THE STUDY OF ANEMIA IN HYPOTHYROIDISM WITH REFERENCE TO VITAMIN B12 DEFICIENCY

By

DR. PALAK PRITESHKUMAR BHUTA

Dissertation submitted to

S.B.K.S. MEDICAL INSTITUTE & RESEARCH CENTRE

SUMANDEEP VIDYAPEETH, PIPARIA, VADODARA

In partial fulfillment
of requirements for the degree of M.D.
in

INTERNAL MEDICINE

Under the Guidance Of

DR. ARTI MULEY

PROFESSOR

M.D. (MEDICINE)

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S.B.K.S. MEDICAL INSTITUTE & RESEARCH CENTRE,
PIPARIA, VADODARA.

YEAR 2015-2018

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Ref: Your study synopsis entitled "The study of anemia in hypothyroidism with reference to vitamin B12 deficiency." Submitted to the SV IEC for approval.

Sub: Approval for conducting the referenced study

Dear Dr. Palak,

The Sumandeep Vidyapeeth Institutional Ethics Committee (SV IEC) is in receipt of your above mentioned study document and as the research study classifies in the minimal risk category; as recommended by HRRP SBKS MI&RC. The SV IEC approves your study to be conducted in the presented form.

The approval remains valid for a period of 1 year. In case the study is not initiated within one year, the Ethics Committee expects to be informed about the reason for the same and a fresh approval will have to be obtained subsequently.

The Sumandeep Vidyapeeth Institutional Ethics Committee expects to be informed about the progress of the study (every 6 months), any Serious Adverse Event (SAE) occurring in the course of the study, and if any changes are made in the protocol or patient information/informed consent the SVIEC needs to be informed about this in advance and an additional permission is required to be taken. The SV IEC also requires you to submit a copy of the final study report.

Dr. Niraj Pandit
Member Secretary
SV Institutional Ethics committee

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SUMANDEEP VIDYAPEETH
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DATE 28/09/17
SIG.

Date: 28th September 2017

STUDY COMPLETION CERTIFICATE

This is to certify that study synopsis entitled: "The Study of Anemia in Hypothyroidism with Reference to Vitamin B12 Deficiency." Research Project was done by **"Dr. Palak Bhuta"** (PG Student, Dept of Medicine, S.B.K.S MI & RC, Dhiraj Hospital, Piparia, Waghodia road, Vadodara-391760, Gujarat) and it was conducted to the satisfaction of the Sumandeep Vidyapeeth Institutional Ethics committee.

Dr. Niraj Pandit
Member Secretary
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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"THE STUDY OF ANEMIA IN HYPOTHYROIDISM WITH REFERENCE TO VITAMIN B12 DEFICIENCY"** is a bonafide and genuine research work carried out by me under the guidance of **DR. ARTI MULEY, Professor, Department of MEDICINE, SBKS Medical Institute & Research Centre, Piparia, Vadodara.**

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Place: PIPARIA **Dr. Palak Bhuta**

SUMANDEEP VIDYAPEETH

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ENDORSEMENT BY THE H.O.D. & DEAN OF THE INSTITUTION

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Place: PIPARIA **Dr. Palak Priteshkumar Bhuta**

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Dr. Palak Bhuta

ABSTRACT

INTRODUCTION:

Hypothyroidism is a condition caused due to decreased synthesis, metabolism or decreased action of thyroid hormone which can be due to various causes. Hypothyroidism is the most common of thyroid disorders in India, affecting one in ten adults. The prevalence of hypothyroidism is 11% in India, compared with U.K & U.S.A, which is only 2% and 4·6% respectively. Despite the known fact that anemia and thyroid dysfunction often occur simultaneously, the pathophysiology remains unclear. Hypothyroid patients often present with symptoms of numbness, paresthesia, poor memory and weakness, despite being on adequate replacement doses of thyroxin**.** Only few studies have been conducted to assess the cause of anemia and specifically role of Vitamin B12**.** So, we planned this study to see for prevalence of anemia in thyroid patients and to see if there is any association between vitamin B12 deficiency and anemia in patients with hypothyroidism either new or in already diagnosed cases that present to our hospital.

METHODOLOGY:

It was an observational study. It was carried out in the Department of Medicine, SBKS Medical Institute & Research Centre. All hypothyroid patients attending the medicine OPD or admitted to medicine wards were enrolled for the study. The patients already diagnosed as hypothyroid >18 years in age and those who give consent for participation in the study were included. Total 60 patients of hypothyroidism were included in the study. A detailed history was taken from all participants. All were subjected to CBC, thyroid function test, S. Vitamin B12.

Sickling, Urine RM, renal function test, liver function test. S. ferritin, retic count was recorded only if required. Data was analysed to assess the burden of B12 deficiency in hypothyroids and to find out any correlation between TSH level, anemia and vitamin B12 deficiency.

RESULT:

Majority of the patients of hypothyroidism belong to > 50 years' age group of 51 to 60 years. Females are more prone to develop hypothyroidism as compared to the opposite gender. About one third of hypothyroids had decreased vitamin B 12 levels. Fatigue and lethargy were the most commonly reported symptoms, followed by breathlessness and generalized swelling. TSH levels of our study population correlated well with hemoglobin levels and MCV values. However, no clinical symptom correlated with TSH levels. Similarly, no blood indices or physical symptom correlated with vitamin B12 levels. TSH levels itself did not correlate with vitamin B12 levels in our patients. However, 28% of the hypothyroid patients had vitamin b12 deficiency.

CONCLUSION:

Our findings suggest that anemia is common among patients with hypothyroidism as is vitamin b12 deficiency, however we could not establish any significant correlation of TSH with vitamin B12. Data published previously demonstrates the role of thyroxin in anemia that could not be corrected by iron alone. Therefore, based on these results, we would recommend testing for TSH levels in anemic patients and testing for vitamin B12 def. anemia in hypothyroid patients. Further studies are required to understand the pathophysiology and mechanisms involved in

hypothyroidism and vitamin B12 deficiency anemia. A multicentric randomized controlled study will help us in elucidating the role of TSH in vitamin B12 deficiency anemia and overall impact on the clinical outcome in these patients.

This study didn't show any significant correlation of vitamin B12 as a cause of anemia in hypothyroid patients.

Keywords: Hypothyroidism, Anemia, Vitamin B12.

INDEX

LIST OF TABLES

LIST OF FIGURES

LIST OF GRAPHS

INTRODUCTION

Hypothyroidism is a condition caused due to decreased synthesis, metabolism or decreased action of thyroid hormone which can be due to various causes.

Hypothyroidism is the most common of thyroid disorders in India, affecting one in ten adults. The prevalence of hypothyroidism is 11% in India, compared with U.K & U.S.A, which is only 2% and 4·6% respectively. The highest prevalence of hypothyroidism (13·1%) is noted in people of 46–54 years of age, while in 18–35 years aged people being less affected (7·5%). [1]

Thyroid synthesis can be affected by various mechanisms at various levels. It can be due to defect in transport, iodine metabolism, autoimmune, growth factors and receptor malfunction or due to decrease or malfunction of binding proteins.

Differences in iodine status affect the prevalence of hypothyroidism, which occurs in both populations –people with a relatively high iodine intake and in severely iodine-deficient populations.

Hypocellular structure of the bone marrow gives rise to the thought that thyroid hormones play a role in hematopoiesis. As decreased thyroid hormone can adversely affect erythropoiesis, anemia develops in hypothyroidism. It is a common, although frequently underestimated, clinical condition accompanying thyroid diseases. A wide variety of anemic disorders with the prevalence variable up to 20-60% can be seen with hypothyroidism. [2]

It was demonstrated in a large population cohort study that the prevalence of thyroid function disturbance was 5.0% and the percentage of anemia was 5.9% at a mean age of 59.4 years. [3]

Another study done by Omar et al [4] reported 40.9% and 57.1% incidence of anemia accompanying hyperthyroidism and hypothyroidism which was higher than in studies done earlier.

The prevalence of anemia in patients with overt and subclinical hypothyroidism was similar and reached 43% and 39% respectively in a study by Erdogan et al.[5]

Despite the known fact that anemia and thyroid dysfunction often occur simultaneously, the pathophysiology remains unclear. However, different forms of anemia might emerge in the course of thyroid dysfunction. Amongst Normocytic, microcytic & macrocytic anemia, Normocytic anemia is the most common. [6,7]

Although macrocytosis might occur with thyroid disorder, there is controversial information on the metabolic relationship between levels of thyroid stimulating hormone (TSH) and serum vitamin B12 in the general population.

Hypothyroid patients often present with symptoms of numbness, paresthesia, poor memory and weakness, despite being on adequate replacement doses of thyroxin. In one study comparing the vitamin B12 deficiency in primary hypothyroidism found out that, out of 116 patients (95 females and 21 males) evaluated, 39.6% of hypothyroid patients had low vitamin B12 levels. [8]

The association between AITD (Autoimmune thyroid disease) and vitamin B-12 deficiency is likely related to the presence of the autoimmune disorders like atrophic gastritis and/or pernicious anemia, both of which lead to impaired absorption of B-12. [9]

The association between hypothyroidism and B-12 deficiency in the absence of AITD has not been evaluated in detail and may vary according to dietary habits across population groups. [8]

So, we planned this study to see for prevalence of anemia in thyroid patients and to see if there is any association between vitamin B12 deficiency and anemia in patients with hypothyroidism either new or in already diagnosed cases that presents to our hospital.

AIMS AND OBJECTIVES

1. To determine the burden of anemia in Hypothyroid patients.

2. To find if there is any correlation between serum TSH level and level of Vitamin B12 in hypothyroid patients.

REVIEW OF LITERATURE

THYROID

Thyroid gland is an essential endocrine gland that helps in maintaining balance between the normal and diseased life. Its function is to regulate growth by various vital functions form of bone development, neurological development, breathing, temperature, weight, menstrual cycles and much more.

ANATOMY & DEVELOPMENT:

Thyroid Gland is a small i.e. 0.5cm thick, 2cm wide & 1-2 cm high; [11] bi-lobed structure connected to each other by isthmus and located anterior to the trachea between cricoid cartilage and suprasternal notch. It weighs approx. 12-20 gram, is highly vascular & soft in consistency. [10] The gland is composed of closely packed spherical units called follicle and its inner core is filled with colloid that is a highly proteinaceous, clear fluid being the major constituent of total thyroid mass. The follicular cells vary in height with the degree of glandular stimulation, becoming columnar when active and cuboidal when inactive. From the apex of the follicular cell, numerous microvilli extend into the colloid. At or near this surface iodination, exocytosis and initial phase of hormone secretion occurs. The extensive Endoplasmic reticulum found in the cytoplasm of follicle that contains thyroglobulin. [11]

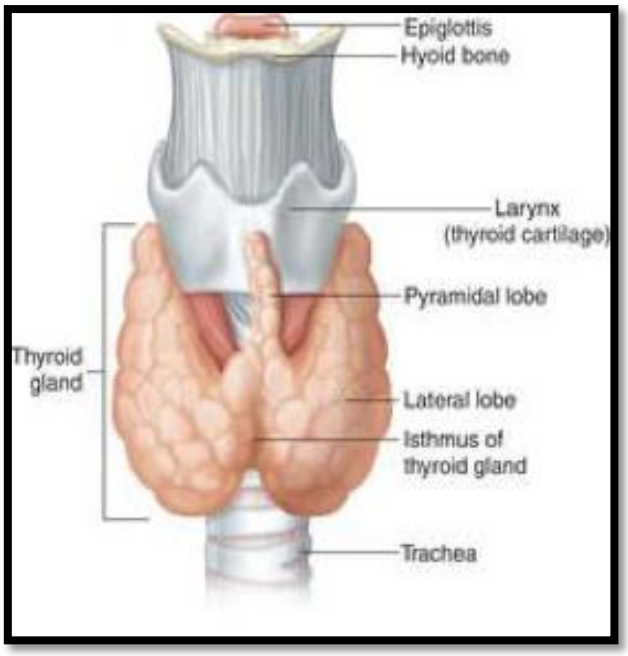


FIGURE 1: ANATOMY OF THYROID GLAND

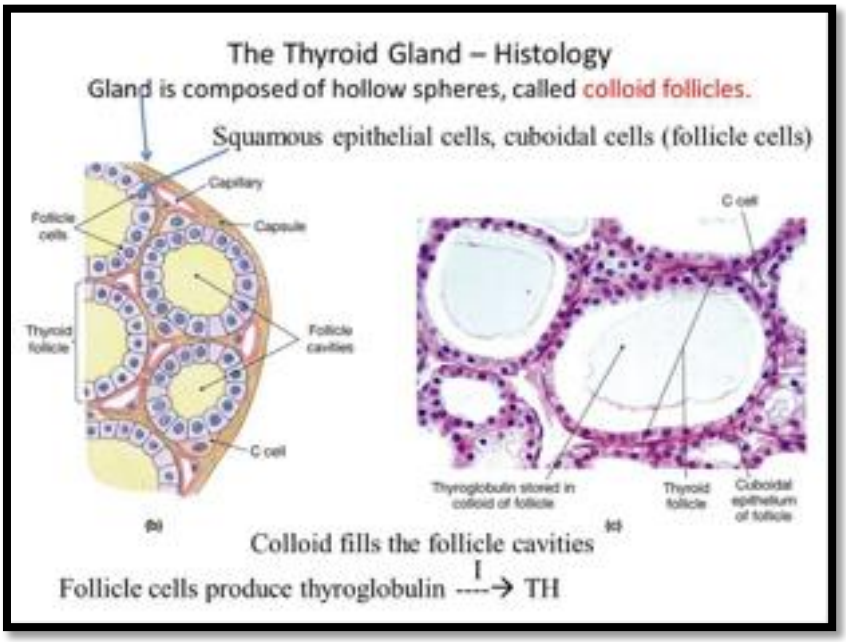


FIGURE 2: THYROID GLAND HISTOLOGY

figure 2- shows thyroid follicles and thyroid cells with colloid in it.

