to the commencement of the study. Informed written consent was obtained from the participant after explaining all the facts of potential dangers to the subjects in case of primary data collection. The participants were assured that the information acquired would be used for academic purpose. They were assured of confidentiality, and for the purpose of data analysis no individual data had been reported rather de-identified data had been preceded for analysis.

Results

Total patients were 74 including 67 females. Mean age of the study subjects was 42.59(±10.98) years. Majority (59.46%) of the study population had body mass index (BMI) in the range of overweight category, 26 patients (35.14%) were in normal weight category and 4 patients (5.41%) were obese. Mean BMI of the study population was 25.87 kg/m^2. Among 74 study subjects, only 9 (12.2%) had hypertension.

Regarding the cause of hypothyroidism, 36 patients were positive for anti-thyroid antibodies, which comprised 48.6% of the study population. Base-line biochemical characteristics of patients with primary and subclinical hypothyroidism are presented in Table I.

There was considerable variation regarding dose of levothyroxine replacement to achieve euthyroid state in the study population. Thirty-four (64.15%) of the 53 overt hypothyroid cases needed thyroxine replacement 100 µgm/dayto achieve euthyroid state, whereas 5 (9.43%) patients needed 75 µgm/day, 7 (13.20%) needed 125 µgm/day and 7(13.20%) needed 150 µgm/day. Of the 21 patients of subclinical hypothyroidism, 6 (28.57%) needed thyroxine 50 µgm/day, 14 (66.67%) needed 75 µgm/day and only 1 (4.76%) patient needed 100 µgm/day. The thyroid hormone profile of the study subjects are presented in Table II. Comparison between clinical features of overt and subclinical hypothyroidism is shown in Table III and IV.

Table I. Baseline biochemical profiles of the study population (N=74)

	Total (N=74)	Primary hypothyroid (n=53)	Subclinical hypothyroid (n=21)
Hemoglobin (gm/dl)	9.91±1,31	9.97±1.34	9.76±1.25
Random blood glucose (mmol/L)	7.12±1.21	7.18±1.24	6.96±1.15
S. creatinine (mg/dl)	0.92±0.11	0.99±0.12	0.85±0.06
Total cholesterol (mg/dl)	187.66±19.90	194.74±19.80	182.13±13.55
HDL (mg/dl)	31.93±2.99	32.20±3.28	31.23±1.97
LDL (mg/dl)	141.88±15.57	148.64±15.24	140.26±13.54
Triglycerides (mg/dl)	236.14±61.10	242.96±62.79	218.93±54.21

Table II. Comparison between thyroid hormone profile before and after 6 months thyroxine replacement in overt (n=53) and subclinical hypothyroidism (n=21)

	Primary hypothyroidism (n=53)		P	Subclinical hypothyroidism (n=21)		P
	Before treatment	After 6 months follow up	value	Before treatment	After 6 months follow up	value
FT_4 (pmol/L)	8.91±1.21	14.67±1.38	<0.001	10.09±1.0	14.81±1.18	<0.001
TSH (µIU/ml)	50.11±27.81	2.93±1.08	<0.001	8.86±0.50	2.62±0.81	<0.001

In primary hypothyroidism patients, after six months thyroxine replacement, total cholesterol, LDL and TG level were reduced but HDL values did not increase significantly. In patients with subclinical hypothyroidism, total cholesterol and LDL levels were reduced but Triglycerides and HDL levels did not change significantly (Table V).

Table III. Comparison between clinical features before and after 6 months thyroxine replacement (N=74)

Symptoms	Before treatment N (%)	After 6 months N (%)	P value
Constipation			0.001
Yes	47 (63.51)	16 (21.62)	
No	27 (36.49)	58 (78.38)	
Cold intolerance			<0.001
Yes	46 (62.16)	02 (2.71)	
No	28 (37.84)	72 (97.29)	
Hoarseness of voice			0.009
Yes	11 (14.86)	04 (5.40)	
No	63 (85.14)	70 (94.59)	
Dry Skin			0.001
Yes	26 (35.14)	07 (9.4)	
No	48 (64.86)	67 (90.6)	
Facial Puffiness			0.001
Yes	32 (43.24)	11 (14.86)	
No	42 (56.75)	63 (85.13)	
Menorrhagia			<0.001
Yes	11 (14.86)	01 (1.35)	
No	63 (85.14)	73 (98.65)	

