

# A Study of Echocardiographic Changes in Patients with Newly Diagnosed Primary Hypothyroidism: A Cross-sectional Study

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## ABSTRACT

**Background:** Hypothyroidism is known to cause reversible cardiac dysfunction in humans. Thyroid hormone alters the cardiovascular hemodynamics. This study was performed to assess echocardiographic changes in untreated newly diagnosed primary hypothyroid states as such studies are scarce in our setting.

**Methods:** This hospital based cross-sectional study was conducted among 71 patients with newly diagnosed primary hypothyroidism who presented to the medicine outpatient department, at Universal College of Medical Sciences and Teaching Hospital (UCMS-TH), Bhairahawa, Nepal from December 2018 to June 2020 after taking ethical clearance from institutional review committee (UCMS/IRC/212/18). Thyroid function test and echocardiography were carried out in patients under study. The data was analyzed with SPSS Version 16.

**Results:** A total of 71 patients (52 females and 19 males) with primary hypothyroidism were enrolled for the study. Among these 58 cases were overt/clinical hypothyroidism, and 13 cases were subclinical hypothyroidism. Echocardiography was abnormal in 63.4% of cases with 43.7% showing diastolic dysfunction, 18.3% diastolic interventricular septal thickness abnormality, 8.5% diastolic left ventricular posterior wall thickness abnormality, and 8.4% pericardial effusion.

**Conclusion:** Our study found diastolic dysfunction, diastolic interventricular septal thickness abnormality, diastolic left ventricular posterior wall thickness abnormality, and pericardial effusion as the common echocardiographic change in patients with newly diagnosed primary hypothyroidism. Therefore, our study highlights the need for cardiac evaluation of patients with primary hypothyroidism so that early intervention can be performed to improve the clinical outcome.

**Keywords:** Primary hypothyroidism, Echocardiography, Diastolic dysfunction.

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## INTRODUCTION

Thyroid dysfunction is a common endocrine disorder affecting about 300 million people worldwide with over half estimated to be unaware of their condition.<sup>1</sup> In Nepal, the prevalence of thyroid disorders in the general population is about 4.32%.<sup>2</sup> Hypothyroidism is a clinical syndrome which results in deficiency of thyroid hormone. In primary hypothyroidism, there is a defect within the thyroid gland and in secondary hypothyroidism, indirect pathologies (disorders of hypothalamus or pituitary gland) contribute to the decrease in circulating hormone levels.<sup>3</sup> Overt hypothyroidism refers to cases in which the serum thyroid stimulating hormone (TSH) concentration is elevated and serum FT4 (free tetra-iodothyroxine) is below the reference range. Subclinical hypothyroidism is defined as a serum TSH above the defined upper limit of the reference range, with a serum FT4 within the reference range.<sup>4</sup>

Thyroid hormone has the ability to alter the cardiovascular hemodynamics. Besides its direct effects, the thyroid hormone also causes a secondary increase in cardiac contractility by increasing the substrate requirement and oxygen consumption.<sup>5</sup> Thyroid hormone is known to increase sympathetic activity, angiotensinogen and atrial natriuretic peptide. It decreases vasopressin.<sup>6</sup> Hypothyroidism impairs the relaxation of the vascular smooth muscle, produces arterial stiffness and also decreases endothelial nitric oxide which leads to increased vascular resistance (leading to an increase in diastolic BP).<sup>7</sup> Patients with severe and longstanding hypothyroidism can develop pericardial effusions. Electrocardiogram (ECG) changes due to hypothyroidism present as sinus bradycardia, low amplitude P wave, QRS complex, prolonged action potential, PR interval, QT interval and ST segment alteration.<sup>8</sup> Various studies have found links between sub-clinical hypothyroidism, ischemic heart disease and cardiovascular mortality.<sup>7</sup> Echocardiography findings in hypothyroidism ranged from pericardial effusion, diastolic dysfunction, interventricular septal thickening, reduced ejection fraction and dilated cardiomyopathy.<sup>9</sup> Being a non-invasive method, echocardiography can play an important role in recognition of the cardiac pathology and follow up effect of the therapy.<sup>10</sup> This study was performed to assess echocardiographic changes in untreated newly diagnosed primary hypothyroid states.