Thyroid gland primarily produces triiodothyronine (T3) & thyroxine (T4) when stimulated by pituitary TSH that gets the signals from hypothalamus by production of TRH. The thyroid gland develops from the floor of the primitive pharynx during the third week of gestation. The developing gland migrates along the thyroglossal duct to reach its final location in the neck. This feature accounts for the rare ectopic location of thyroid tissue at the base of the tongue (lingual thyroid) as well as the occurrence of thyroglossal duct cysts along this developmental tract. Thyroid hormone synthesis normally begins at about 11 weeks' gestation. Thyroid transcription factor (TTF)-1, TTF-2, and paired homeobox-8 (PAX-8) are expressed selectively, but not exclusively, in the thyroid gland. In combination, they dictate thyroid cell development and the induction of thyroid-specific genes such as thyroglobulin (Tg), thyroid peroxidase (TPO), the sodium iodide symporter (Na+/I–, NIS), and the thyroid-stimulating hormone receptor (TSH-R). **[10]**

The Phylogy, embryogenesis and certain aspects of thyroid function are closely interlinked with gastrointestinal tract. Thyroid also contains parafollicular cells or "C" cells that bilaterally migrate from the neural crest and are the source of calcitonin. **[11]**

STRUCTURE OF THYROID HORMONE:

The thyrotrope cells of the anterior pituitary secrete TSH. TSH is a 31-kDa hormone composed of α and β subunits; the α subunit is common to the other glycoprotein hormones (luteinizing hormone, follicle stimulating hormone, human chorionic gonadotropin [hCG]), whereas the TSH β subunit is unique to TSH. **[10]**

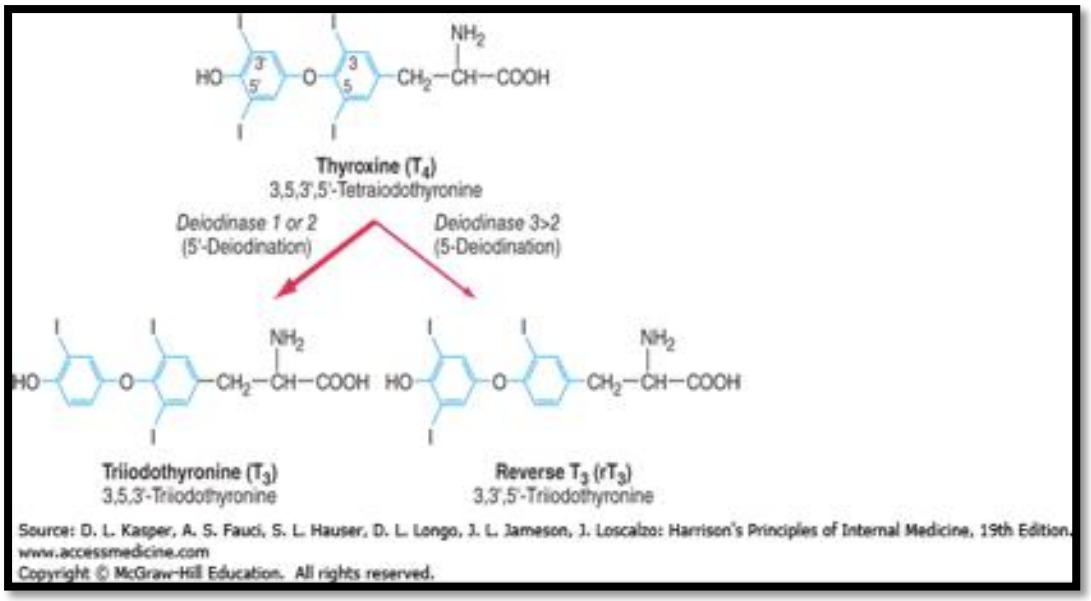


FIGURE 3: THIS FIGURE SHOWS MOLECULAR REPRESENTATION OF THYROID HORMONES T3 AND T4 AND ITS CONVERSION.

THYROID HORMONE SYNTHESIS AND ITS REGULATION:

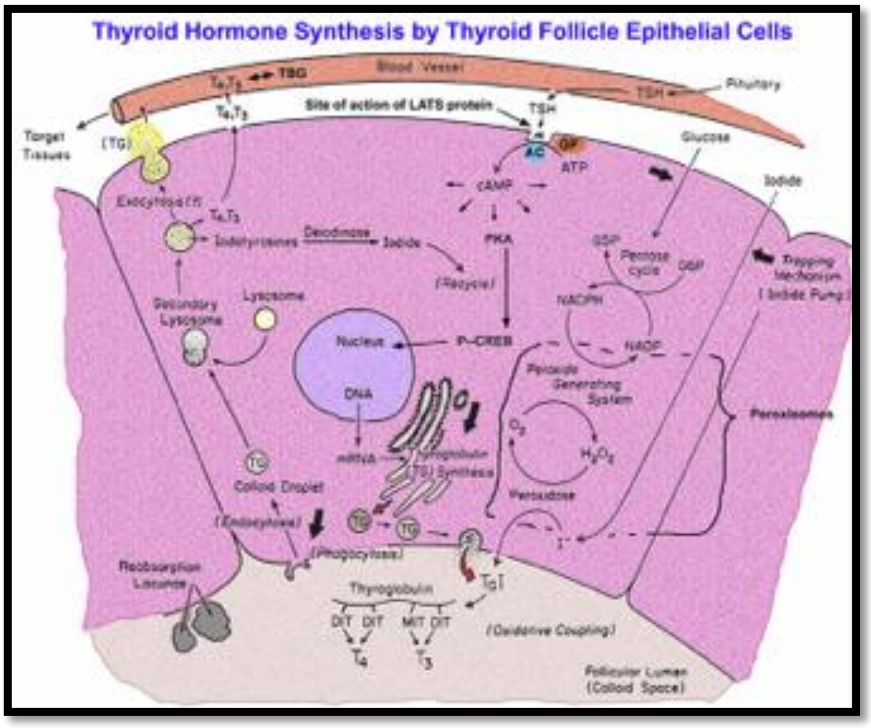


FIGURE 4: THYROID HORMONE SYNTHESIS IN THYROID FOLLICLE.

Thyroid hormone synthesis comprises of 7 important steps.

1. Iodine trapping
2. Synthesis of thyroglobulin
3. Release of Tg (thyroglobulin) in lumen
4. Storage as colloid (Tg, T4, T3)
5. Reabsorption of modified Tg chain in follicular cells
6. Formation of T3, T4
7. Release of T3, T4 in blood

IODINE METABOLISM AND TRANSPORT:

The function of thyroid is to generate the quantity of thyroid hormone necessary to meet the demands of the peripheral tissues. Source of Iodine is mainly diet. Other includes medications, diagnostic agents, dietary supplements and food additives. 20% is absorbed by thyroid gland & rest is excreted in Urine. The requirement of Iodine is different in different countries according to its content in soil, water & dietary practice. Daily requirement in adult is approx. 150 microgram /day. **[11]**

According to the Consumers Affairs volume 2017, the general rule of iodizing salt in India which is not less than 30 parts per million on dry weight basis at manufacture level or not less than 15 ppm on retail, people get enough content through salt.

Iodide per say is rapidly absorbed from GIT (within 30 minutes) and little is lost in stool. In body, iodide is confined largely to extracellular fluid. It is also found in RBC, intraluminal fluid of GIT like in saliva, gastric juice from where it is re-

absorbed to re-enter in ECF (Extra cellular fluid). Normal concentration of iodide in ECF is 10-15 microgram/L, in peripheral pool is 250 microgram and maximum in thyroid is approx. 8000 microgram in form of MIT, DIT. Iodine uptake or trapping is done by the membrane protein thyroidal sodium-iodine symporter (NIS) found in basement membrane of follicular cell by active process. NIS is also located in salivary gland, choroid plexus, gastric mucosa, cytotrophoblast, syncytiotrophoblast and lactating mammary glands so iodine concentration is more in breast milk to supply to the newborn for thyroid synthesis. Iodide is transferred to the colloid and its oxidation is done by thyroperoxidase (TPO) to convert it into iodine. The result is daily synthesis of approximately 110 nmol/L (85 microgram) of T4, which is 65% of iodine by weight. **[11]**

Follicular cells also produce thyroglobulin which is a chain of amino acids containing tyrosine which is formed through activation of gene, mRNA is activated and forms thyroglobulin which further gets glycosylated in Endoplasmic reticulum of cell & through golgi bodies it gets released by the apical membrane of follicular cell into lumen.

Specific tyrosine residues of Tg homodimers are then iodinated at apical border of thyroid cell to form MIT and DIT with the help of DUOX1, DUOX 2 and TPO. Coupling of 2 molecules occur within thyroglobulin chain to form T4 and T3, which further is pinocytosed by phagolysosome in cell after which breakdown occurs by proteolytic enzyme of thyroglobulin chain and t3, t4, MIT & DIT is produced. **[11]** Further T4 & T3 is to be removed out of thyroid cell across the basolateral membrane to enter the circulation. The remaining tyrosine residues are deiodinated by thyroid deiodination enzyme and are reused by another thyroglobulin chain.

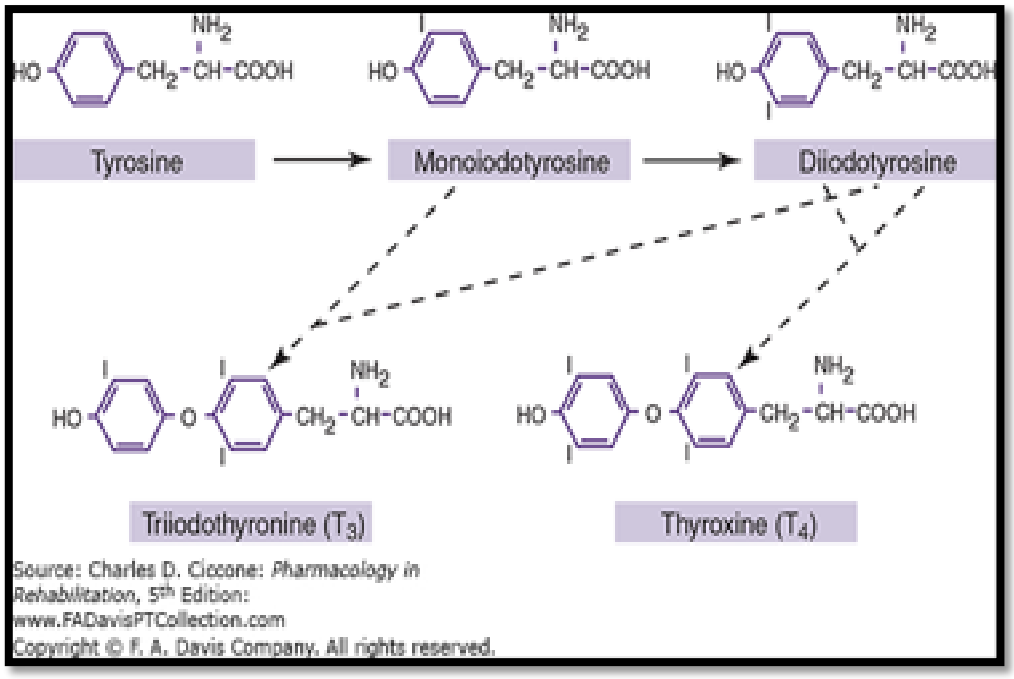


FIGURE 5: FORMATION OF T3 AND T4 VIA MONOIODOTYROSINE AND DIIODOTYROSINE.