Table IV. Comparison between body weight, systolic and diastolic blood pressure before and after 6 month thyroxine replacement in primary (n=53) and subclinical hypothyroidism (n=21)

	Primary hypothyroidism (n=53)			Subclinical hypothyroidism (n=21)		
	Before treatment	After 6 months follow up	P value	Before treatment	After 6 months follow up	P value
Weight (Kg)	66.98±6.93	62.03±6.45	<0.001	60.73±6.49	59.06±6.27	<0.001
SBP (mmH)	143.13±11.75	127.27±8.58	<0.001	132.33±12.37	123.66±9.15	<0.001
DBP (mmHg)	81.49±8.12	72.47±6.63	<0.001	72.33±8.20	70.0±5.34	0.38

Table V. Comparison between fasting lipid profile before and after 6 months thyroxine replacement in primary (n=53) and subclinical hypothyroidism (n=21)

	Primary hypothyroidism (n=53)			Subclinical hypothyroidism (n=21)		
	Before treatment Mean (±SD)	After 6 months follow up	P value	Before treatment Mean (±SD)	After 6 months follow up	P value
Total Cholesterol (mg/dl)	194.74±19.80	163.49±17.69	<0.001	182.13±13.55	163.46±11.32	<0.001
HDL(mg/dl)	32.20±3.28	32.39±2.75	0.4	31.23±1.97	31.52±1.83	0.1
LDL (mg/dl)	148.64±15.24	114.66±12.52	<0.001	140.26±13.54	119.60±11.0	<0.001
Triglycerides (mg/dl)	242.96±62.79	210.17±56.27	<0.001	218.93±54.21	217.89±55.13	0.47

Mean serum creatinine level of the primary hypothyroidism group reduced significantly from 0.99 (±0.12) mg/dl to 0.83 (±0.11) mg/dl after 6 months of thyroxine replacement, with a corresponding increase in eGFR ($p<0.001$). Subclinical hypothyroidism group also showed a similar type of response (Table VI).

Table VI. Comparison between renal function before and after 6 months thyroxine replacement in primary (n=53) and subclinical hypothyroidism (n=21)

	Primary hypothyroidism (n=53)			Subclinical hypothyroidism (n=21)		
	Before treatment	After 6 months follow up	P value	Before treatment	After 6 months follow up	P value
S. creatinine(mg/dl)	0.99±0.12	0.83±0.11	<0.001	0.85±0.06	0.73±0.06	0.01
eGFR(ml/min/1.73m^2)	73.52±15.54	87.39±19.07	<0.001	80.05±6.75	95.70±11.34	0.005

Discussion

The aim of this study was to observe the effect of thyroxine replacement on hypothyroid patients in terms of improvements in lipid profile and renal function. The study population had mean age of 42.59(±10.98) years. In a previous study done at Center for Nuclear Medicine and Ultrasound, Bogra Medical College in 2007, the mean (±SD) age of hypothyroid patients was 35.59 (±6.91) years.[10] Nessa et al conducted a study in Medical Out-patient Department in Combined Military Hospital from 2008 to 2010 and found mean age of the hypothyroid patients was 32.18 ± 9.82 years.[11] Majumder et al conducted a study where age of the patients ranged from 20-60 years, and peak age of the subjects at presentation was observed at 3rd and 4th decade.[12]

In this study male to female ratio was 1:9.6, which correlates with other studies, like Nessa et al[11] and Majumder et al[12] showing male to female ratio 1:6.8 and 1:5 respectively. It may be due to the fact that sex hormones may have an important role in the autoimmune thyroid disease.[13]

Among the 74 hypothyroid patients included in this study, 36 patients were positive for antithyroid antibodies [Anti Thyroid Peroxidase (anti-TPO) and/ or Anti Thyroglobulin ((anti-Tg) antibodies], which comprised 48.6% of the study population. A previous study shows similar results, with 34.75% patient havingpositive anti-TPO and 21.18% positive anti-Tg antibodies.[11]

The mean hemoglobin level of the study population was 9.91 (±1.31)gm/dl. It reflects the well known fact that there may be normocytic, macrocytic or microcytic anemia in hypothyroidism.[14] Nessa et al found that 57.63% of hypothyroid patients in their study had hemoglobin level below 10.0 gm/d.[11]

