Original Article

The effect of levothyroxine substitution on lipid profile parameters in patients of subclinical hypothyroidism in tertiary care centre of kumaon region

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Abstract

Introduction- Subclinical hypothyroidism (SCH) also called as mild thyroid failure is defined as the presence of serum thyroid stimulating hormone (TSH) above the statistically defined upper limit of the reference range, with a serum free thyroxine (T4) and tri-iodothyronine (T3) within the reference range. Various studies of serum lipid profile parameters in SCH showed inconsistent results. Further studies done to quantify the effect of levothyroxine substitution had also shown conflicting results. This study was therefore planned to study the effects of SCH on lipid profile parameters and to evaluate the effect of thyroxine replacement therapy on thyroid and lipid profile in area around Kumaon region. **Materials and Methods-** out of total 175 subjects, 75 euthyroids were taken as control and 100 newly diagnosed SCH patients as cases. Estimation of thyroid function tests (TSH, T3, T4) and lipid profile parameters [Total cholesterol (TC), Low Density Lipoprotein cholesterol (LDLc), Triglycerides (TG), High Density Lipoprotein cholesterol(HDLc)] were estimated in all subjects after an overnight fast. Out of 100 SCH patients 58 selected patients were given thyroxine replacement therapy and were followed up after 3 months with repeat thyroid and lipid profile. **Results-** In the present study the mean levels of TC, LDLc, TG were significantly high in comparison to euthyroid controls**.** HDLc levels were raised in SCH patients but insignificant statistically. There was a significant decrease in TC and LDLc levels in SCH patients after 3 months of thyroxine replacement therapy. The mean levels of TG and HDLc were also reduced after treatment but were insignificant. **Conclusion** – This study conclude that dyslipidemias are present in SCH cases as compared to euthyroid controls. The thyroxine replacement therapy in selected patients demonstrated the favorable effects on TC, LDLc and in the ratios of TC/HDLc and LDLc/HDLc.

Key words- Subclinical hypothyroidism (SCH), Levothyroxine, Dyslipidimias.Fo

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Received Date: 22/07/2016 Revised Date: 15/08/2016 Accepted Date: 14/10/2016

Access this article online	
Quick Response Code:	Website: www.statperson.com
	DOI: 16 October 2016

INTRODUCTION

Subclinical hypothyroidism (SCH) also called as mild thyroid failure is defined as the presence of serum thyroid stimulating hormone (TSH) above the statistically defined upper limit of the reference range, with a serum free thyroxine (T4) and tri-iodothyronine (T3) within the reference range.[1] Most patients of SCH have few or no symptoms or signs of thyroid dysfunction, therefore it is a diagnosis based on laboratory evaluation observed specially in tertiary care centre (2).With the development of highly sensitive TSH estimation assays, the frequency of SCH detection and hence its prevalence has increased.[1,2,3] According to various population based studies the prevalence of SCH ranges from 4-8.5% in

How to site this article: Sangeeta Singh, Seema Gupta, Paramjeet Singh, Basant Joshi. The effect of levothyroxine substitution on lipid profile parameters in patients of subclinical hypothyroidism in tertiary care centre of kumaon region. *International Journal of Recent Trends in Science and Technology*. October 2016; 20(3): 385-389. http://www.statperson.com (accessed 18 October 2016).

females to 3-4% in males which further increases with age.[4,5]

SCH has a number of possible consequences including neuropsychiatric symptoms[5], adverse effects on cardiac functions[6], effects on lipids[7] and systemic hypothyroid symptoms.[8] A majority of cardio vascular signs and symptoms are found to be associated with lipid profile derangements.[8,9,10] Various observational studies of serum lipid profile parameters in patients of SCH have shown inconsistent results.[7,11-15] In addition multiple studies done to quantify the effect of levothyroxine substitution had also shown conflicting results.[14-16] Therefore this study was planned to study the effects of different grades of SCH on lipid profile parameters and to evaluate the effect of levo-thyroxine replacement therapy on lipids in SCH patients.

MATERIAL AND METHODS

This study was conducted after approval by the Institutional Ethical Committee and informed consent given by each patient in duration of one year. A total of 175 patients in the age of 15-65 years attending the medicine OPD at Dr. Susheela Tiwari Government Hospital and Medical College were enrolled in the study.

Out of these 75 patients with normal thyroid profile parameters were taken as controls. 100 newly diagnosed patients having signs and symptoms suggestive of hypothyroidism and TSH values > 4.2µIU/ml along with peripheral thyroid hormones T3, T4 within their normal reference ranges were included as cases in the study. Subjects with history of thyroid disease, obesity, diabetes mellitus, hyper tension, T.B or any other acute or chronic illness were excluded from the study. Patients taking antithyroid drugs thyroxine replacement or any other drug affecting thyroid function tests (oral contraceptives, steroids, lipid lowering drugs, anti epileptics etc.), pregnant and infants were also excluded from the study.

Out of 100 SCH patients 58 patients were given the thyroxine replacement therapy mean dose for the duration of 3 months by the treating physician. These patients were called up telephonically and repeat blood tests were done for biochemical parameters of thyroid function and lipid profile.