Normally in good iodine supplementation t4 is produced more than t3. Once secreted in the blood, it is transported in two forms. One is bound form, in which T3 and T4 are bound to plasma proteins namely thyroid binding globulin, pre-albumin and albumin. T4 is predominantly bound to **thyroid binding globulin** whereas T3 is predominantly bound to albumin. The other form is free T3 and T4. These free forms are in equilibrium with bound form **[12, 13]**. Approximately 99.98% of T4 and 99.7% of T3 are protein bound. T4is converted toT3 by the deiodinase enzymes **{12]** In the periphery one third of T4 is converted to T3 by 5' **Deiodenase an** *45%* to rT3 by*5'* **deiodenase.** They are further metabolized to Diiodothyronines. Only about 13% of T3 is produced from thyroid gland and remaining 87% is formed fromT4.

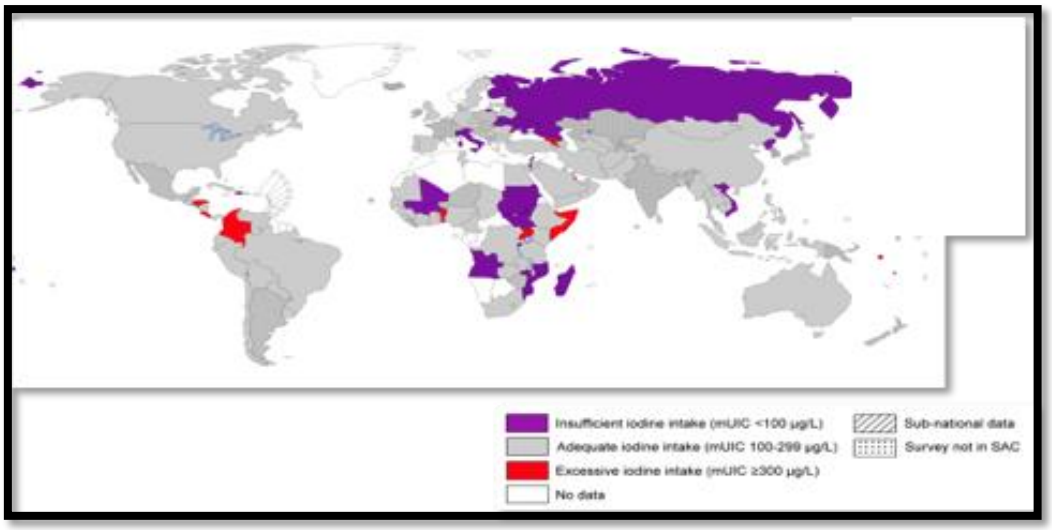


FIGURE 6: GLOBAL MAP OF IODINE STATUS -2016 (INDIAN GLOBAL NETWORK REPORT-2016)

TSH ACTION:

TSH regulates thyroid gland function through the TSHR (Thyroid stimulating hormone receptor), a seven-transmembrane G protein–coupled receptor (GPCR). The TSH-R is coupled to the α subunit of stimulatory G protein (Gsα), which activates adenylyl cyclase, leading to increased production of cyclic adenosine monophosphate (AMP). TSH also stimulates phosphatidylinositol turnover by activating phospholipase C. The functional role of the TSH-R is exemplified by the consequences of naturally occurring mutations. Recessive loss-of-function mutations cause thyroid hypoplasia and congenital hypothyroidism. Dominant gain of-function mutations cause sporadic or familial hyperthyroidism that is characterized by goiter, thyroid cell hyperplasia, and autonomous function. Most of these activating mutations occur in the transmembrane domain of the receptor. They mimic the conformational changes induced by TSH binding or the interactions of thyroid-stimulating immunoglobulins (TSI) in Graves' disease. Activating TSH-R mutations also occur as

somatic events, leading to clonal selection and expansion of the affected thyroid follicular cell and autonomously functioning thyroid nodules. [10]

Other Factors That Influence Hormone Synthesis and Release: Insulin-like growth factor I (IGF-I), epidermal growth factor, transforming growth factor β (TGF-β), endothelins, and various cytokines. Iodine deficiency increases thyroid blood flow and upregulates the NIS, stimulating more efficient iodine uptake. Excess iodide transiently inhibits thyroid iodide organification, a phenomenon known as the Wolff-Chaikoff effect. [10]

Daily TSH production is approx. 100-400mU with a calculated circulating half-life of approx. 50 minutes. Although TSH secretion is pulsatile the low pulse amplitudes and long TSH half-life result in modest circulating variances. Secretory pulses every 2-3 hours are interspersed with periods of tonic, non-pulsatile TSH secretion. Circadian TSH secretion peaks between 11 p.m. and 5 a.m., mainly due to pulse amplitude, which does not appear to be sleep entrained. [11]

Primary Hypothyroidism is associated with enhanced TSH pulse amplitudes occurring throughout the day, and nocturnal TSH surges are abrogated in patients with critical illness. Secretion rates are enhanced up to 15 fold in hypothyroid patients. [11]

THE HYPOTHALAMIC PITUITARY THYROID AXIS:

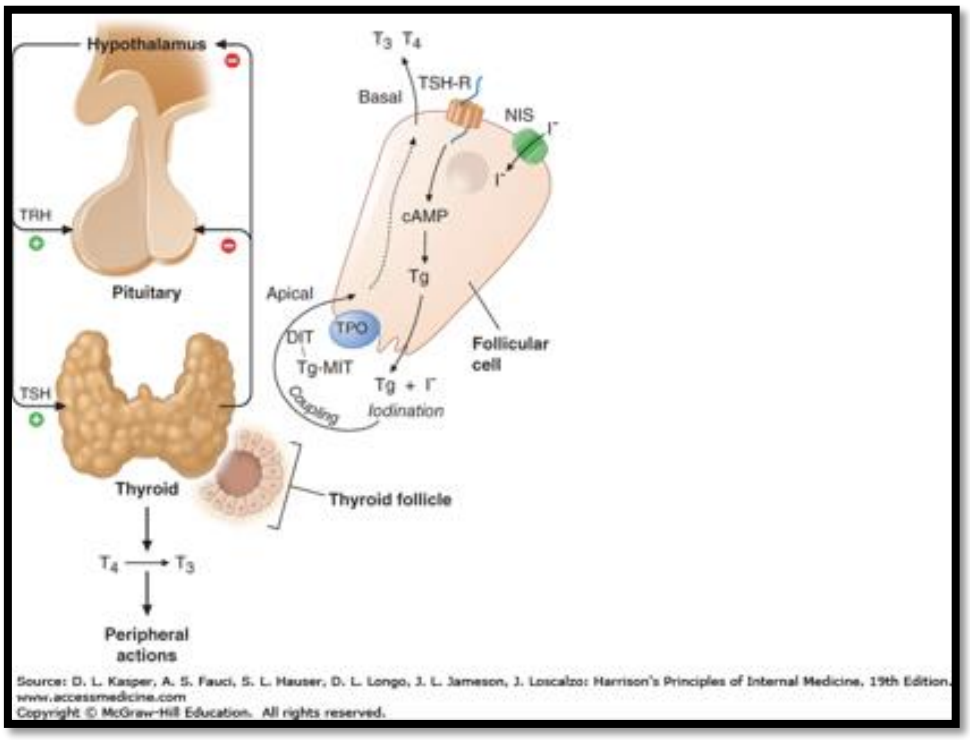


FIGURE 7: HYPOTHALAMIC PITUITARY THYROID AXIS WITH FEEDBACK MECHANISM.

The thyroid participates with the hypothalamus and pituitary in a classic feedback control loop. In addition there is an inverse relationship between the iodine level in the thyroid and the fractional rate of hormone formation. Such auto-regulatory mechanisms stabilize the rate of hormone synthesis despite fluctuations in the availability of iodine. Stability in hormone production is achieved in part because the large intraglandular store of hormone buffers the effect of acute increases or decreases in hormone synthesis. Auto-regulatory mechanisms within the gland, in turn tend to maintain a constant thyroid hormone pool. Finally, the hypothalamic pituitary feedback mechanism senses variations in availability of free thyroid hormones, however small, and acts to correct them. There is a close relationship among the

hypothalamus, anterior pituitary, thyroid gland, higher centers in the brain and function of the entire complex being modified in a typical negative feedback manner by the availability of the thyroid hormones. In addition, other hormones and neuropeptides also influence the axis like Somatotropin release inhibiting factor, Dopamine, Glucocorticoids, sex steroids, cytokines etc**. [11]**

FUNCTIONS OR PHYSIOLOGICAL EFFECTS OF THYROID HORMONES IN BODY ARE:

Metabolic rate and heat production- it increases metabolic activities and so the O_2 consumption. BMR is increased by 60-100%. Since increase metabolism results in increase heat production, thyroid hormone effect is calorigenic.

Intermediary metabolism: modulates rates of many specific reactions involved in fuel metabolism.

Sympathomimetic effect: thyroid hormone increases target cell responsiveness to catecholamine's of adrenals and sympathetic nervous system. Thyroid hormones are permissive and so lead to increase production of specific catecholamine's target cell receptors.

The cardiovascular system: it increases hearts responsiveness to circulating catecholamine's. Increases heart rate and force of contraction, which leads to increase cardiac output. In response to heat load it also leads to peripheral vasodilation to eliminate extra heat.

Effect of growth is manifested mainly in growing children. Thyroid hormone stimulates GH (growth hormone) secretion and promotes GH effects. It has been seen that absence of thyroid hormone can lead to stunting of growth, which is reversible on

supplementing thyroid hormone. It is different in a form that its excess does not lead to gigantism or acromegaly, which is seen in excess GH.

Thyroid hormones are considered important in promoting growth and development of the brain during fetal and postnatal life. Therefore, thyroid hormone deficiency can lead to mental retardation if therapy is not administered days or weeks after birth.

Thyroid hormones are also known to influence synthesis and degradation of carbohydrate, fat and proteins.

Its effect on respiratory system is via its role in production of surfactant and thereby influencing lung development.

Its role in skin and tooth is also seen. It is found to be necessary for tooth development and eruption. In skin, it is important for growth and maturation of epididymis and hair follicles.

Thyroid hormone precursor TRH (Thyroid releasing hormone) is a potent Prolactin releasing factor. TRH has found to cause occasional hyper-prolactenemia with or without galactorrhoea in hypothyroid patients.

NORMAL LEVELS OF THYROID HORMONES:

Normal level of Total T3= 0.79-1.58 ng/dl while of Total T4= 4.00-11.00 μg/dl Normal level of free T3 is 2.1-3.8 pg/ml while of Free T4= 0.82-2.00 ng/dl. Normal level of S. TSH= 0.39-5.0 μIU/ml.

HYPOTHYROIDISM:

Reduced production of thyroid hormone is the central feature of clinical state termed Hypothyroidism. S.TSH >5 is considered as a limit to diagnose the patient as hypothyroid with decrease fT4 levels <0.82 and fT3 <2.1 in a variable manner.

