An Echocardiographic Evaluation of Diastolic Dysfunction in Patients with Subclinical Hypothyroidism & the effect of L-Thyroxine treatment: A hospital based study.

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ABSTRACT:

Background & Aims: *Diastolic dysfunction is the common condition with Subclinical Hypothyroidism and is reversible in many cases after treatment. We aimed to investigate the response of diastolic dysfunction to thyroid hormone replacement therapy in patients of Subclinical Hypothyroidism.*

Methods: *Forty newly diagnosed cases of Subclinical Hypothyroidism (38 females and 2 males) and age more than 18 years were included. Diagnosis was made on the basis of history, clinical examination and thyroid function tests. Echocardiography was performed in all and was repeated after 4-6 months in those who had diastolic dysfunction. Distribution of Diastolic dysfunction among the involved cases and their response to treatment with L-thyroxine were studied.*

Results: *The diastolic dysfunction was found in 15 (37.5%) and pericardial effusion (PE) in five (12.5%) patients. Fourteen of them had impaired relaxation abnormality and only one patient had pseudonormal pattern. With replacement therapy, 13 reverted back to the normal whereas one having grade 2 diastolic dysfunction (pseudonormal pattern) reverted to grade 1. One patient who had grade 1 diastolic dysfunction (impaired relaxation) did not improve. Pericardial effusion subsided in all 5 cases.*

Conclusions: *Echocardiography may be a useful tool for monitoring the response of diastolic dysfunction to thyroid hormone replacement therapy in patients with Subclinical Hypothyroidism. Our findings suggest that Thyroid Hormone Replacement Therapy may reverse diastolic dysfunction in Subclinical Hypothyroidism.*

Citation

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Keywords

Hypothyroidism, Echocardiography, Diastolic Dysfunction, L-thyroxine

INTRODUCTION:

Thyroid dysfunction is a major public health problem among the local population in Eastern Nepal. Subclinical hypothyroidism (SCH) is defined as a state of increased serum thyroid-stimulating hormone (TSH) levels, with circulating thyroxine (T 4) and tri-iodothyronine (T 3) concentrations within the population reference range.

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In a study, done in B. P. Koirala Institute of Health Science (BPKIHS),Nepal in 2010, the prevalence of subclinical hypothyroidism amongst the suspected cases was 20.42 % which was much higher compared to the other parts of the world.[1]

Cardiovascular effects of thyroid hormones are quite dramatic and the cardiac abnormalities associated with thyroid dysfunction have attracted a great deal of investigative report.[2] The most-consistent cardiac abnormality recognized in patients with hypothyroidism is impairment of left Ventricular (LV) diastolic function, which is characterized by slowed myocardial relaxation and impaired early ventricular filling. LV systolic function is usually subnormal, as demonstrated by slightly reduced values of ejection fraction and stroke volume.

As hypothyroidism has numerous effects on the cardiovascular system, increased capillary permeability leads to pericardial effusion, increased systemic vascular resistance causes hypertension.[3] Pericardial effusion is mainly related to thyrotrophin plasma levels. Pericardial effusion occurs in 30-80% of subjects with hypothyroidism and it depends upon the severity of disease.[4] In almost all cases these cardiovascular changes are reversible when the underlying thyroid disorder is recognized and treated.[5]

The present study aimed to find out Echocardiography findings of cardiac changes with special regards to diastolic function in patients of Subclinical hypothyroidism and response to treatment.

METHODS

The present descriptive cross sectional study was conducted in the Department Of Internal Medicine at (BPKIHS), Dharan, Nepal which included 40 newly diagnosed and pre-consented cases of subclinical hypothyroidism in adult population aged>18 yrs, recruited over a period of one year. Patients with known primary heart disease, hypertension, diabetes mellitus, poor echo window and those taking medicines that could alter cardiac functions, like β-blockers, Calcium channels blocker, Amiodarone were excluded from the study. We only screened those patients where there was strong suspicion of hypothyroidism clinically.The diagnosis of hypothyroidism was made on the basis of history, clinical examination and thyroid function test report. Assessment of Thyroid function tests (TFT): FT3, FT4, TSH) was done by ELISA method using standardized commercially available kits employing Competitive ELISA for FT3 & FT4 and Sandwich ELISA for TSH. The normal reference values for TFT were fT3:1.4-4.2 pg/ml, fT4:0.8-2.2 ng/dl, TSH: 0.3-6.2 mIU/l