After an overnight fast[10-12] hours venous blood sample of 5~6 ml was collected, centrifuged, separated sera was divided into 2 alliquots. The one for lipid profile (total cholesterol (TC), triglycerides(TG), high density lipoprotein cholesterol (HDLc) was estimated immediately in fully automated analyser cobas c501of Roche diagnostics. The one for thyroid profile tests (TSH, T3, T4) was analysed in fully automated Immunoanalyser cobas E411 of Roche diagnostics based on the principle of Electro-chemiluminisence. Low density lipoprotein cholesterol (LDLc) was calculated using Friedwalds Formula :(TC)-(HDL)-(TG)/5.[17]

Statistics-Statistical analysis was done by SPSS statistical software (SPSS 17.0 for windows) .Results were presented as Mean± SD. Mann Whitney U test and Students 't' test was applied to the data.The Pearson correlation was used to test whether TSH was correlated with TC, LDLc , HDLc ,TC/HDLc and LDLc/HDLc.

RESULTS

Table-1 shows the baseline profile of subclinical hypothyroid patients and euthyroid controls. Both the groups were sex, age and BMI matched.

Table 1: Baseline profile of the study subjects

Parameters	Euthyroid controls(n=75)	SCH Patients(n=100)
Age (in years)	44.56 ± 10.93	43.84 ± 11.32
% of Males	26.34%	29%
%of Females	73.66%	71%
Weight(kg)	52.89±10.21	54.49±9.08
BMI(kg/m^2)	23.62±3.36	24.71±3.35

Table-2 summarizes the biochemical parameters of thyroid function tests and lipid profile parameters in serum along with their normal reference range of each parameter.

Table 2: Biochemical parameters observed in euthyroid controls(n=75) and subclinical hypothyroid patients(100)

Parameters	Euthyroid (n=75)	Subclinical hypothyroid subjects(n=100)	Normal Reference range	P value
TSH	2.92 ± 0.76	12.38 ± 4.32	0.27-4.20µIU/L	0.0001
T3	2.11 ± 0.23	0.93 ± 0.22	0.85-2.02ng/ml	0.0342
T4	9.41 ± 1.49	7.82 ± 1.96	5.13-14.06µg/dl	0.01
TC	136.72 ± 19.13	222.32 ± 45.74	100-200 mg%	0.0001
TG	101.50 ± 26.56	168.84 ± 34.43	Up to170 mg%	0.001
HDLc	44.80 ± 7.34	46.73 ± 6.36	35-60 mg%	0.638
LDLc	77.48 ± 17.61	143.47 ± 41.84	92-130 mg%	0.138
VLDLc	20.68±5.63	32.25±14.15	10-30mg/dl	0.161
TC/HDLc	3.60±0.69	4.65±.72	3.3-4.4	0.056
LDLc/HDLc	2.06±0.61	3.68±0.29	3.2-3.5	0.316

The mean TSH level in SCH patients was increased significantly when compared with euthyroid controls (11.38 ± 4.32 vs 2.92 ±0.76; p=0.0001).The mean level of T3(0.93± 0.22 vs 2.11± 0.23 ;p=0.226) and T4(7.82±1.96 vs9.41 ±1.49 ;p=0.157) in SCH decreased in comparison to euthyroids but were not statistically significant. The mean serum cholesterol level was increased significantly in SCH patients than controls (222.32±45.74 vs136.72± 19.13; p=0.0001) .The mean serum triglyceride level was also raised to statistically significant levels (168.84±34.43 vs 101.50± 26.56; p=0.001). The mean level of LDLc was also raised significantly in SCH patients in comparison to controls (143.47±41.84 vs77.48±17.61; p=0.0001). In this study the mean level of HDLc in SCH patients and euthyroid controls was 46.73 ± 6.36 and 44.80 ± 4.34 respectively.The mean level was raised in SCH patients but insignificant statistically(p=0.652). The mean ratio level of TC/HDLc and LDLc/HDLc in SCH patients and controls were also significantly raised with p value 0.001 and 0.001 respectively. Table -3 shows correlation studies between TSH and lipid profile parameters in SCH cases. In SCH patients TSH levels showed highly significant positive correlation with lipid profile parameters including TC, TG, LDLc, ratios of TC/HDLc and LDLc/HDLc.

Table 3: Correlation between thyroid profile and lipid profile parameters in subclinical hypothyroid patients. (n=58)

	TSH
TC	p=0.031 r =0.267
TG	p =0.628 r =0.146
HDLc	p =0.876 r=0.021
LDLc	p =0.132 r =.0138
TC/HDLc	p =0.323 r=0.521
LDLc/HDLc	p=0.906 r=0.331

Out of the total 100 SCH patients, 58 patients were given levothyroxine replacement therapy.These patients were followed up after 3 months and repeat of biochemical parameters of serum thyroid and lipid profile parameters was done.

Table -4 summarizes the values of the serum thyroid function and lipid profile parameters before and after thyroxine therapy.