Permanent loss or destruction of the thyroid, through process such as autoimmune destruction or irradiation injury, is describes as primary hypothyroidism. Central or Secondary hypothyroidism caused by insufficient stimulation of a normal gland, is a result of hypothalamic or pituitary disease or defects in the TSH molecule. Reduced action of thyroid hormone at tissue level in the face of normal or increased thyroid hormone production from thyroid gland can also be associated with clinical hypothyroidism. Consumptive hypothyroidism is the result of accelerated inactivation of thyroid hormone by the type 3 iodothyronine deiodenase (D3). Defects of activation of the pro-hormone T4 to active form T3 is also seen. **[11]**

Subclinical Hypothyroidism is defined as elevated serum TSH with normal free t4 concentration. Estimates of incidence of hypothyroidism vary depending on population studied. In U.S 0.3% of the population have overt hypothyroidism defined as elevated serum TSH and reduced free t4 and 4.3% have subclinical or mild hypothyroidism. **[11]**

Among adult people in India, the prevalence of hypothyroidism has been recently studied. In this population-based study done in Cochin on 971 adult subjects, the prevalence of hypothyroidism was 3.9%. **[14]** The prevalence of subclinical hypothyroidism was also high in this study, the value being 9.4%. In women, the prevalence was higher, at 11.4%, when compared with men, in whom the prevalence was 6.2%. The prevalence of subclinical hypothyroidism increased with age. About

53% of subjects with subclinical hypothyroidism were positive for anti-TPO antibodies. This was a population-based study, which used cluster sampling strategy.[14] In this study, Urinary Iodine Status was studied in 954 subjects from the same population sampled, and the median value was 211 μg/l; this suggested that this population was iodine sufficient.[15]

Subclinical hypothyroidism (SCH) is defined as a S.TSH level above the upper limit of normal despite normal levels of serum free thyroxin (fT4). Subclinical hypothyroidism or mild thyroid failure is a common problem, with a prevalence of 3% to 8% in the population without known thyroid disease. [16]

Causes of Hypothyroidism: [11]

1) Primary Hypothyroidism:
    a. Acquired
    i. Hashimotos thyroiditis
    ii. Iodine deficiency (endemic goiter)
    iii. Drugs blocking synthesis or release of T4 (Lithium, ethionamide, sulfonamides, iodide)
    iv. Goitrogens in foodstuffs or as endemic substances or pollutants
    v. Cytokines (interferon gamma, interlukin-2)
    vi. Thyroid infiltration (amyloidosis, hemochromatosis, sarcoidosis, Riedels struma, cystinosis, scleroderma)
    vii. Post ablative thyroiditis due to ^{131}I surgery or therapeutic radiation for non-thyroidal malignancy.

b. Congenital

i. Iodide transport or utilization defect (NIS or pendrin mutation)

ii. Iodotyrosine dehalogenase deficiency

iii. Organification disorders (TPO deficiency or dysfunction)

iv. Defects in thyroglobulin synthesis or processing

v. Thyroid agenesis or dysplasia

vi. TSH receptor defects

vii. Thyroidal Gs receptor abnormalities (pseudohypoparathyroidism type Ia)

viii. Idiopathic TSH unresponsiveness

2) Transient (Post-thyroiditis) Hypothyroidism: Following subacute, painless or postpartum thyroiditis

3) Consumptive Hypothyroidism: Rapid destruction of thyroid hormone due to D3 expression in large hemangiomas or hemangioendotheliomas

4) Defects of Thyroxine to triiodothyronine conversion: Selenocystiene insertion sequence- binding protein 2 defect

5) Drug induced thyroid destruction: tyrosine kinase inhibitor (sunitinib)

6) Central Hypothyroidism:

a. Acquired

i. Pituitary origin (secondary)

ii. Hypothalamic disorders (tertiary)

iii. Bexarotene (retinoid X receptor agonist)

iv. Dopamine and/or severe illness

b. Congenital

i. TSH deficiency or structural abnormality

ii. TSH receptor defect

7) Resistance to Thyroid hormones:
    a. Generalised
    b. Pituitary Dominant

Thyroid dysfunction can cause various manifestations on basis of various system affected.

Amongst them important ones are:

Tiredness, weakness, Dry skin, Feeling cold, Hair loss, Difficulty concentrating and poor memory, Constipation, Weight gain with poor appetite, Dyspnea, Hoarse voice, Menorrhagia (later oligomenorrhoea or amenorrhoea), paresthesia and Impaired hearing [10]

Important signs to see in these patients are: Dry coarse skin; cool peripheral extremities, puffy face, hands, and feet (myxedema), diffuse alopecia, bradycardia, peripheral edema, delayed tendon reflex relaxation, carpal tunnel syndrome, serous cavity effusions. [10]

THE EFFECT OF HYPOTHYROIDISM ON HEMATOPOIETIC SYSTEM

In response to diminished oxygen requirements and decreased production of erythropoietin, the red cell mass is decreased; this is evident in mild normocytic normochromic anemia that often occurs. Less commonly, the anemia is macrocytic, sometimes due deficiency of vitamin B12. Conversely overt and subclinical hypothyroidism is present in 12% and 15 % of patients respectively, with pernicious anemia. Folate deficiency can also cause macrocytic anemia. The frequent mennorghia and defective absorption of iron resulting from achlorhydria may contribute to a microcytic, hypochromic anemia. [11]

ANEMIA:

The World Health Organization (WHO) has defined anemia in adults as a hemoglobin of <13 g/dL in males (a hematocrit [Hct] of about 39) and <12 g/dL in females (Hematocrit about 36). For African-Americans, the hemoglobin is about 0.5 g/dL less. **[17]**

The classification systems for anemia emphasize either erythrocyte size or the mechanism that reduced the number of red cells. The morphologic scheme divides anemia into three groups, based on mean corpuscular volume (MCV): (1) normocytic (MCV 90–100); (2) macrocytic (MCV >100); and (3) microcytic (MCV <80). In some disorders, the red cells may vary considerably and can cause anemia of more than one category. In hypothyroidism, for example, the red cells may be normocytic or macrocytic. **[17]**

Macrocytic anemia is primarily between those whose cause is impaired DNA synthesis in the bone marrow, leading to megaloblastic changes in the red cell precursors, and those whose macrocytosis originates from other mechanisms. Among the latter are alcoholism, liver disease, hypothyroidism, and hemolysis or hemorrhage that causes the release of immature, enlarged red cells. **[17]**

The megaloblastic anemia's arise from deficiencies in folic acid or vitamin B12 or from medications that impair DNA synthesis, such as cytotoxic agents used in cancer chemotherapy or immunosuppression (e.g., cyclophosphamide, azathioprine, hydroxyurea) and drugs that interfere with folic acid metabolism (e.g., methotrexate, trimethoprim). The result is defective nuclear maturation of hematopoietic cells in the bone marrow, in which nuclear division diminishes, but cytoplasmic growth, regulated by RNA, continues unabated. The discrepancy between maturation of the

nucleus and cytoplasm is called nuclear–cytoplasmic asynchrony. Early in the course of disease, the only finding in the peripheral blood may be mild macrocytosis (usually >110 fl). As anemia emerges, other abnormalities become apparent on the peripheral blood smear, including anisocytosis, poikilocytosis, teardrop cells, schistocytes, and basophilic stippling. **[17]**

THE ERYTHROPOIESIS PROCESS:

Erythropoiesis is the maturation of erythroblast to form red blood cell (RBC). It is stimulated by decreased O2 availability in circulation due to which the kidney is stimulated to secrete the erythropoietin hormone EPO (Erythropoietin) stimulates proliferation and differentiation of red blood cell precursors, which activates erythropoiesis in the hematopoietic tissues and forming more RBC's.

Erythropoesis mainly occur in bone marrow but few extramedullary sites are also there which produces RBC like spleen and liver.

Erythrocyte differentiation occurs in multiple steps as described below.

1) Multipotent hematopoietic stem cell is converted to myeloid stem cell (common myeloid progenitor)
2) Myeloid stem cell is converted to Pronormoblast
3) Pronormoblast is converted to basophilic normoblast
4) basophilic normoblast is converted to Polychromatic normoblast
5) Polychromatic normoblast is converted to Orthochromatic normoblast
6) Orthochromatic normoblast is converted to Polychromatic erythrocyte (Reticulocyte)
7) Polychromatic erythrocyte is converted to Erythrocyte.

3 important things occur in formation of RBC. Earlier the precursor cell is large and has basophilic cytoplasm due to presence of ribosomes and messenger RNA, which is further required to form proteins like enzymes and hemoglobin, which at last becomes very small when RBC is formed. Second, the earlier basophilic cytoplasm converts to eosinophilic stained due to hemoglobinisation. Third, the nuclear maturation occurs the earlier open nuclear chromatin gets condensed and at last gets removed from reticulocytes to form RBC.

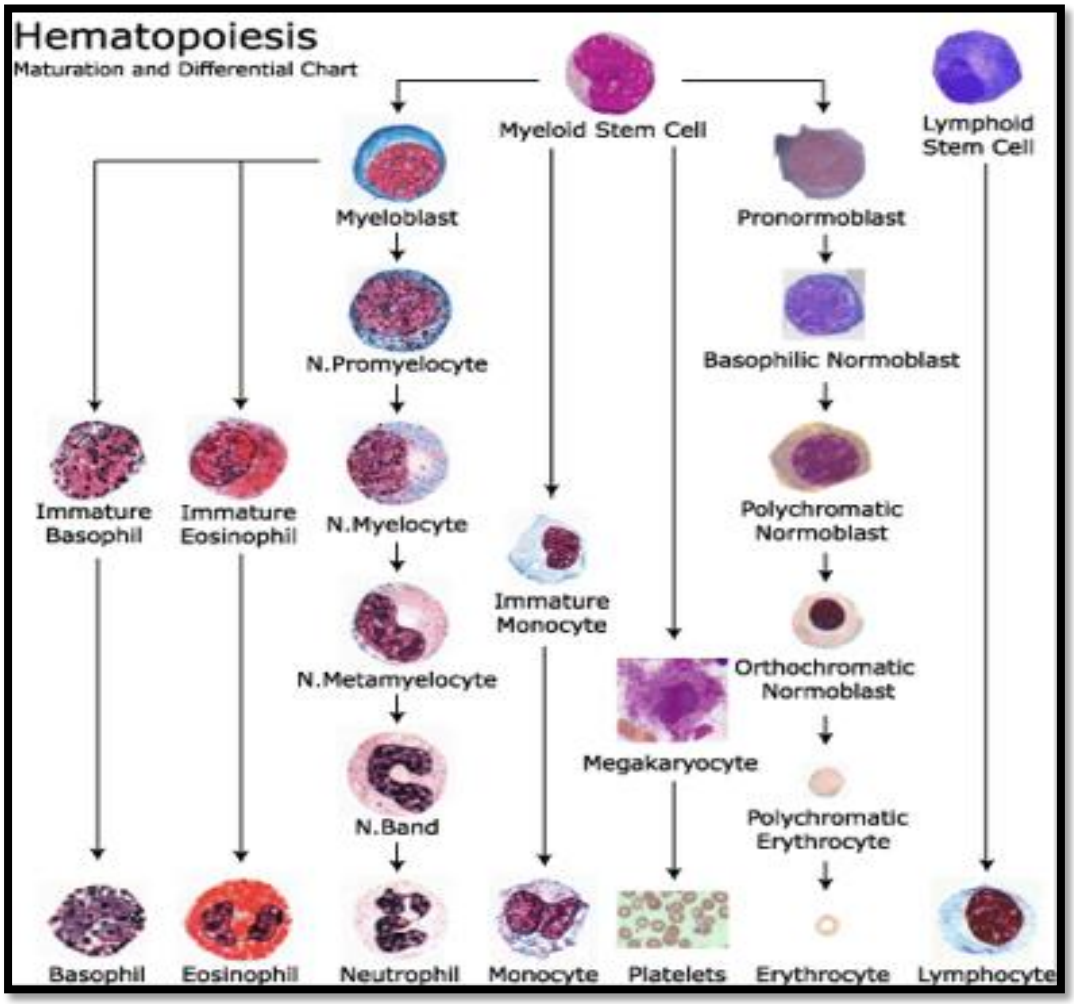


FIGURE 8: STAGES OF HEMATOPOIESIS

ROLE OF THYROID HORMONES IN ERYTHROPOIESIS:

It is well known that anemia is associated with cases of thyroid disorders**.**

Thyroid hormones play a crucial role in hematopoiesis, particularly in erythropoiesis. They exert a direct stimulating effect on the proliferation of erythrocyte precursors, but also promote erythropoiesis by increasing erythropoietin gene expression and erythropoietin production in the kidneys. **[18-21]** Experimental studies demonstrated an enhanced erythroid colony growth induced by free triiodothyronine.**[22]** In hypothyroid patients, the number and proliferative activity of erythroid cells in the marrow is reduced. **[23]** Additionally, gelatinous transformation of the marrow ground substance, characterized by mucopolysaccharide accumulation, was observed in a patient with profound hypothyroidism. **[3]**

ANEMIA IN HYPOTHYROIDISM:

Anemia, usually normocytic, occurs in several endocrine disorders. About 30% of patients with hypothyroidism have anemia, and about one-third of these are macrocytic. The etiopathogenesis of anemia in hypothyroidism is complex and may be related to depressed bone marrow stimulation, decreased erythropoietin production, nutrient deficiency (including iron, vitamin B12, or folate), as well as comorbid diseases or may be from the hormone deficiency itself, and its severity is related to the duration and degree of the hypothyroidism. **[3]**

ABOUT VITAMIN B12 AND ITS ROLE IN ERYTHROPIESIS:

