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Research Article

PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM IN JANAKPUR NEPAL

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ABSTRACT

Objective: To determine mode of presentation, frequency and prevalence of subclinical hypothyroidism in Janakpur, Nepal. **Methods:**This study was conducted at provincial hospital Janakpur and Madanta Research Clinic Pvt.Ltd. Janakpur from December 2020-2021. This was a cross-sectional study of patients presented with symptoms and signs suggestive of hypothyroidism. Diagnostic algorithms were based on 2013 guidelines from European Thyroid Association. Subclinical hypothyroidism was defined as an elevated thyrotropin (TSH) concentration with normal serum level of thyroxine(fT4). Patients below 85 years old presented with symptoms and signs of hypothyroidism, who had given written consent were included in study. Those with current prescription of levothyroxine, anti-thyroid drugs, amiodarone and who had history of thyroid surgery or receipt of radioactive iodine within previous 12 month or having history of recent hospital admission for myocardial infarction and other terminal illness were excluded from study. Data were analysed using IBM SPSS 25. **Results:** A total of 697 patients were enrolled in this study out of which 582(84.94%) were female and 105(15.1%) were male. Among them 58.97% of cases were from age group between 20 to 40 years. Symptoms like constipation (86.4%), tingling/numbness (85.5%), weight gain (85.5%), edema (85.5%), palpitation (85.5%), lethargy (85.5%) and easy fatigability (85.5%) were overall common clinical presentation documented. Overall mean TSH value(29.5mU/L) was significantly higher among age group 70 to 80 year followed by mean TSH value of 12.03021mU/L among age group 30 to 40 year. Symptoms like lethargy, easy fatigability, edema, tingling/numbness, weight gain, palpitation and constipation showing relatively high mean TSH value of around 7mU/L. TSH was normal in 529(75.9%) of cases, mildly increase in 121(17.4%) of cases and severely increased in 47(6.7%) of cases. Overall, 24.1% of cased were having TSH more than 4mU/L. Prevalence of subclinical hypothyroidism as calculated in this study was 12.3 percent whereas prevalence among group with TSH value more than 4mU/L was 45.83 percent. Overall, 6.7 percent of cases were having THS value more than 10mU/L. **Conclusion:** Subclinical hypothyroidism is common in Janakpur around half among those with hypothyroidism and so in other part of Nepal significantly higher in female with most patients complaining of constipation, lethargy, easy fatiguability, palpitation, edema and weight gain as main complain. **Categories:** Endocrinology, Internal Medicine, MD general practice.

Keywords: subclinical hypothyroidism, high TSH, thyroid disorder.

INTRODUCTION

Hypothyroidism refers to any condition in which the thyroid gland fails to produce or secrete sufficient amounts of thyroxine[1]. Because thyroxine is an essential hormone for regulating heart rate, digestion, physical growth and brain development and functioning, an insufficient supply to cells can disrupt cellular metabolism throughout the body, leading to organ and tissue damage and result in life-threatening complications. Subclinical hypothyroidism (SCH) is a biochemical condition characterized by serum levels of Thyroid Stimulating Hormone (TSH) above the statistically defined upper limit of reference range, with normal concentration of thyroid hormones, and without clinical features of hypothyroidism[2]. SCH is a common disorder with a prevalence of 1-10% in adults and about 2% in children. SCH is most commonly (50-80% of cases) caused by chronic autoimmune thyroiditis, which is typically characterized by high titers of thyroid peroxidase antibodies, thyroglobulin antibodies and rarely TSH- receptor blocking antibodies. There are many causes of potentially reversible/irreversible subclinical hypothyroidism[15]. Non-thyroidal causes include diabetes mellitus, cystic fibrosis, celiac disease, and chronic renal failure. Other causes are:

Chronic autoimmune thyroiditis (risk factors: family history of autoimmune thyroid disease, personal or family history of associated autoimmune disorders, Down syndrome, Turner syndrome)

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Persistent TSH increase - subacute thyroiditis, postpartum thyroiditis, painless thyroiditis

Thyroid injury – Partial thyroidectomy or other neck surgery, radioactive iodine therapy, external radiotherapy of the head and neck

Drugs impairing thyroid function – Iodine and iodine-containing medications (amiodarone, radiographic contrast agents), lithium carbonate, cytokines (especially interferon alfa), aminoglutethimide, ethionamide, sulfonamides, and sulfonylureas