## MATERIALS AND METHODS

This study was conducted in Universal College of Medical Sciences Teaching Hospital, Bhairahawa, Nepal in the context of newly diagnosed primary hypothyroidism. Case screening for cardiovascular manifestations with echocardiography was performed at

the time of diagnosis of primary hypothyroidism. Study was conducted for one and half year's duration from 9th December 2018 to 30th June 2020. It is a cross sectional observational study carried out on patients with newly diagnosed case of primary hypothyroidism visiting out-patient department of internal medicine at UCMS-TH.

Sample size was calculated by using the formula.  $N = (Z^2PQ)/d^2$ , where,  $Z = 1.96$  for 95% Reliability;  $P =$  Estimated proportion 0.16 (from study done by aryal et.al).<sup>11</sup> and  $d =$  Maximum tolerance error = 0.1. Considering a 10% attrition rate, a minimum of 58 patients were required for the study. In our study 71 newly diagnosed cases of primary hypothyroidism were enrolled.

All newly diagnosed cases of primary hypothyroidism presenting to the OPD of Internal Medicine in Universal College of Medical Sciences & Teaching Hospital (UCMSTH) age 18 years and above were included in the study. Whereas, patients below 18 years of age, patients with secondary hypothyroidism, patients with underlying heart disease, chronic obstructive pulmonary disease, severe anemia, diabetes mellitus or any other endocrine disorder, patients taking beta blockers, lithium, oral contraceptive pills, steroids, amiodarone, and those consuming alcohol, patients refusing participation in the study and pregnant patients were excluded from the study.

**Investigations:** Thyroid function test was measured using vitro chemiluminescent immunoassay for quantitative determination of free T3 (fT3), T4 and TSH in human serum using the MAGLUMI series fully auto chemiluminescence immunoassay analyzer. Thyroid hormone abnormalities were considered if patients' thyroid hormone levels were outside the normal values; fT3 (2.0-4.2 pg/ml), fT4 (8.9-17.2 pg/ml) and TSH (0.3-4.5 mIU/ml).

Echocardiographic studies were done with a two-dimensional (2-D) echocardiography machine GE VIVID-3 with 2 Megahertz (MHz) transducer probe. All studies were performed during normal quiet respiration. Two dimensional and M-mode tracing were obtained in the parasternal window in the slight left lateral position. Five consecutive sinus beats were measured and averaged. Cursor-derived M-mode recordings obtained during two dimensional echocardiographic examinations were used to validate electronic measurements.

**Data Management:** The data were collected and entered in the proforma for each patient by the investigator. The data collected were entered in Statistical Package for Social Sciences (SPSS) Version 16.

Categorical data were expressed as frequencies and corresponding percentage. Quantitative variables were

presented as mean ( $\pm$ standard deviation). Independent t-test, Paired t-test were applied to test the significant difference between quantitative and categorical variables and chi-square test was applied to test the significant difference between two categorical variables. Statistical significance was determined at 5% level of significance.

**Ethical Clearance:** The permission to conduct this research was taken from the institutional review committee of UCMS-TH (UCMS/IRC/212/18) on 18<sup>th</sup> December 2018. Written informed consent was obtained from all the participants.

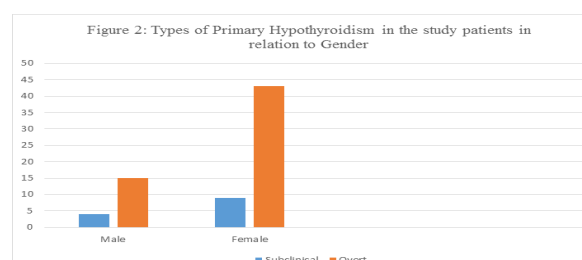
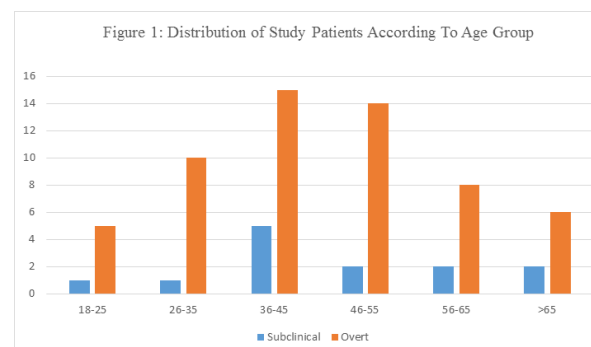
## RESULTS