Cobalamin (vitamin B_{12}) exists in a number of different chemical forms. All have a cobalt atom at the center of a corrin ring. In nature, the vitamin is mainly in the 2-deoxyadenosyl (ado) form, which is located in mitochondria. It is the cofactor for

the enzyme methylmalo- nyl coenzyme A (CoA) mutase. The other major natural cobalamin is methylcobalamin, the form in human plasma and in cell cytoplasm. It is the cofactor for methionine synthase. There are also minor amounts of hydroxocobalamin to which methyl- and adocobalamin are converted rapidly by exposure to light. **[10]**

Erythropoiesis is the process in which new erythrocytes are produced. These new erythrocytes replace the oldest erythrocytes (normally about one percent) that are phagocytosed and destroyed each day. Folate, vitamin B12, and iron have crucial roles in erythropoiesis. Erythroblasts require folate and vitamin B12 for proliferation during their differentiation. Deficiency of folate or vitamin B12 inhibits purine and thymidylate syntheses, impairs DNA synthesis, and causes erythroblast apoptosis, resulting in anemia from ineffective erythropoiesis. **[24]**

On Peripheral blood smears oval macrocytes, usually with considerable anisocytosis and poikilocytosis, are the main features. The MCV is usually >100 fL unless a cause of microcytosis is concomitantly present. Some of the neutrophils are found to be hypersegmented (more than five nuclear lobes). There may be leukopenia due to a reduction in granulocytes and lymphocytes, but this is usually $>1.5 \times 10^9$/L; the platelet count may be moderately reduced, rarely to $<40 \times 10^9$/L. The severity of all these changes parallels the degree of anemia. **[10]**

ABSORPTION OF VITAMIN B12:

The sources of vitamin b12 are mainly non-vegetarian sources like meat, chicken, eggs and few vegetarian sources like milk and milk products. Animal proteins are better absorbed than plant protein. Vitamin b12 is once taken orally binds

to R-Binder secreted from salivary glands. Further going in stomach this complex dissociates and cobalamine set free now binds to intrinsic factor in duodenum which is secreted by gastric parietal cells. Reaching the terminal ileum this complex dissociates and the cobalamine is absorbed in the cell in combination with transcobalamine which is a delivery protein for Cobalamine (20%) other 80% of cobalamine binds to haptocorin.

Important causes of B12 deficiency are: Decrease intake, hypochlorhydria, gastrectomy, Decrease production of intrinsic factor (Pernicious anemia), Exocrine pancreatic insufficiency, Ileal resection, Chron's disease, transcobalamine deficiency, fish tapeworm infection, gluten induced enteropathy, Zollinger Ellison syndrome and few drugs like metformin, cholestyramine which interferes with B12 absorption.

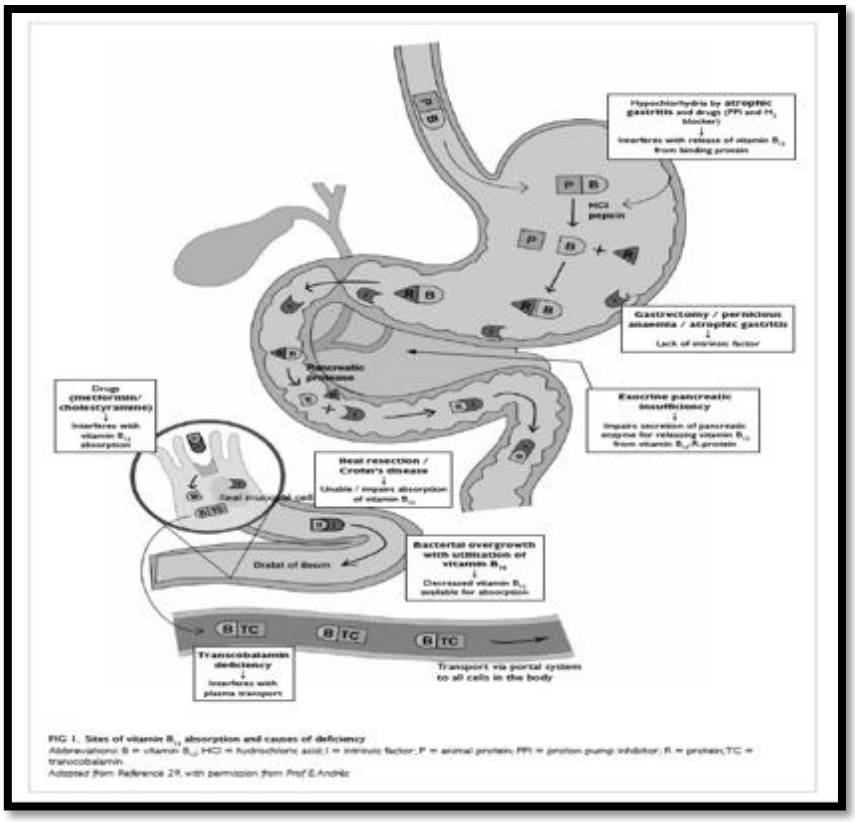


FIGURE 9: ILLUSTRATES THE ABSORPTION OF VITAMIN B12 AND THE CAUSES OF VITAMIN B12 DEFICIENCY.

FEATURES OF VITAMIN B12 DEFECIENCY:

A wide variety of signs and symptoms may occur including a decreased ability to think and behavioral and emotional changes such as depression, irritability, and psychosis. Abnormal sensations, changes in reflexes, and poor muscle function can also occur as may inflammation of the tongue, decreased taste, low red blood cells, reduced heart function, and decreased fertility. In young children symptoms include poor growth, poor development, and difficulties with movement.

The most frequent cause of macrocytosis due to vitamin B12 deficiency is Addison–Biermer disease, or the so-called pernicious anemia. **[25]**

TABLE 1: PREVALENCE OF VITAMIN B12 DEFICIENCY IN PATIENTS WITH HYPOTHYROIDISM OR AUTOIMMUNE THYROID DISEASE IN VARIOUS STUDIES:

Author	Threshold for vitamin	Prevalence of vit. b12 deficiency	Study group	Mean (SD) age	Control group	P value
Jabbar et al[59]	<200 pg/ml	40.5%	116 patients with hypothyroidism (95 F, 21 M)	44 (13.7)	Not provided	Not provided
Erdogan et al[15]	<189 pg/ml	25.6%	100 patients with subclinical hypothyroidism (85 F, 15 M)	44.9 (14.2)	200 healthy people	0.002
Erdogan et al[15]	<189 pg/ml	18.6%	100 patients with overt hypothyroidism (88 F, 12 M)	44.5 (13.9)	200 healthy people	0.002
Das et al[2]		10%	60 patients (42 F, 18 M) with overt hypothyroidism (44) and subclinical hypothyroidism (16)	36.5	Not provided	Not provided
Ness-Abramof	≤133 pmol/l	28%	115 patients with AITD (108 F, 7 M)	47 (15)	Not provided	Not provided
Jaya Kumari et	<200 pg/ml	55.5%	350 patients with AITD (250 F, 100 M)	32.2	Not provided	Not provided
Wang et al[60]	<200 pg/ml	6.3%	190 patients with positive antithyroid autoantibodies (173 F, 17 M)	60.5 (11.7)	190 healthy people (173 F, 17 M; mean [SD] age, 60.5 [11.7] y)	0.139

There is a significant difference between the study and control groups.

Abbreviations: AITD, autoimmune thyroid disease; F, female; M, male

The above table is from the Polish Archives of internal medicine showing the Metanalysis of various studies:

Jabbar et al was conducted in Pakistan, both studies of Erdogan et al were conducted in Turkey, Das et al was conducted in Eastern India, Ness-Abramof et al was conducted in Israel, Jaya kumari et al study was conducted in South India and Wang et al was conducted in Taiwan. [3]

The symptoms of B-12 deficiency in patients with thyroid disorders have not been evaluated in detail. Jabbar et al [8] noted that hypothyroid patients reported symptoms of weakness, numbness, diarrhea, abdominal pain, impairment of memory, paresthesia, dysphagia, dizziness and depression. Numbness, paresthesia, and dysphagia, in particular were reported most often by hypothyroid patients with B-12 deficiency compared to those with sufficient B-12**.** [8]

Wang et al noted that among 190 patients with thyroid antibodies attending an oral mucosal disease clinic, the most commonly reported symptoms were burning sensation of the tongue, dry mouth, lingual varicosity, and numbness of the tongue. [26]

VITAMIN B12 DEFICIENCY AND HYPOTHYROIDISM:

The association of thyroid disorders and abnormalities in hematological parameters is well known. [27] Pernicious anemia in the course of Hypothyroidism may occur at any age. Anemia might be one of the clinical manifestations of congenital hypothyroidism in children and should imply further assessment of thyroid function.[28]

Patients with AITD are at higher risk of developing vitamin B12-deficiency anemia. However, Lippi et al [27] reported a significant correlation between TSH and folate concentrations, but not vitamin B12 concentrations. Hypothyroidism can cause

certain forms of anemia on the one hand or hyperproliferation of immature erythroid progenitors on the other hand. The anemia is usually macrocytic hypochromic anemia of moderate severity. [29]

Hypothyroidism may be associated with pernicious anemia as part of the autoimmune polyglandular endocrinopathy. [30] Vitamin B12 deficiency may occur as a result of autoimmune pernicious anemia, malabsorption, malnutrition or use of drugs including proton-pump inhibitors, H2 receptor antagonists or metformin. [31,32] Metformin can cause malabsorption secondary to its effect on ileal mucosa or membrane receptors. [33,34] Proton Pump Inhibitors and H2 receptor antagonists cause gastric hypochlorhydria and malabsorption of vitamin B12. Untreated helicobacter pylori infection is occasionally associated with B12 deficiency. [35-37] In our study we found no association between use of drugs and B12 deficiency, although the numbers may not have been large enough to demonstrate this association. Intrinsic factor and gastric parietal cell antibody assays were not available locally at the time of the study, hence while we demonstrated frequent occurrence of B12 deficiency in hypothyroid patients, it was not possible to determine the underlying etiology of this association.[8]

In 1979, Fein showed that Graves' disease is associated with anemia. [38] It has been found that all hematological parameters return to normal when a euthyroid state is achieved. [39]

There are various cases reported worldwide showing the relation of grave's disease with pancytopenia. [40-43]

MATERIALS AND METHODOLOGY

It was an observational study. It was carried out in the Department of Medicine, SBKS Medical Institute & Research Centre. The study was started after obtaining clearance from institutional ethical committee. It was started in March 2016 until the 60 participants were enrolled.

INCLUSION CRITERIA:

All hypothyroid patients attending the medicine OPD or admitted to medicine wards were enrolled for the study. The patients already diagnosed as hypothyroid >18 years in age and those who give consent for participation in the study were included.

EXCLUSION CRITERIA:

Patients with known comorbid conditions like Diabetes Mellitus on Metformin, Cirrhosis of Liver, already on vitamin B12 supplementation and chronic alcoholic were excluded from the study.

METHOD OF STUDY

A detailed history was taken from all participants. All were subjected to CBC, thyroid function test, S. Vitamin B12. Sickling, Urine RM, renal function test, liver function test, S. ferritin, retic count was recorded only if required. Anemia was defined as hemoglobin levels lower than 12 g/dl in women and 13 g/dl in men. Normal S. TSH will be taken as 0.39 – 5.0 μIU/ml. Vitamin B12 deficiency was defined as serum vitamin B12 levels lower than 211 pg/ml as per AI 360 Immunoassay method (TOSOH). Data so collected was analyzed to assess the burden of anemia in the hypothyroid patients and also to assess the relation between hypothyroidism and vitamin B12 deficiency.