Echocardiographic Diagnostic Criteria of Diastolic Dysfunction:

Indices used were: (with normal values)

- Peak E (86 ± 16 cm)
- Peak A (56 ± 18 cm)
- E/A ratio (1.6 ± 0.5)
- Deceleration time (DT) (160-240 m sec)
- Left ventricular isovolumetric relaxation time (IVRT) (70-90 m sec)

A mitral inflow pattern of **abnormal relaxation** [E<A; prolonged IVRT; prolonged DT].

- in patients less than 55 yrs of age E/A <1
- in patients more than 55 yrs <0.8
- DT >240 msec
- IVRT >90 msec

All the cases that fulfilled the inclusion and exclusion criteria included in the study underwent echocardiography on the first visit using Echo machine HP **SONOS 1800** and both the normal as well as abnormal echo findings were included. Treatment of hypothyroidism was started with tablet L-thyroxine 100 microgram daily, as **the evidence suggests that a daily dose of L -thyroxine between 50 and 100 µg daily is adequate to normalise serum TSH in most SCH patients 6.**

TSH was repeated after 3 months and the dose of thyroxine titrated accordingly.

Statistical analysis: Data were analyzed using Statistical package for social sciences (SPSS version-10) for windows. Student's T test was used to compare the Mean values between the two groups i.e., diastolic dysfunction and no diastolic dysfunction, using P-value<0.05 as statistically significant. Percentage, Proportion, and other Statistical parameters were calculated and applied as applicable to other variables.

Ethical clearance was taken from the institution Ethical Review Board (ERB) of BPKIHS, Dharan, Nepal.

Result:

Hypothyroidism patients who had diastolic dysfunction on echocardiography were older than those who did not have diastolic dysfunction (42.73±16.13 vs 35.20±11.41) but it was not statistically significant. (p value= 0.092).

Age distribution

Study Group	Mean age (yrs) ± std. deviation	P value
Normal (n=25)	35.20 ±11.41	0.092
Diastolic dysfunction (n=15)	42.73± 16.13	

Diastolic dysfunction was detected in 15 patients (37.5%), while. Pericardial effusion was observed only in 5 (12.5%) cases. Among the 15 cases with diastolic dysfunction, impaired relaxation abnormalities was found in 14 (93.33%) and one patient had a pseudonormal pattern of left ventricular filling. None of them had a restrictive physiology pattern. (**Table 1)**

Table 1. Variables evaluated in the study subjects (N=40)

Variables	Diastolic dysfunction		P value
	Present(n=15) (Mean±SD)	Absent (n=25) (Mean±SD)	
Age	42.73±16.13	35.20±11.41	0.092
Duration of illness (months)	3.27±1.44	2.52±0.82	0.043
BMI (kg/m2)	25.33±0.82	24.64±0.91	0.020
T3	2.28±0.96	2.46±0.76	0.50
T4	1.64±0.63	1.40±0.60	0.24
TSH	23.21±10.21	15.10±7.97	0.008
E	0.59±0.14	0.77±0.14	0.001
A	0.72±0.16	0.53±9.76	0.001
E/A	0.82±0.15	1.45±0.22	0.001
DT	222±38.95	189±29.87	0.092
IVRT	124.27±18.71	98.24±16.26	0.082

All the patients had highly raised TSH values before treatment Thirty-eight patients (95%) had normal T4 values before treatment whereas two cases (5%) had slightly decreased T4 values. Thirty six patients (90%) had normal T3 before treatment whereas only 4 cases had decreased T3 values.