Out of 71 newly diagnosed primary hypothyroid patients, 73.2 % are female and 26.8 % are male. The median age was 45 years for all primary hypothyroidism, subclinical and overt hypothyroidism patients. The results showed that both subclinical and overt hypothyroidism was mostly seen in the age group 36-45 years and was least in the 18-25 years age group. This is shown in Figure 1. The association between age group and subclinical and overt hypothyroidism was found to be statistically insignificant ( $p=0.87$ ). The bivariate logistic regression showed that age group 36-45 were about 1.67 times more likely to have subclinical hypothyroidism as compared to age group 18-25 ( $OR=1.67$ , 95%  $CI=0.15-17.89$ ,  $p=0.67$ ) and age group 35-45 were two times more likely to have overt hypothyroidism as compared to age group 18-25 years ( $OR=2.0$ , 95%  $CI=0.10-39.07$ ,  $p=0.65$ ).

Regarding presenting complaint in the study, as shown in Table 1, the most common was constipation (50.70%) followed by weight gain (42.30%). Other symptoms were lethargy (39.40%), and dyspnea (23.90%). Few cases (19.70%) presented with dry skin.

As depicted in Table 2, the mean TSH value of subclinical and overt cases was 8.73 & 41.72 respectively with a mean difference of 27.42 and the mean difference was found to be statistically significant ( $P<0.001$ ). It can be concluded that the mean TSH value of overt hypothyroidism was significantly high. Similarly, there was significant mean difference in T3 & T4 value between Subclinical and Overt hypothyroidism. T3 and T4 were found significantly high in overt hypothyroidism.

The prevalence of abnormal echocardiographic findings was found to be 63.4% (45/71) for hypothyroid patients with 67.2% (39/58) in overt and 46.2% (6/13) in subclinical hypothyroidism. As shown in Table 4, the odds ratio of overt hypothyroidism for different Echocardiographic changes are ejection fraction ( $OR=0.09$ , 95%  $CI=0.08-1.16$ ,  $p=0.065$ ), diastolic interventricular septal thickness ( $OR=0.62$ , 95%  $CI=0.16-2.99$ ,  $p=0.62$ ), pericardial effusion ( $OR=1.13$ , 95%  $CI=0.12-10.59$ ,  $p=0.91$ ), and diastolic dysfunction ( $OR=12.85$ , 95%  $C.I.=1.57-105.41$ ,



$p=0.017$ ). The odds ratio of subclinical hypothyroidism for different echocardiographic changes are ejection fraction ( $OR=10.36$ , 95%  $CI=0.86-124.46$ ,  $p=0.065$ ), diastolic interventricular septal thickness ( $OR=1.14$ , 95%  $CI=0.33-6.19$ ,  $p=0.62$ ), pericardial effusion ( $OR=0.88$ , 95%  $CI=0.09-8.27$ ,  $p=0.91$ ), and diastolic dysfunction ( $OR=12.85$ , 95%  $CI=1.57-105.41$ ,  $p=0.04$ ).

## DISCUSSION

In this study, echocardiographic changes were studied in newly diagnosed primary hypothyroid patients attending outpatient department at our center. A total of 71 cases were enrolled in the study including subclinical and overt hypothyroidism who presented for the first time without any known co-morbidities and medication use.

Table 1: Distribution of Study Patients According to Clinical Presentation

| Presenting Complaints    | Frequency | Percentage |
|--------------------------|-----------|------------|
| Constipation             | 36        | 50.70%     |
| Weight Gain              | 30        | 42.30%     |
| Lethargy                 | 28        | 39.40%     |
| Dyspnea                  | 17        | 23.90%     |
| Cold Intolerance         | 17        | 23.90%     |
| Menstrual Irregularities | 16        | 22.50%     |
| Dry Skin                 | 14        | 19.70%     |