Inadequate replacement therapy for overt hypothyroidism (inadequate dosage, noncompliance, drug interactions [iron, calcium carbonate, cholestyramine, dietary soy, fiber, etc.], increased T4 clearance [phenytoin, carbamazepine, phenobarbital, etc.], malabsorption)

Thyroid infiltration (amyloidosis, sarcoidosis, hemochromatosis, Riedel's thyroiditis, cystinosis, AIDS, primary thyroid lymphoma)

Central hypothyroidism with impaired TSH bioactivity

Toxic substances, industrial and environmental agents

TSH receptor gene mutations; G-alpha gene mutations

Thyroid dysfunction is one of the most common endocrine disorders seen in clinical practice. The prevalence of thyroid dysfunction varies by age, sex, race/ethnicity, and geographically through variations in dietary iodine intake. Abnormal thyroid function has important ramifications on health outcomes pertinent to older adults, including cardiovascular arrhythmia, metabolism, bone health, and mental

health[3]. Experience shows that, in daily clinical practice, sub- clinical hypothyroidism may be diagnosed in both the outpatient and the inpatient setting on the basis of TSH measurements, not always prompted by symptoms or any specific suspicion of disease[4]. Individuals classified as having SCH are usually asymptomatic, although signs and symptoms of hypothyroidism, such as dry skin, fatigue, cold sensitivity, constipation and muscle cramps, are sometimes present[5].Thus, it is usually not symptoms reported by patients, but incidental findings of laboratory tests, that may lead to the diagnosis or suspected diagnosis of subclinical hypothyroidism.The moment when the diagnosis of subclinical hypothyroidism is documented in the medical records is the moment when the patient is defined as ill. In itself, a moderately raised TSH value (>4 to<10 mU/L) on its own is not a health condition requiring treatment, but the risk does exist that the patient will go on to develop overt hypothyroidism with its potential for associated cardiovascular sequelae.Individuals with subclinical hypothyroidism are at risk for progression to overt thyroid dysfunction with an average yearly progression rate of 2% to 6% and an increased risk in females, individuals with higher levels of TSH, and in the presence of antithyroid peroxidase antibodies, although those without antithyroid peroxidase antibodies have also a higher risk of progression[10]. In contrast, TSH levels normalize in 15% to 65% of those with a single elevated TSH without treatment, over follow-up periods going from 1 to 6 years, and the likelihood of spontaneous recovery is higher with TSH levels <10 mIU/l.Given the important interplay between thyroid hormone (TH) and its receptor present on reproductive organs, thyroid dysfunction may be directly causative for menstrual disturbances and subfertility. Moreover, thyroid dysfunction may act indirectly by altering the secretion of gonadotropin-releasing hormone (GnRH) and other hormones like prolactin[7]. Although restoring thyroid function can normalize the menstrual pattern and/or the reproductive hormonal profile, it is not always followed by pregnancy. In case of male subfertility, endometriosis or tubal obstruction, surgery, and/or an ART procedure may be necessary.The thyroid hormones triiodothyronine (T3) and thyroxine (T4) are created from iodine and tyrosine. The thyroid also produces the hormone calcitonin, which takes on a role in calcium homeostasis. Hormonal output from the thyroid is regulated by thyroid-stimulating hormone (TSH) secreted from the anterior pituitary gland, which itself is regulated by thyrotropin-releasing hormone (TRH) produced by the hypothalamus[6]. All patients with overt hypothyroidism and subclinical hypothyroidism with TSH >10mIU/L should be treated[8]. There is consensus on the need to treat subclinical hypothyroidism of any magnitude in pregnant women and women who are contemplating pregnancy, to decrease the risk of pregnancy complications and impaired cognitive development of the offspring. However, controversy remains regarding treatment of non-pregnant adult patients with subclinical hypothyroidism and serum TSH values ≤10mIU/L. In this subgroup, treatment should be considered in symptomatic patients, patients with infertility, and patients with goiter or positive anti-thyroid peroxidase (TPO) antibodies. Limited evidence suggests that treatment of subclinical hypothyroidism in patients with serum TSH of up to 10 mIU/L should probably be avoided in those aged >85 years.