In patients without diastolic dysfunction the mean T3 level was 2.46±0.76 pg/ml T4 was 1.40±0.60 ng/dl and TSH value was 15.10 ± 7.97 mIU/L. Likewise, patients with diastolic dysfunction had mean T3 of 2.28 ±0.96 pg/ml, T4 1.64 ±0.63 ng/dl and TSH of 23.21 ±10.21 mIU/L. **(Table 2)**

Table 2. Thyroid Profile before starting treatment

Variable	Normal (n=25)	Diastolic dysfunction (n=15)	P value
T3 (pg/ml)	2.46 ±0.76	2.28 ±0.96	0.50
T4 (ng/dl)	1.40 ±0.60	1.64 ±0.63	0.24
TSH (mIU/L)	15.10 ± 7.97	23.21 ±10.21	0.008

Although TSH was raised in both the group of patients, the mean TSH value in the diastolic dysfunction group (n=15) was significantly higher than the normal echo group. (p=0.008) and were therefore, treated with L-thyroxine. FT3 (pg/ml) values before treatment in these patients were 2.28 ±0.96 and FT4 (ng/dl) was 1.64 ±0.63 which on treatment were raised to 2.244±0.78 and 2.09±0.98 respectively; however, the changes were not statistically significant. The TSH value before treatment in the diastolic dysfunction group was 23.21 ±10.21mIU/L, which was significantly lowered to 10.35 ±3.93 mIU/L (p= 0.0001) following treatment **(Table 3)**. After a follow up of 4-6 months, pericardial effusion subsided in all 5 cases and diastolic dysfunction was reverted towards normal side (increase in E/A ratio, P=0.001).

Table 3. Thyroid function parameters before and after treatment in patients having Diastolic Dysfunction (n=15).

Variable	Before Treatment (n=15)	After Treatment (n=15)	P-value
T3(pg/ml)	2.28 ±0.96	2.244 ±0.78	0.50
T4 (ng/dl)	1.64 ±0.63	2.09 ±0.98	0.20
TSH (mIU/L)	23.21 ±10.21	10.35 ±3.93	0.0001

The variables that were obtained in patients included in the study by echocardiography. Patients without diastolic dysfunction had an E wave of 0.77± 0.14 cm/sec, A wave of 0.53±9.76 cm/sec, E/A ratio of 1.45±0.22, DT of 189±29.87msec and IVRT of 98.24±16.26 msec. In contrast, those with diastolic dysfunction had an E wave of 0.59±0.14 cm/sec, A wave of 0.72±0.16cm/sec, E/A ratio of 0.82±0.15, DT of 222±38.95 msec and IVRT of 124.27±18.71 msec.

Of the fifteen patients of diastolic dysfunction, one had grade 2 diastolic dysfunction with pseudonormal pattern and the rest fourteen were having grade 1 diastolic dysfunction which was impaired relaxation. The patient who was having pseudonormal pattern had mean E value of 0.49 and mean A value of 0.64 after valsalva maneuver and mean E/A of 0.76.

Following treatment with L- thyroxine, and on repeated Echocardiography after a period of 4-6 months, 13/15 cases reverted back to the normal diastolic function. One patient with grade 2 diastolic dysfunction (pseudonormal pattern) reverted to grade1diastolic dysfunction but the one who was having grade 1 diastolic dysfunction did not improve at all. The difference in the A wave and E/A ratio before and after treatment was found to be statististically significant on repeat echocardiography in patients with diastolic dysfunction.

DISCUSSION

The overall prevalence of LV diastolic dysfunction in a random sample of general population, as estimated from echocardiographic measurements, was found to be as high as 27. 3 %.[7] After a follow up of 4-6 months, on repeat Echocardiography, 13 out of 15 patients of diastolic dysfunction group reverted back to the normal state where as one persisted with grade-I diastolic dysfunction (impaired relaxation) and one having grade-II diastolic dysfunction (pseudonormal) reverted to grade-I.

The duration of illness was 2.52± 0.82 months in patients without evidence of diastolic dysfunction and 3.27±1.44 months in patients with diastolic dysfunction. It was observed that patients who had diastolic dysfunction had a longer periods of hypothyroidism than those who did not have and this finding was statistically significant (p value= 0.043).

Studies done by Biondi et al[8] and Tielens et al[9] on cardiovascular effects of hypothyroidism showed that diastolic dysfunction in hypothyroidism is a reversible condition after treatment with L- thyroxine.

Before treatment T3 values were normal in 90 % and T4 in 95 % of the cases. TSH was found to be highly raised in all the cases. Both T3 and T4 were reduced in 10 % and 5% cases respectively.