In this study among randomly selected 71 cases, 19 cases (26.8%) were males and 52 cases (73.3%) female. A study by Mahato RV et al. in 2015 in Tribhuvan University Teaching hospital also had similar sex distribution.<sup>12</sup> Higher prevalence of thyroid disease among women can be attributed to female sex hormones.<sup>13</sup> Of these the most

Table 2: Distribution of Study Patients with Respect to Thyroid Function Test

| Thyroid function test | Number (n)  | Mean | Standard Deviation (SD) | Mean Difference | p-value |
|-----------------------|-------------|------|-------------------------|-----------------|---------|
| T3                    | Subclinical | 13   | 2.37                    | 0.61            | .088    |
|                       | Overt       | 58   | 1.76                    |                 |         |
| T4                    | Subclinical | 13   | 9.56                    | 5.30            | <0.001  |
|                       | Overt       | 58   | 4.27                    |                 |         |
| TSH                   | Subclinical | 13   | 8.73                    | 33.99           | <0.001  |
|                       | Overt       | 58   | 41.72                   |                 |         |

Table 3: Association of ECHO Abnormality in Relation to Types of Primary Hypothyroidism

| Echo     | Hypothyroidism |           | Total     | Chi-Square | p value |
|----------|----------------|-----------|-----------|------------|---------|
|          | Subclinical    | Overt     |           |            |         |
| Normal   | 7(53.8%)       | 19(32.8%) | 26(36.6%) | 2.03       | 0.2     |
| Abnormal | 6(46.2%)       | 39(67.2%) | 45(63.4%) |            |         |
| Total    | 13             | 58        | 71        |            |         |

common age group was 36-45 years accounting for 28.2% of cases. In a study by Dangi V and Meena RS in 2018 in Bhopal, India most cases were of age group 31-40 years.<sup>14</sup> Among the 71 cases in our study, 13 cases (18.3%) were of subclinical hypothyroidism while 58 cases (81.7%) were of overt hypothyroidism which is in contrast with study by Aryal M et al which showed equal number of subclinical and overt hypothyroidism.<sup>11</sup>

In a study by Kumbhalkar et.al, most common symptom observed in hypothyroidism was weight gain followed by easy fatigability, dry skin, menstrual disturbance, constipation, depression, voice change and least of all neck swelling.<sup>15</sup> Compared to this, in our study, the most common presenting complaint was constipation followed by weight gain. A reduction in gastrointestinal motility is responsible for constipation.<sup>16</sup> In hypothyroidism there occurs a decreased basal metabolism and thermogenesis, an accumulation of hyaluronic acid and a decreased renal flow. These factors collectively lead to water retention and thus weight gain.<sup>17</sup> Among other symptoms noted were lethargy, and dyspnea. Few cases presented with dry skin.

Our study revealed a normal echocardiography in 36.6% of patients which is similar to the study done by Ramesh et.al which showed normal echocardiographic changes in 32.5%.<sup>18</sup> In a study by Al-Fartooosi et al., significant changes in ejection fraction, fractional shortening,

changes in IVS thickness, IVS and LVPW ratio were found.<sup>19</sup> In our study, 63.4% cases had abnormal echocardiographic changes. Two patients (2.9%) had abnormal IVS/LVPW ratio, 6 patients (8.4%) had pericardial effusion and 3 patients (4.3%) had abnormal ejection fraction. Changes in diastolic interventricular septal thickness were seen among 13(18.3%) cases.

The most common abnormality found was diastolic dysfunction which was seen among 31(43.1%) patients; 28(90.3%) of them had impaired relaxation abnormality and 3(9.7%) had pseudonormal filling. Diastolic dysfunction was significantly high in overt hypothyroidism as compared to subclinical hypothyroidism. All patients with 3(9.7%) with pseudonormal filling belonged to overt hypothyroidism. Shrivastava et al had found an abnormal echocardiography in 64% cases with the most common findings being diastolic dysfunction, which is very similar to our study.<sup>20</sup> Diastolic dysfunction in hypothyroidism is due to decreased activity of sarcoplasmic reticulum calcium ATPase which is an enzyme that regulates intracellular calcium uptake.<sup>21</sup> In a study by Behera et al. done in Eastern India, abnormal echocardiography findings were found in 67%. There were diastolic dysfunction and pericardial effusion each in 26.6% of cases.<sup>23</sup> Whereas in our study diastolic IVS thickness abnormality was the second most common abnormality after diastolic dysfunction.