It is a well known fact that hypothyroidism is associated with dyslipidaemia, but the magnitude of restoration of euthyroidism over lipid profiles is controversial. In this study, it was found that total cholesterol, LDL and TG level were high and HDL was low at initial visit and after six months treatment with thyroxine total cholesterol, LDL and TG level were reduced, but HDL did not increase significantly. Subclinical hypothyroid patients showed decrease in total cholesterol and LDL levels, but Triglycerides and HDL levels did not change significantly. A study on 80 primary hypothyroid patients and 30 healthy euthyroid controls concluded that hypothyroid patients have lipoproteins abnormalities in the form of high total cholesterol, LDL, triglycerides and low HDL and therapy with L-thyroxine significantly reduces total cholesterol and LDL but has no significant effect on triglycerides and HDL.[12]

There is much speculation regarding relationship of renal function with hypothyroidism. This study showed that mean serum creatinine level of the study population was 0.92(±0.11) mg/dl initially which reduced to 0.79(±0.10) mg/dl after 6 months thyroxine replacement. There was a corresponding increase in eGFR, at initial visit 74.78(±13.70) ml/min/1.73 m^2 and 89.23(±18.24) ml/min/1.73 m^2 after 6 months. In the subclinical hypothyroid patients, serum creatinine was 0.85(±0.06) mg/dl initially and 0.73(±0.06) after 6 months, and eGFR increased accordingly, at initial visit 80.05(±6.75) ml/min/1.73 m^2 and 95.70(±11.34) ml/ min/1.73 m^2 after 6 months. Similar results were found

in a study performed on hypothyroid patients in Bogra Medical College, where the mean (±SD) eGFR was lower in hypothyroid (70.3±14.2 ml/min/1.73 m^2) compared to euthyroid (98.9±18.5ml/min/1.73 m^2) group. The mean (±SD) serum creatinine was significantly higher in hypothyroid (1.447±0.34 mg/dl) than euthyroid(1.026±0.2 mg/dl) group.[10]

Mean body weight of the study subjects at initial presentation was 63.77(±7.18) kg, which reduced to 61.92(±6.72) kg after 6 months thyroxine replacement. Mean systolic and diastolic blood pressures also significantly reduced after 6 months thyroxine replacement. In subclinical hypothyroidism patients mean weight reduced significantly from 60.73(±6.49) kg at initial presentation to 59.06(±6.27) kg after 6 months. Mean systolic BP also reduced significantly from 132.33(±12.37) mmHg to 123.66(±9.15) mmHg, but diastolic BP reduction was not significant. Dernellis & Panaretou conducted a study on hypertensive hypothyroid patients and concluded that hypertension is completely reversible in 50% of patients by hormone replacement therapy.[15] Similar results were found in subclinical hypothyroid patients. Anagnostis et al in their study found that L-thyroxine replacement and achievement of euthyroidism significantly reduced systolic blood pressure in patients with subclinical hypothyroidism (from 135.2±18.5 to 129.7±15.8 mmHg) and diastolic BP only in those with baseline TSH levels >7 µIU/ml (from 79.5±9.8 to 72.1±7.3 mmHg).[16]

Limitations

Every research work may have some limitations. The following limitations have been pointed out about the present study, but the list is not exclusive -

- As the study was done as a part of thesis work, there was time constraint, so that adequate number of patients could not be followed up.
- The study was done in a specialized hospital in the capital city, and does not reflect the picture of the entire country.
- As it was a descriptive study, the decision regarding which patient of subclinical hypothyroidism should be treated was made by the treating physician, which ideally should be made by researcher and in an interventional study setting.
- Although the improvement in study parameters were statistically significant, they may not be significant clinically, as their impact on cardiovascular morbidity and mortality was not looked for.

Recommendations

- There should be further studies, preferably interventional and with control groups, to follow up patients with Subclinical hypothyroidism for a reasonable period of time to find out the beneficial effects of thyroxine replacement in this group.
- As it is evident that thyroxine replacement is beneficial for patients with overt hypothyroidism, early diagnosis and management is of utmost importance.
- There should be nationwide large scale studies to find out the prevalence of thyroid disorders in our country.

Conclusion

Hypothyroidism is one of the commonest endocrine diseases in our country, but data regarding effects of restoration of euthyroidism are lacking. Moreover, there is scarce data regarding subclinical hypothyroidism in our country. The present study is consistent with the previous knowledge that hypothyroidism is associated with dyslipidaemia and renal dysfunction. Adequate replacement of thyroxine can, at least in part, reverse these problems. It also shows that patients with subclinical hypothyroidism can have significant benefits after receiving adequate thyroxine replacement.

Conflict of Interest: None

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