METHODS

Study design

This was a cross-sectional study of patients presented with features suggestive of hypothyroidism. conducted at provincial hospital Janakpur and Madanta research clinic private limited from December 2020 to December 2021. Provincial hospital Janakpur is the only referral center in province-2 of Nepal.

Diagnostic criteria for subclinical hypothyroidism:

Diagnosis is made on the basis of clinical suspicion, the characteristic of clinical signs and TSH, T3, T4 level. Subclinical hypothyroidism is defined as an elevated thyrotropin (TSH) concentration with normal serum levels of thyroxine (T4)[9]. Subclinical hypothyroidism was defined as a TSH level between 4.5–19.9mIU/L with fT4 levels in the reference range, and was further subdivided into subclinical hypothyroidism with mildly elevated TSH 4.50–6.9mU/l, moderately elevated TSH 7.0–9.9mIU/l, and markedly elevated TSH 10.0–19.9mIU/l[10].

Inclusion criteria

- Patient with definite history suggestive of thyroid disorders like those with history suggestive of lethargy, easy fatigability, tingling and numbness, palpitation, cold and hot intolerance, constipation and hoarseness of voice. Also, those having facial puffiness, pedal edema and dry lusterless skin.
- Patient with age below 85-year-old.
- Those with goiter.
- Patient or relatives who gave written consent.

Exclusion criteria

The main exclusion criteria for the trial were

- Current prescription for levothyroxine, antithyroid drugs, amiodarone, or lithium.
- Thyroid surgery or receipt of radioactive iodine within the previous 12 months.
- Those with features suggestive of dementia.
- History of hospitalization for a major illness or an elective surgery within the previous 4 weeks.
- History suggestive of an acute coronary syndrome (including myocardial infarction or unstable angina) within the previous 4 weeks; and terminal illness[11].

Data collection

All data from suspected patients were collected and documented. Parameters like age, sex, address, blood pressure, underlying comorbidities were documented. Clinical features like lethargy, easy fatigability, weight gain, cold intolerance, hoarseness of voices, dry lusterless skin, palpitation, constipation, tingling/numbness, facial puffiness, edema and goiter were noted. Laboratory test like TSH, T3 and T4 were sent and reports were collected. Age was classified into different age class interval for simplicity of analysis as <10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80 and >80. TSH was categorized into different severity level as those having normal TSH, mildly increased and severely increased TSH level. TSH value less than 4mU/L was told as having normal TSH, value between 4-10mU/L were told as having mildly increased and value above 10mU/L were told as having severely increased[14]. Diagnostic algorithms were based on 2013 guidelines from European Thyroid Association[12,13,14]. Measurement of TSH, T3 and T4 were done in all patients, whereas anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies could not be done due to economic issues and non-availability of funds. These tests were performed on automated immunoassay analyzers with standard prescribed procedures.

Statistical methods

Data were analyzed using IBM SPSS statistic 25. Descriptive data were summarized using standard technique and reported as percentage with 95% confidence interval. Continuous data were

presented as mean +/- SD and categorized data as absolute number and percentage. The student t-test and chi-square tests were used for comparison of continuous and categorical variables between groups respectively. Fisher's exact test used for analyzing difference between two groups when there were cells < 5. Correlation between continuous variable were assessed using Pearson's correlation. Predictive values of subclinical hypothyroidismwere assessed by logistic regression.

OBSERVATIONS AND RESULTS:

A total of 697 patients were included in this study out of which 582(84.94%) were female and 105(15.1%) were male. Among them, 58.97% of them were lying in age group 20-40 while 12.20% were teens and around 18.37% were lying in age group 40-60. Only few around 9.04% of them were with age more than 60 year. Patients presented with varied symptoms and signs more common being constipation (86.4%), edema (85.5%), easy fatigability (85.5%), tingling/numbness (85.5%), weight gain (85.5%), palpitation (85.5%) on the other hand less common being dry lusterless skin (15.8%), goiter (15.6%), hoarseness of voice (14.1%), cold intolerance (16.5%) and facial puffiness (16.4%).