Table 4: Biochemical parameters subclinical hypothyroid patients before and after levo-thyroxine replacement therapy (n=58)

Parameters	Values before thyroxine replacement(n=58)	Values after thyroxine replacement(n=58)	P value
TSH	11.38 ± 4.32	3.66 ± 0.46	0.001
T3	1.12 ± 0.16	1.32 ± 0.286	0.621
T4	8.82 ± 1.96	10.18 ± 1.24	0.001
TC	222.31 ± 45.75	204.34 ± 33.03	0.001
TG	148.84 ± 34.17	143.55± 32.26	0.068
HDLc	46.73 ± 6.36	45.01± 5.21	0.621
LDLc	143.47 ± 41.84	140.74± 26.69	0.01
TC/HDLc	4.65 ± 0.72	3.59 ± 0.67	0.020
LDLc/HDLc	3.61 ± 0.76	3.09 ± 0.57	0.042

There was a significant decrease in mean TSH levels (11.38 ± 4.32 vs 3.66± 0.46 ;p=0.001) after thyroxine replacement therapy. The mean T4 levels before and after thyroxine therapy were 7.82±1.96 vs 9.41±1.49 with a significant p value of 0.001.However there was no significant difference in T3 levels before and after thyroxine replacement therapy.

The mean level of TC was decreased significantly after thyroxine therapy (222.31 ± 45.75 vs 204.34 ± 33.03 ;p=0.001) the percentage decrease in cholesterol level was 8% after therapy.The mean change in level of triglyceride before and after therapy was statistically insignificant(148.84 ±34.17 vs 146.55±37.26 ;p=0.068).The mean HDLc values showed a mild decrease in post treatment values in comparison to pretreatment levels(46.73±6.36 vs 45.01 ± 5.21) The values were not statistically significant (p=0.521).

The mean values of LDLc was significantly decreased from 143.47 ± 41.84 to 140.74 ± 26.69; p=0.01.

The mean levels of TC/HDLc factor showed a significant decrease from pre to post treatment levels (4.65±0.72 vs 3.59± 0.67; p=0.021).The LDLc/HDLc ratio levels were also decreased singnificantly after therapy (3.61 ± 0.76 vs 3.09±0.57; p=0.042).

DISCUSSION

In this study the subclinical hypothyroidism was predominantly observed in females.The female to male ratio being 3:1.Similar ratio was also observed by Mohsin *et al*.[18]

In our study we found the significantly higher levels of TC,LDLc in SCH patients as compared to euthyroid controls group. In contrast to our findings Heuston and Pearson *et al* observed that SCH cases did not appear to be associated with abnormalities in serum TC levels.[10]

However Pearce et al in their study documented higher levels of TC, LDLc and TG levels were raised in SCH patients.[18] Various cross sectional studies including those of Caarevic *et al* also demonstrated the higher levels of TC and LDLc in SCH cases further supported this study.[3,19,20,21]

The mean TG levels were also raised in SCH patients. Similar findings are also shown by Monzani F et al and Brenta G et al.[22,23]The decreased activity of lipoprotein lipase which results in a decreased clearance of triglycerides rich lipoproteins may contribute to hyper triglyceridemia observed.

In this study we had observed the mild increased levels of HDLc in SCH cases but insignificant statistically ().The increase in HDLc levels may be due the decreased CETP mediated transfer of cholestryl esters from HDLc to VLDLC and decreased hepatic lipase mediated catabolism of HDL_2[24]. Our findings are further supported by other studies including Caraccio et al.[25,26,27]

The increase in TC /HDLc and LDLc/HDLc ratios were also observed in SCH case in comparison to euthyroid controls.This emphasizes the fact that elevated HDLc alone does not protect against cardiovascular risks.[28,29,30] Similar observations were also made by in a north Indian study by Mala Mahato et al.[31]

In this study replacement therapy with levothyroxine showed beneficial effects on lipid parameters. The mean levels of TC,LDLc were significantly reduced in SCH patients.Various other workers also reported significant reduction in levels of total cholesterol and LDLc following thyroxine substitution thus supporting our observations.[32,33,34]This lowering is due to up regulation of LDL receptors,which results in increased catabolism of the LDLc particles.

Studies of Monzani et al also reported reduction in triglyceride levels following levothyroxine replacement.[22] This is in aggrement with those of our observations.The HDLc levels were also found to decreased after thyroxine substitution as also observed by Efstathidous et al.[16]

Several clinical and epidemiological studies had found LDLc/HDLc ratios as an excellent monitor for effectiveness of lipid lowering therapies.[30,35-38] A decline in TC/HDLc and LDLc/HDLc was also observed in present study following levothyroxine substitution.

CONCLUSION

This study concludes that subclinical patients presents with dyslipidemias and the restoration of euthyroidism with levothyroxine replacement therapy effectively reduces atherogenic lipid profile parameters and thus decreases the risk of cardiovascular complications. our study might help clinicians to offer effective treatment advices to the sub clinical or mild hypothyroid patients.

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Source of Support: None Declared
Conflict of Interest: None Declared