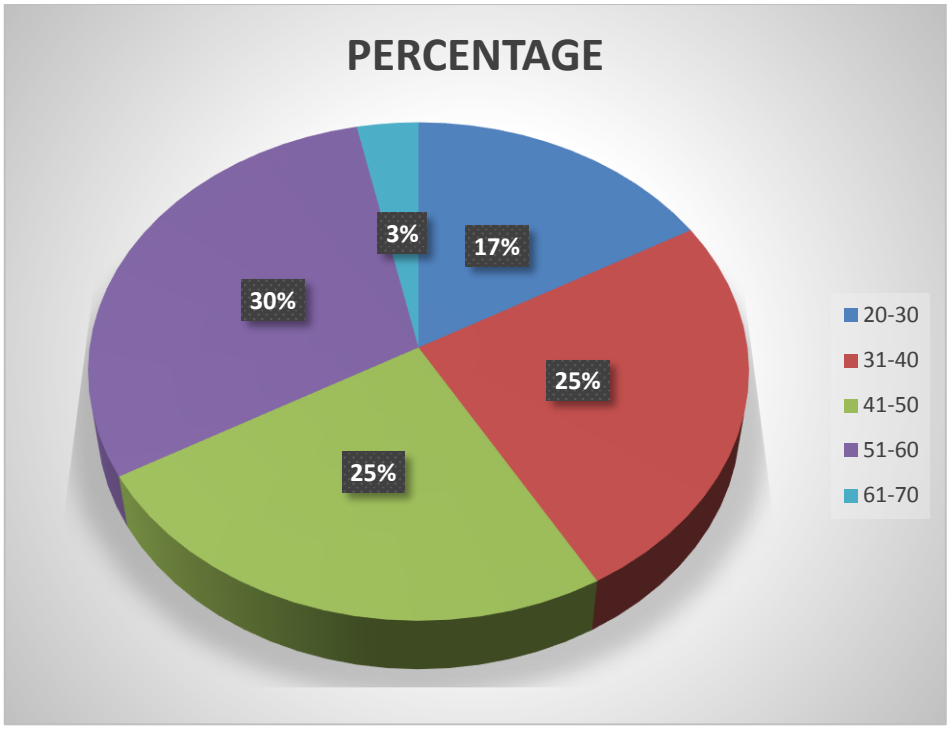
RESULTS

Total 60 patients of hypothyroidism were enrolled. Out of 60 patients enrolled 10 (16.7%) were of age 20-30 years, 15 (25%) each were in the age group of 31-40 years and 41-50 years. 18 (30%) were in age group of 51-60 years and 2 (3.3%) were in the age group of 61-70 years. **(Table 2.1)**

AGE DISTRIBUTION

TABLE 2.1: - DISTRIBUTION OF PARTICIPANTS BY AGE.

Age group	Frequency	Percent
20-30	10	16.7
31-40	15	25
41-50	15	25
51-60	18	30
61-70	2	3.3
Total	60	100

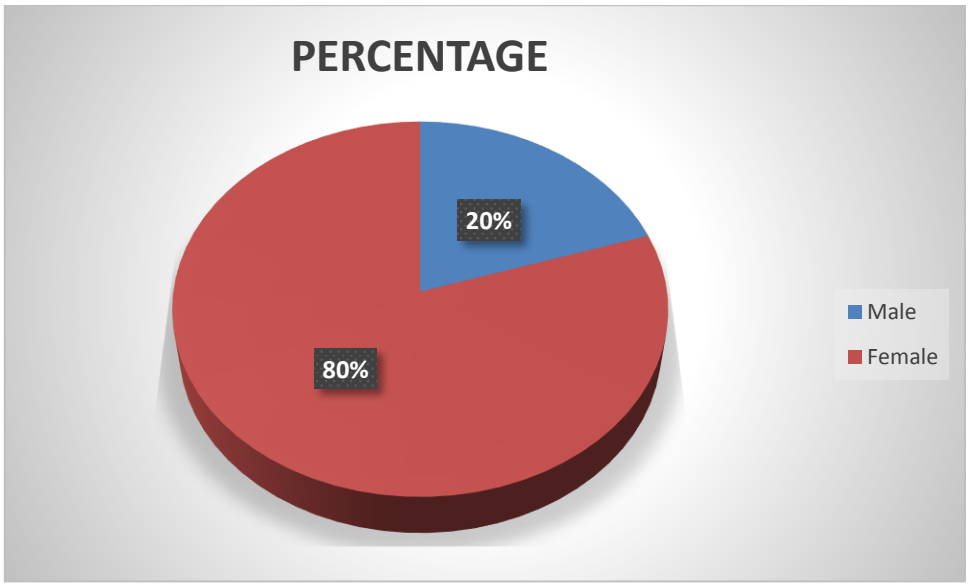


GRAPH 1: - GRAPH SHOWING AGE DISTRIBUTION

GENDER DISTRIBUTION

TABLE 2.2: - DISTRIBUTION OF PARTICIPANTS BY GENDER.

Sex	Frequency	Percent
Male	12	20
Female	48	80
Total	60	100



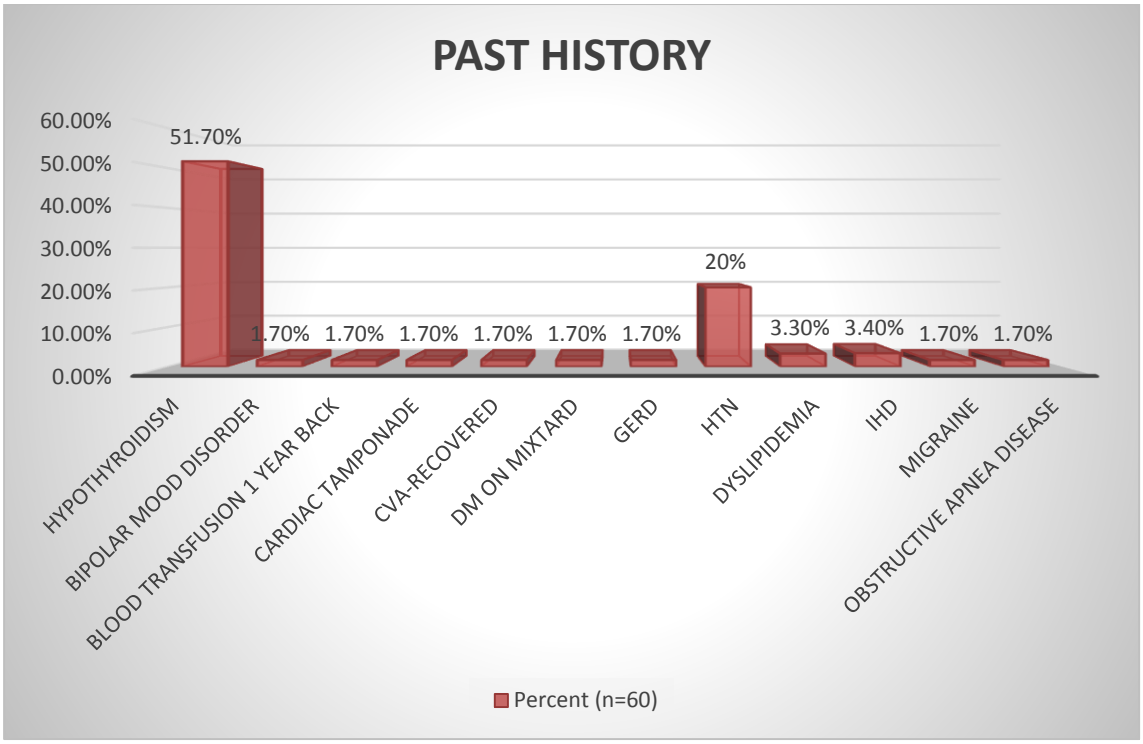
GRAPH 2: - GRAPH SHOWING GENDER DISTRIBUTION

There was female preponderance in overall population i.e. 48 (80%) and only 20% were males. **(Table 2.2)**

PAST HISTORY OF THE PATIENTS.

TABLE 2.3: - DISTRIBUTION ACCORDING TO THE PAST HISTORY OF THE PATIENTS.

PAST HISTORY	Frequency	Percent (n=60)
Hypothyroidism	31	51.7
Bipolar mood disorder	1	1.7
Blood transfusion 1 year back	1	1.7
Cardiac Tamponade	1	1.7
CVA-recovered	1	1.7
DM on mixtard	1	1.7
GERD	1	1.7
HTN	12	20
Dyslipidemia	2	3.3
IHD	2	3.4
Migraine	1	1.7
Obstructive apnea Disease	1	1.7



GRAPH 3: - GRAPH SHOWING PAST HISTORY OF PATIENT

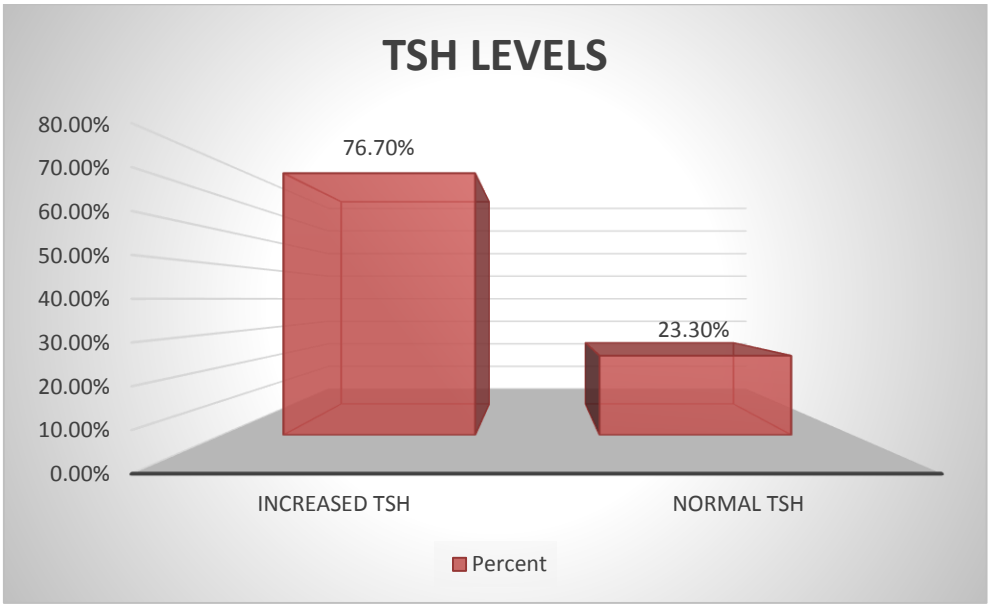
31 (51.7%) were known cases of hypothyroidism. 12 (20%) out of 60 had hypertension. 3.3 and 3.4% of patients had dyslipidemia and ischemic heart disease(IHD) respectively. Only 1(1.7%) each had bipolar mood disorder, blood transfusion in past 1 year, cardiac tamponade, CVA, GERD, diabetes, migraine, obstructive apnea disease. **(Table 2.3)**

TSH LEVELS

TABLE 2.4: - DISTRIBUTION OF PATIENTS ACCORDING TO RAISED AND NORMAL TSH.

TSH	Frequency	Percent
Increased TSH	46	76.70%
Normal TSH	14	23.30%
Total	60	100%

46 (76.7%) of patients had raised S. TSH (irrespective of on treatment or new cases) while 23.3 % had normal TSH level. **(Table 2.4)**



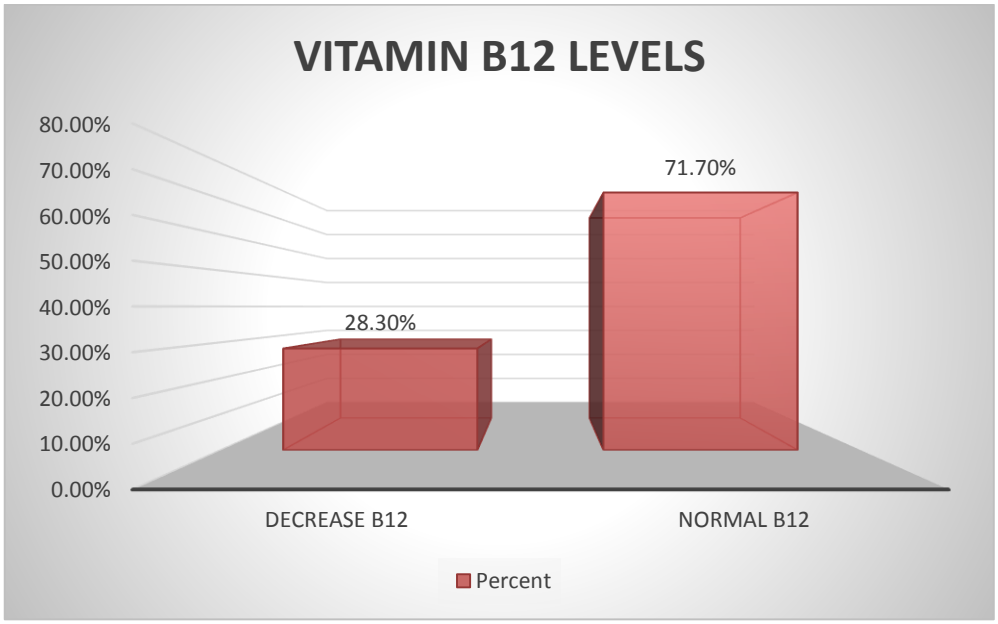
GRAPH 4: - GRAPH SHOWING TSH LEVELS

VITAMIN B12 LEVELS

TABLE 2.5: - DISTRIBUTION OF PATIENTS ACCORDING TO DECREASED AND NORMAL VITAMIN B12 LEVELS.