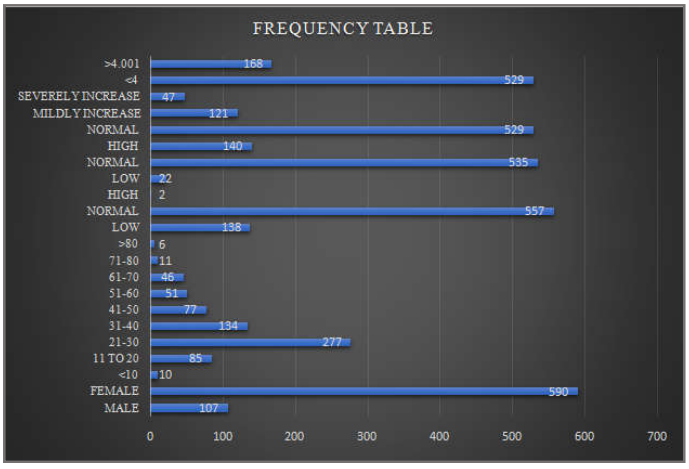


Figure 01- frequency of TSH>4.001 &<4, TSH levels, T3/T4 levels, age class interval and sex

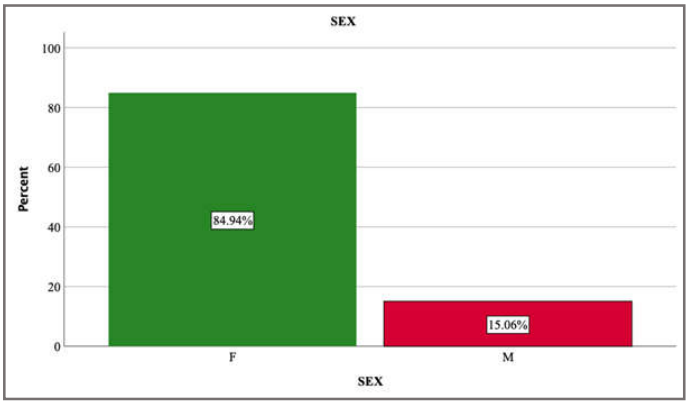


Figure-02 (showing frequency (%) of male and female enrolled in this study.

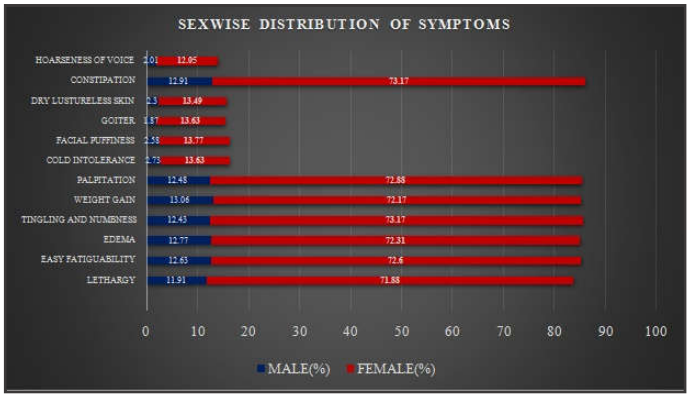


Figure-03

Most of the symptoms like lethargy, weight gain, easy fatigability, palpitation, edema and tingling and numbness were more common in female (figure-03).

MEAN TSH ACROSS DIFFERENT AGE GROUPS

THS AGE CLASS INTERVAL	Mean	N	Std. Deviation	Minimum	Maximum
<10	3.3896	10	3.308733	0.156	12
11-20	3.44927	85	7.138031	0.22	63.4
21-30	5.64002	277	31.160075	0.01	493.53
31-40	12.03021	134	45.469054	0.015	389.15
41-50	5.60009	77	12.781072	0.04	100
51-60	5.11204	51	13.276708	0.03	94.06
61-70	5.78193	46	15.117425	0.05	100
71-80	29.51	11	57.873121	0.14	154.4
>80	1.85333	6	1.004682	0.53	3.32
Total	6.87954	697	29.932124	0.01	493.53

figure-04

Mean TSH among age group 30-40 year was 12.03021mU/L, that among age group 20-30 year was 5.64mU/L and that among 10-20 year was around 3mU/L. However mean TSH among age group 40-70 was around 5mU/L while that among 70-80 was significantly high around 29.5mU/L(figure-04). While calculating mean TSH among different symptoms and signs presented by patients, symptoms like lethargy, easy fatigability, edema, tingling/numbness, weight gain, palpitation and constipation showing high mean TSH of around 7mU/L however symptoms like goiter and dry lusterless skin showing low mean TSH of around 4mU/L(figure-05).