Table 4: Association of Specific ECHO Changes in Relation to Types of Primary Hypothyroidism

| Echocardiographic Changes                           |          | Subclinical, n (%) | Overt, n (%) | Total     | Chi-square | p-value |
|---|----------|--------------------|--------------|-----------|------------|---------|
| Ejection Fraction                                   | Normal   | 11(84.6%)          | 57(98.3%)    | 68(95.8%) | 4.89       | 0.08    |
|   | Abnormal | 2(15.4%)           | 1 (1.7%)     | 3(4.2%)   |            |         |
| Diastolic Inter ventricular septal thickness        | Normal   | 10(76.9%)          | 48(82.8%)    | 58(81.7%) | 0.24       | 0.44    |
|   | Abnormal | 3(23.1%)           | 10(17.2%)    | 13(18.3%) |            |         |
| Diastolic Left ventricular posterior wall thickness | Normal   | 13(100%)           | 52(89.7%)    | 65(91.5%) | 1.46       | 0.28    |
|   | Abnormal | 0(0%)              | 6(10.3%)     | 6(8.5%)   |            |         |
| IVS/LVPW Ratio                                      | Normal   | 13(100%)           | 56(96.6%)    | 69(97.2%) | 0.46       | 0.66    |
|   | Abnormal | 0(0%)              | 2(100%)      | 2(2.8%)   |            |         |
| Pericardial Effusion                                | Present  | 1(7.7%)            | 5(8.6%)      | 6(8.5%)   | 0.012      | 0.69    |
|   | Absent   | 12(92.3%)          | 53(91.4%)    | 65(91.5%) |            |         |
| Diastolic Dysfunction                               | Present  | 1(7.7%)            | 30(51.7%)    | 31(43.7%) | 8.37       | 0.004   |
|   | Absent   | 12(92.3%)          | 28(48.3%)    | 40(56.3%) |            |         |

The cause for pericardial effusion in hypothyroidism is thought to be due to an increased capillary permeability and reduced lymphatic drainage from the pericardial space.<sup>24</sup> Diastolic IVS thickness abnormality was found to be 18.3% in our study which is comparable with the study done by Preshant et al which showed 16.6%.<sup>19</sup> Diastolic left ventricular posterior wall thickness abnormality was about 8.5% in our study while in a study done by Mulki et.al it was 15.6%.<sup>25</sup>

In a study by Dangi V and Meena RS, 60% had abnormal echocardiography of which 32% had pericardial effusion, 18% had diastolic dysfunction and 4% has interventricular septum thickening.<sup>12</sup> The deposition of mucopolysaccharides or edema in the cardiac wall is thought to alter the cardiac remodeling in hypothyroidism<sup>26</sup>. However, our study reported diastolic dysfunction as the most common abnormality followed by interventricular septum thickening and pericardial effusion. In our study, 8.5% of the patients had pericardial effusion whereas it was 18% in a study done by Sashikanth et.al.<sup>27</sup> A meta-analysis done by Chen Xin et al. published in 2011 had concluded that hypothyroidism is significantly correlated with left ventricular diastolic dysfunction. However, no obvious correlation with left ventricular systolic dysfunction was found, suggesting that hypothyroidism leads to changes in cardiac function.<sup>28</sup> Our study also showed significant diastolic dysfunction.

This is a single hospital-based study, so the results obtained from this study cannot be generalized. No controls were recruited making it difficult to interpret whether findings were incidental or not. This is important regarding diastolic dysfunction as about 27% of normal population can have some degree of diastolic dysfunction.<sup>29</sup> Comparing pre and

post-treatment ECHO changes would have helped to better explain cardiac changes secondary to hypothyroidism.

## CONCLUSION

We studied echocardiographic changes in newly diagnosed primary hypothyroidism patients with no known comorbidities. Commonest abnormality in our study was diastolic dysfunction. Other findings were diastolic IVS thickness abnormality, diastolic left ventricular posterior wall thickness abnormality, and pericardial effusion. Our study highlights the need for cardiac evaluation of patients with primary hypothyroidism so that early intervention can be performed to improve the clinical outcome.

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