Vitamin B12	Frequency	Percent
Decrease B12	17	28.30%
Normal B12	43	71.70%
Total	60	100%

Only 17 (28.3 %) of patients out of 60 hypothyroid patients had decreased vitamin B12 levels, rest 43 (71.7%) had vitamin B12 levels within normal limits. **(Table 2.5)**



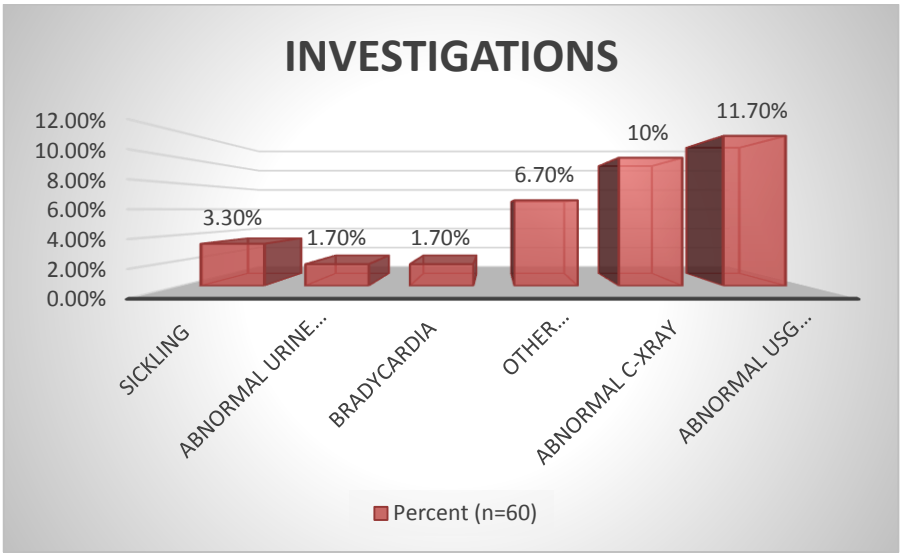
GRAPH 5: - GRAPH SHOWING VITAMIN B12 LEVELS IN PATIENTS

LAB REPORTS

TABLE 2.6: LAB REPORTS OF THE STUDY POPULATION.

Investigations	Frequency	Percent (n=60)
Sickling	2	3.30%
Abnormal urine RM	1	1.70%
Bradycardia	1	1.70%
Other Abnormality	4	6.70%
Abnormal C-Xray	6	10%
Abnormal USG Abdomen	7	11.70%

Out of 60 hypothyroid patients only 3.3% i.e. 2 patients had sickle hemoglobinopathy, 1.7% had Abnormal urine RM and Bradycardia on Electrocardiogram. 6.7 % had other abnormalities on ECG, 10% had abnormal Chest x-ray 11.7% had abnormal abdominal ultrasonography findings. **(Table 2.6)**



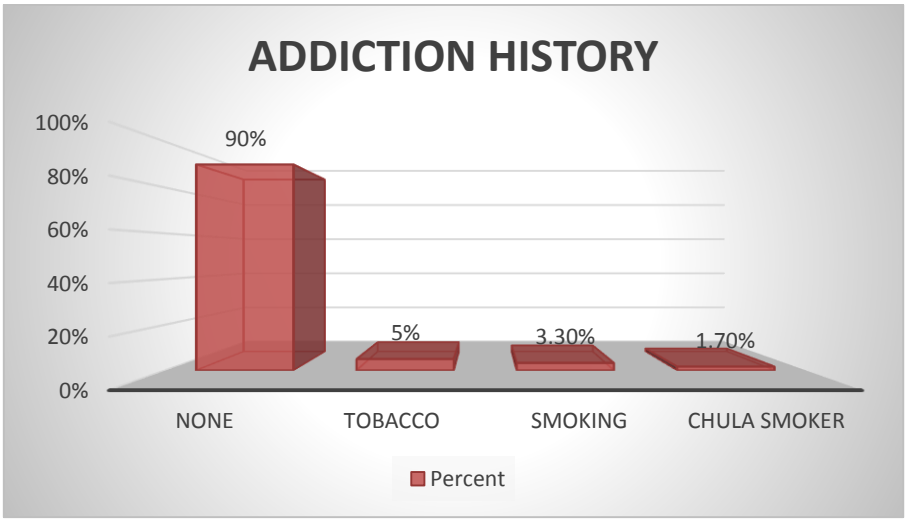
GRAPH 6: - GRAPH SHOWING LAB REPORTS OF THE STUDY POPULATION

ADDICTION HISTORY

TABLE 3.1: FREQUENCY OF ADDICTION HISTORY IN STUDY POPULATION.

Personal History	Frequency	Percent
None	54	90%
Tobacco	3	5%
Smoking	2	3.30%
Chula smoker	1	1.70%
Total	60	100%

Out of 60 patients 3 (5%) had history of tobacco chewing, 2 (3.3%) were cigarette or bidi smokers and 1 (1.7%) was Chula smoker. Majority of them i.e. 54 (90%) had no history of addiction. **(Table 3.1)**



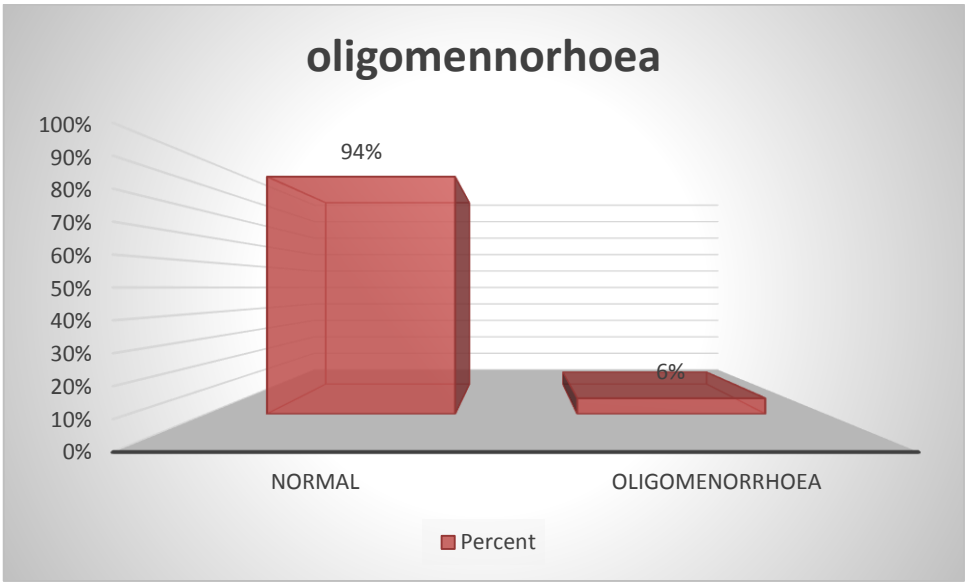
GRAPH 7: - GRAPH SHOWING FREQUENCY OF ADDICTION HISTORY IN STUDY POPULATION.

OLIGOMENNORHOEA

TABLE 3.2: FREQUENCY OF PATIENTS HAVING OLIGOMENNORHOEA.

OBS & MENS	Frequency	Percent
Normal	45	94%
Oligomenorrhoea	3	6%
Total	48	100%

Out of 60 patients no. of females were 48 i.e. 80%. Only 6.25% had oligomennorhoea while 94% had no obstetrics or gynecological complaints. (Table 3.2)



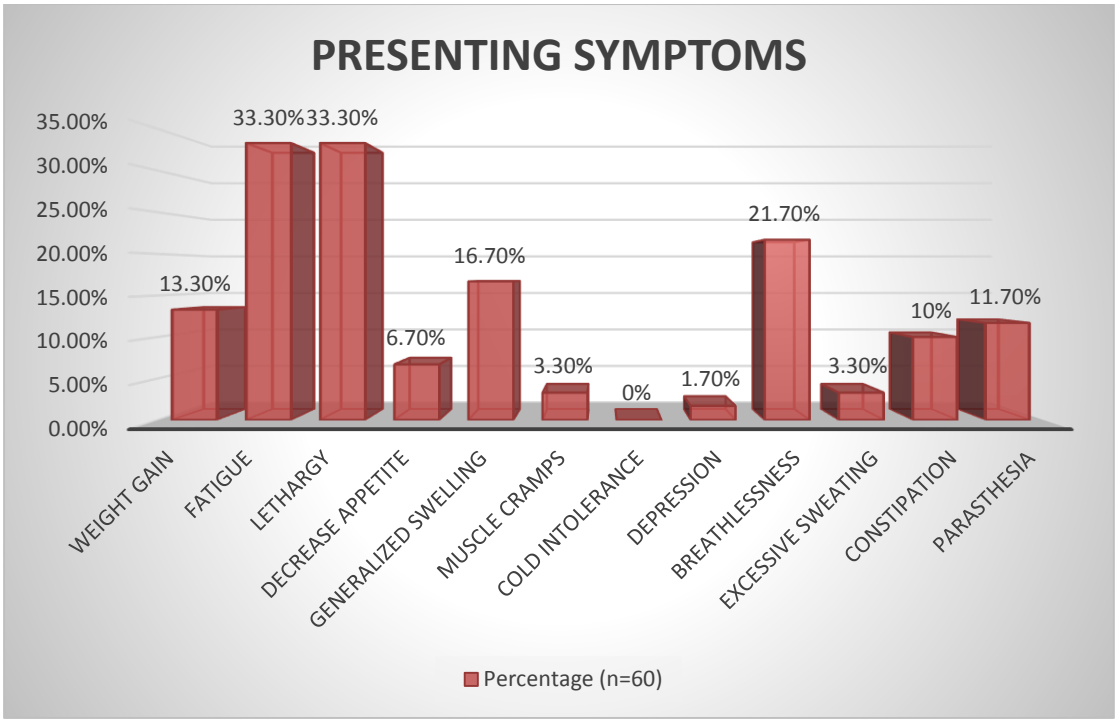
GRAPH 8: - GRAPH SHOWING FREQUENCY OF PATIENTS HAVING OLIGOMENNORHOEA

PRESENTING SYMPTOMS

TABLE 4: DISTRIBUTION ACCORDING TO PRESENTING SYMPTOMS:

Symptoms	No. of patients	Percentage (n=60)
Weight gain	8	13.30%
Fatigue	20	33.30%
Lethargy	20	33.30%
Decrease appetite	4	6.70%
Generalized swelling	10	16.70%
Muscle cramps	2	3.30%
Cold intolerance	0	0%
Depression	1	1.70%
Breathlessness	13	21.70%
Excessive sweating	2	3.30%
Constipation	6	10%
Paresthesia	7	11.70%

Majority of the patients i.e. 20 each (33.3%) out of 60 presented with fatigue and lethargy making them the most common presenting complaint, followed by breathlessness seen in 13 (21.7%), generalized swelling seen in 10(16.7 %), weight gain seen in 8(13.3%), paresthesia's present in 7(11.7%) and constipation seen in 6(10%). Only 4(6.7%) had complaint of decreased appetite, 2(3.3%) had muscle cramps and excessive sweating and 1(1.7%) had depression. None of the patients had complaint of cold intolerance. **(Table 4)**



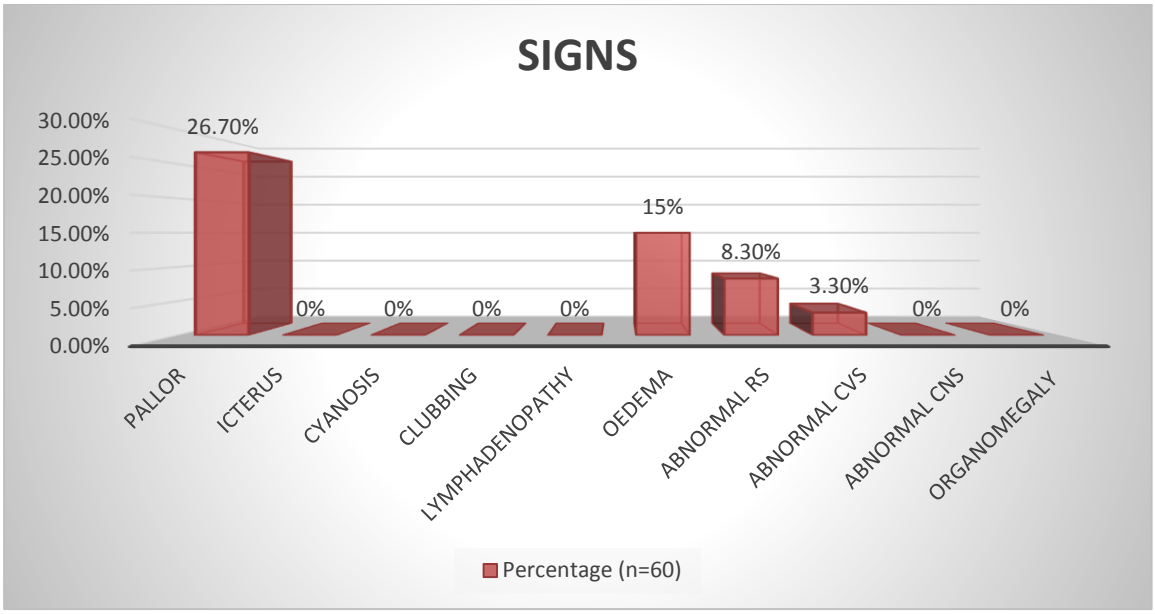
GRAPH 9: - GRAPH DISTRIBUTION ACCORDING TO PRESENTING SYMPTOMS

SIGNS

TABLE 5: DISTRIBUTION ACCORDING TO THE SIGNS.