MEAN TSH LEVEL ACROSS DIFFERENT SYMPTOMS

SYMPTOMS	MEAN TSH	STD. DEVIATION	MINIMUM	MAXIMUM
LETHARGY	7.37	31.99	0.01	493.53
EASY FATIGABILITY	7.32	32.21	0.15	493.53
TINGLING AND NUMBNESS	6.75	30.78	0.15	493.53

EDEMA	6.23	22.73	0.01	389.53
WEIGHT GAIN	7.09	31.44	0.01	493.53
PALPITATION	7.14	31.72	0.01	493.53
COLD INTOLERANCE	5.86	17.79	0.025	150
FACIAL PUFFINESS	6.72	20.28	0.03	159
GOITER	3.68	7.38	0.01	63
DRY AND LUSTURELESS SKIN	4.09	5.64	0.14	37.71
CONSTIPATION	7.17	31.77	0.01	493.53

figure-05

Normal TSH was found in 529(75.9%) of cases while TSH was mildly increase in 121(17.4%) of cases and was severely increased in 47(6.7%) of cases. So overall 24.1% of all cases having TSH more than 4mU/L. When all the samples were taken into consideration as a population with signs and symptoms suggestive of thyroid disorders specially hypothyroidism, then overall prevalence of hypothyroidism come to be around 24.1% if 4mU/L is considered as upper limit of TSH13,14. As only 12.3% of case were having normal fT4 level, so overall prevalence of subclinical hypothyroidism will be around 12.3%. However, when taking cases with TSH level more than 4mU/L into calculation then among this group, overall prevalence of subclinical hypothyroidism will come around N=77(45.83%).

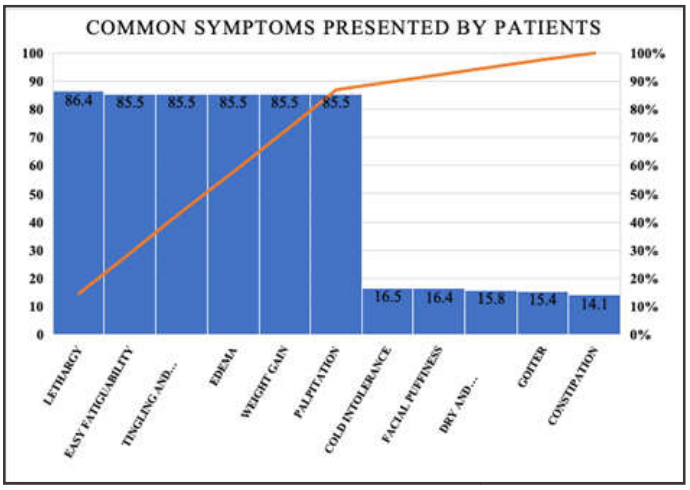
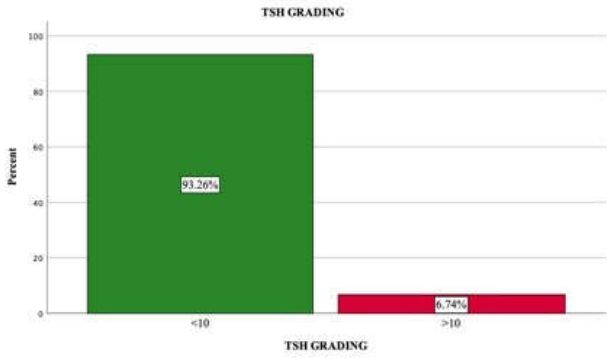


figure-06

This is prevalence of subclinical hypothyroidism among group with hypothyroidism in this study. Overall, 93.26% of case were having TSH value less than 10mU/L and 6.74% of cases with TSH value more than 10mU/L.



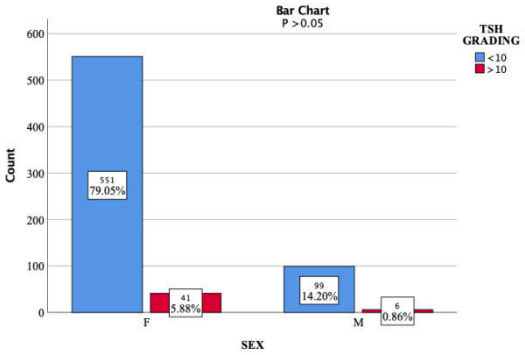


Figure-07(1st-showing frequency of patients with TSH <10 and >10mU/L; 2nd- showing percentage of male and female among patients with TSH >10 and < 10mU/L.