It was also found that the mean value of T3 and T4 before treatment in normal as well as diastolic dysfunction group was not statistically significant. Whereas the mean TSH value was statistically significant between the two groups before treatment (p=0.008).

As fifteen patients were found to have diastolic dysfunction on echocardiography on their first visit, they were started on treatment with L-thyroxine. After a period of 4-6 months these particular group of patients were followed up and the thyroid function test as well as echocardiography were repeated irrespective of achieving euthroid state. In a study done by De Andrade et al.[10] 13 patients with documented primary hypothyroidism were evaluated through the echocardiography, followed by re-evaluation done six months following L-thyroxine therapy and found that most of the Echocardiographic changes were reversed after treatment. These findings are in consistence with the similar studies done by Biondi et al.[8] T3 value before treatment in the patients who were having diastolic dysfunction was 2.28 ±0.96 pg/ml. Similarly T4 was 1.64

±0.63 ng/dl which became 2.244 ±0.78 and 2.09 ±0.98 after treatment respectively. Our study findings were similar to the that of Biondi et al. [8] in which decrease in mean plasma TSH value after treatment was statistically significant in patients with diastolic dysfunction (P <0.001).

We observed mild pericardial effusion in five out of 15 cases of diastolic dysfunction which reverted back to normal after treatment with L-thyroxine as evident on repeat echocardiography. In a similar study done in 20 overt hypothyroid patients, all but one were found to have disappearance of pericardial effusion with thyroid hormone supplementation as evident by Echocardiographic reevaluation [2].

Biondi et al, [8] in a case control study involving 26 patients of hypothyroidism, observed that Doppler-derived indices of diastolic function showed significant prolongation of the isovolumic relaxation time (94 ± 13 *vs.* 84 ± 8 msec; $P < 0.001$), increased A wave (55 ± 13 *vs.* 48 ± 9 cm/sec; $P < 0.05$). Following L-thyroxine replacement therapy, echocardiography was repeated. The diastolic function showed significant shortening of isovolumic relaxation time (77 ± 15 *vs.* 91 ± 8; $P < 0.05$), reduction of A wave (51 ± 13 *vs.* 60 ± 12; $P < 0.01$). The reduction of A wave in this study is in consistent with our result.

The findings of the present study has been compared with the similar studies that were done earlier by Virtanen et al[11], Di Paola et al[12] **Table 4.** The results demonstrated were compared with the present study. E/A ratio were found to be significant in previous two studies as well as in our study too. In contrast to other studies, A value was found to be significant in our study.

Table 4. Comparison of Echocardiographic findings in different studies:

Author (Year) Eco data	Virtanen et al [28] (2002)	Di Paola et al [47] (2004)	Tayyibe et al [48] (2007)	Present study (2009)
E-wave	-	73 ± 17 vs 65±12, p = 0.01	0.83±0.25 vs 0.99±0.17 P= 0.0001	0.59±0.14 vs 0.67±0.11 P=0.068
A-wave	-	62±19 vs 58±14, p = NS	-	0.72±0.16 vs 0.56±0.12 P=0.01
E/A ratio	1.679 ±0.432 vs 1.947±0.335, p = 0.006	1.2 ±0.5 vs 1.1 ±0.3, p = NS	1.18±0.33 vs 1.33±0.23 p=0.003	0.82±0.15 vs 1.22±0.27 P=0.001
DT	-	233±48 vs 235 ± 45 ms, p = NS	-	222±38.9 vs 200.6 ±29.39 P=0.09
IVRT	88 ± 23 vs 75 ± 24 p = 0.005	93 ± 16 vs 95 ± 37 ms, p = NS	0.98±0.12 vs 0.91±0.08 p=0.001	124.27±18.71 vs 108.67 ±23.56 P=0.08

Considering the low sample size, and lower duration of follow-up, it is recommended to include larger sample size to include both the Subclinical and overt hypothyroid cases and follow them up for a longer duration so that the course of complications with hypothyroidism can be well managed.Septal e' and E/e' measurement would have been ideal but in our study it was not done because of non-availability of Echo machine with that option.

CONCLUSION

The reversal to the normal echocardiographic findings was possible with the L-thyroxine treatment and therefore has an advantage on treating subclinical hypothyroidism cases

depending on the high level of TSH and subsequent Echocardiographic studies.

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