DISCUSSION

In a population-based study, the prevalence of subclinical hypothyroidism ranges from 4-15 percent[1,2] which is comparable to our study where we have found prevalence of subclinical hypothyroidism to be 12.3 percent. In united states Third National Health and Examination Survey (NHANES III); which excluded subjects with known thyroid diseases, 4.3 percent of 16533 people had subclinical hypothyroidism[3]. In our study; we have not included known case of hypothyroidism in study as well and included only cases who presented with symptoms and signs suggestive of hypothyroidism like lethargy, constipation, tingling/numbness, palpitation, weight gain, edema, cold intolerance and facial puffiness. We have found prevalence of subclinical hypothyroidism to be 12.3 percent in our study and while among those with TSH value more than 4mU/L (with hypothyroidism), prevalence come around 45.83 percent meaning around half of all cased of hypothyroidism found to have subclinical hypothyroidism.In a study conducted by Kanya AM, Harris F, Volpato S et al[4]; prevalence of subclinical hypothyroidism raised with age, was higher in female than male which was comparable to findings of our study. We have also found prevalence of subclinical hypothyroidism to be higher in female however we did not find significant increase in prevalence with age. The prevalence has been reported as 13.6 percent in female and 9.2 percent in male from a cohort karachi[5], which is comparable to findings of our study.Generally; there are two categories of subclinical hypothyroidism according to the elevation in serum TSH level; slightly increased TSH level(4-10mU/L) and severely increased TSH value(>10mU/L) but lower limit of TSH that should be used is still controversial with many studies using different cut offs[6]. Almost 90 percent of patients with subclinical hypothyroidism have milder level of increased TSH. Similar to this study, in our study, TSH was mildly increase in 121(17.4%) and was severely increased in 47(6.7%) of cases. These are findings when calculated among all samples. When calculated among those with TSH level more than 4mU/L, TSH was found to be mildly increase in 72% and was severely increased in 28% of cases.Most patients with subclinical hypothyroidism have serum TSH levels <10 mU/L and are asymptomatic. In particular, older patients with subclinical hypothyroidism appear to be asymptomatic, although many euthyroid older individuals also have symptoms that might be construed as being related to hypothyroidism, including dry skin, constipation, and low energy[16,17,18]. In a population-based, prospective study of 558 individuals in the Netherlands who were screened for hypothyroidism during the month of their 85th birthday and again three years later, 5 percent had subclinical hypothyroidism[16]. At baseline, there was no association between baseline serum TSH concentration and cognitive function, depressive symptoms, or disability in activities of daily living.

Although measures of performance declined over time, increased serum TSH at baseline was associated with a slower decline in ability to perform activities such as preparing one's own meals, shopping for groceries and personal items, managing one's money, using the telephone, and doing housework. In another community-based study of individuals ≥65 years, subclinical hypothyroidism was not associated with depression, anxiety, or cognition[17].Some patients with subclinical hypothyroidism, however, may have vague, nonspecific symptoms suggestive of hypothyroidism, such as fatigue and constipation, but attempts to identify patients clinically have not been successful[2,19].On the other hand, in our study we have not included asymptomatic patients in study. We have included all those patients who presented at our center with symptoms and signs suggestive of hypothyroidism. In our study, common presentationswere constipation (86.4%), lethargy (85.5%), edema (85.5%), weight gain (85.5%), palpitation (85.5%) and easy fatiguability (85.5%). We found mean TSH value of around 7mU/L among cases with above mentioned symptoms.

CONSLUSION

Subclinical hypothyroidism is common in Janakpur around half among those with hypothyroidism and so in other part of Nepal significantly higher in female with most patients complaining of constipation, lethargy, easy fatiguability, palpitation, edema and weight gain as main complain.

Recommendation

Patients presented with symptoms and signs like constipation, lethargy, easy fatigability, palpitation, weight gain, edema and tingling/numbness must be screened for subclinical hypothyroidism. A substantial proportion of patients with subclinical hypothyroidism eventually develops overt hypothyroidism. Annual rate of progression to overt hypothyroidism is around 2 to 4 percent. So subclinical hypothyroidism must be evaluated timely and treated as per guideline.

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