SIGNS	No of patients	Percentage (n=60)
Pallor	16	26.70%
Icterus	0	0%
Cyanosis	0	0%
Clubbing	0	0%
Lymphadenopathy	0	0%
Oedema	9	15%
Abnormal RS	5	8.30%
Abnormal CVS	2	3.30%
Abnormal CNS	0	0%
Organomegaly	0	0%

According to the signs noted in all the patients, 16(26.7%) had pallor that comes to majority compared to all other signs. 9(15%) had oedema, 5(8.3%) had abnormal findings in respiratory examination, 2(3.3%) had abnormal cardiovascular system findings. None of the patient had icterus, cyanosis, clubbing, lymphadenopathy and abnormal per abdominal findings or abnormal central nervous system findings. **(Table 5)**



GRAPH 10: - GRAPH SHOWING DISTRIBUTION ACCORDING TO THE SIGNS.

LAB REPORTS OF THE STUDY POPULATION

TABLE 6: LAB REPORTS OF THE STUDY POPULATION.

Variable	N	Mean	Std. Deviation
AGE (years)	60	44.08	11.706
K/C/O since YEARS	31	4.162	6.188
DOSE OF THYROXINE (in µg/day)	31	75.03	41.718
PULSE (per minute)	60	79.73	10.618
SBP (mmHg)	60	118.87	14.694
DBP (mmHg)	60	73.3	10.375
S. TSH (µIU/ml)	60	22.78	31.379
FREE T3 (pg/ml)	34	2.41	1.222
TOTAL T3 (ng/ml)	11	8.84	25.264
FREE T4 (ng/dl)	34	1.23	1.109
TOTAL T4 (µg/dl)	11	7.326	3.807
RBS (mg%)	32	104.69	21.418
UREA (mg%)	26	31.38	19.938
CREATININE (mg%)	30	0.99	0.554
BILIRUBIN (mg%)	11	0.77	0.502
SGPT (IU/L)	14	27.57	12.936
SGOT (IU/L)	11	36	22.72
URINE RM	21	1.95	0.218
Vitamin B12 (pg/ml)	60	447.92	456.585

Mean age of the patients was 44.08 ± 11.706 years. Mean duration of illness in patients with known case of hypothyroidism was 4.162± 6.188. Mean dose of thyroxin taken by the patients was 75.03 ± 41.718 μg/day. Mean pulse was 79.73± 10.618/min. Mean systolic and diastolic blood pressures were 118 ± 14.694 mmHg and 73.30 ± 10.375 mmHg respectively. Thus, most of the patients were in the younger age group, with pulse and blood pressure in the normal range. Mean of S. TSH was 22.78 ± 31.379 μIU/ml. Mean of Total T3 and Total T4 was 8.84 ± 25.264 ng/ml and 7.326 ± 3.807 μg/dl respectively. Mean of Free T3 and Free T4 in was 2.41 ± 1.222 pg/ml and 1.23 ± 1.109 ng/dl respectively.

Mean of RBS in all patients was 104.69 ± 21.418 mg%. Mean of blood urea and serum creatinine were 31.38 ± 19.938 (mg%) and 0.99 ± 0.554 (mg%) respectively. Mean serum bilirubin, SGOT and SGPT were 0.77 ± 0.502 (mg%), 36.0 ± 22.720 (IU/L) and 27.57 ± 12.936(IU/L) respectively. Mean of Vitamin B12 levels, in all patients was 447.92 ± 456.585 pg/ml. **(Table 6)**

LAB REPORTS OF THE BLOOD COUNT AND INDICES

TABLE 7: LAB REPORTS OF THE BLOOD COUNT AND INDICES.

Variable	N	Mean	Std. deviation
Hb (gm%)	60	11.168	2.411
Total count (cell/mm^3)	60	8133.33	3244.639
PMNs (%)	60	62.93	9.66
Lymphocytes (%)	60	28.82	11.7
Monocytes (%)	60	3.6	0.741
Eosinophils (%)	60	4.47	0.724
PLATELET COUNT lacs/ mm^3	60	2.618	0.77
HEMATOCRIT (%)	60	34.358	7.801
MCV (fL)	60	79.58	10.909
MCH (pg)	60	25.719	4.248
MCHC (%)	60	32.15	1.92
TOTAL RBC (mil/µL)	60	4.381	0.998
RDW (%)	60	15.225	2.288
RETIC COUNT (%)	12	1.75	1.055

Out of 60 patients mean hemoglobin level found was 11.168 ± 2.411 gm%. Mean of Total count was 8133.33 ± 3244.639 cell/mm^3. Mean of Platelet count was 2.618 ± 0.77 lacs/ mm^3. The Mean hematocrit was 34.358 ± 7.801 %. Mean of MCV was 79.58 ± 10.909 fL. Mean of MCH was 25.719 ±4.248 pg. Mean of MCHC was 32.150 ±1.920 %. Mean of Total RBC was 4.381 ±0.998 mil/µL. Mean of Red cell distribution width (RDW) was 15.225 ±2.288 %. However, mean of Retic count out of 12 patients investigated was 1.750 ± 1.055 %. (Table 7)

TABLE 8.1: TABLE SHOWING CO-RELATION OF HEMOGLOBIN, TOTAL COUNT, PACKED CELL VOLUME, MEANCORPUSCULAR VOLUME AND RETIC COUNT WITH VITAMIN B12 LEVELS AND SERUM TSH LEVELS.

		VITAMIN B12	TSH
TC	Pearson Correlation	0.233	-0.123
	P-value	0.073	0.347
PCV	Pearson Correlation	-0.165	-0.172
	P-value	0.208	0.188
MCV	Pearson Correlation	-0.053	0.004
	P-value	0.69	0.979
RETIC COUNT	Pearson Correlation	-0.299	-0.032
	P-value	0.345	0.922
HAEMOGLOBIN	Pearson Correlation	-0.158	-0.32
	P-value	0.228	0.013

There was no significant correlation of total count with Vitamin B12 level (r 0.233, p 0.073), neither it showed correlation to TSH (r -0.123, p 0.347). There was no significant correlation even between PCV and Vitamin B12 or TSH (r -0.165, p 0.208) and (r -0.172, p 0.188) respectively; MCV with Vitamin B12 or TSH (r -0.053, p 0.690), (r 0.004, p 0.979); retic count with Vitamin B12 or TSH (r -0.299, p 0.345), (r -0.032, p 0.922) and Hemoglobin with vitamin B12 (r -0.158, p 0.228). However, there was significant correlation between Hemoglobin and TSH levels (r -0.320, p 0.013). **(Table 8.1)**

TABLE 8.2: CORRELATION BETWEEN PCV, MCV, HEMOGLOBIN AND VITAMIN B12 LEVELS IN PATIENTS HAVING KNOWN HYPOTHYROID DISEASE AND ARE ON TREATMENT.

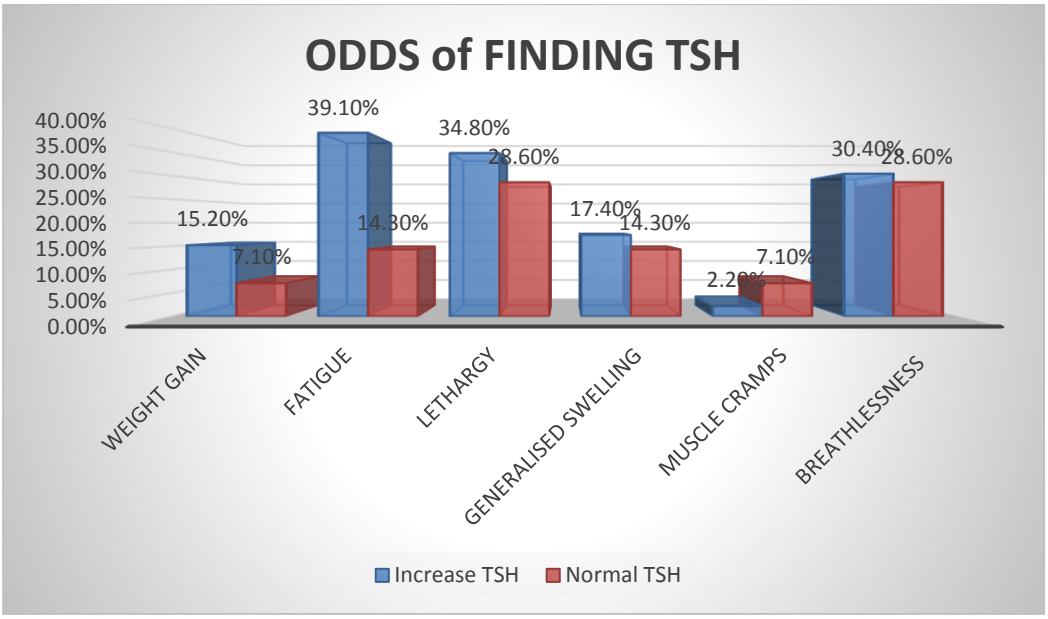
		K/C/O since YEARS	DOSE OF THYROXINE
PCV	Pearson Correlation	-0.13	0.089
	P-value	0.486	0.634
MCV	Pearson Correlation	-0.211	-0.004
	P-value	0.256	0.983
Hb.	Pearson Correlation	0.174	0.09
	P-value	0.348	0.629
VITAMIN B12	Pearson Correlation	-0.161	-0.144
	P-value	0.386	0.44

There was no significant correlation found between PCV and duration of hypothyroid years (r -0.130, p 0.486) or with dose of thyroxin (r -0.089, p 0.634); MCV and duration of hypothyroid years (r -0.211, p 0.256) or with dose of thyroxin (r -0.004, p 0.983); Hb. (Hemoglobin) and known case of hypothyroid years (r 0.174, p 0.348) or with dose of thyroxin (r 0.090, p 0.629); Vitamin B12 and duration of hypothyroid years (r -0.161, p 0.386) or with dose of thyroxin (r -0.144, p 0.440) or any other parameters with duration of hypothyroid years. **(Table 8.2)**

TABLE 9.1: ODDS OF FINDING SYMPTOMS IN PATIENTS WITH INCREASE TSH VS. NORMAL TSH.

Exposure	Increase TSH	Normal TSH	p-value	Confidence interval	OR
Weight Gain	7(15.2)	1(7.1)	0.436	0.262-20.792	2.33
Fatigue	18(39.1)	2(14.3)	0.084	0.771-19.293	3.857
Lethargy	16(34.8)	4(28.6)	0.666	0.360-4.935	1.333
Generalized Swelling	8(17.4)	2(14.3)	0.785	0.235-6.777	1.263
Muscle Cramps	1(2.2)	1(7.1)	0.364	0.017-4.943	NA
Breathlessness	14(30.4)	4(28.6)	0.894	0.293-4.089	1.094

There was >2 times chances of finding **weight gain** in patients with raised TSH (OR 2.33; 95% CI 0.262-20.792; p= 0.436), >3.5 times chances of finding **fatigue** (OR 3.857; 95% CI 0.771-19.293; p= 0.084), 1.3 times chances of finding **lethargy** (OR1.33; 95% CI 0.360-4.935; p=0.666), 1.2 times chances of finding **generalized swelling** (OR 1.263; 95% CI 0.235-6.777; p= 1.263) and >1.5 times chances of finding **breathlessness** (OR 1.094, 95% CI 0.293-4.089; p= 0.894) as compared to those with normal TSH. As only 1 patient each in both groups had muscle cramps odds ratio was not calculated for it.

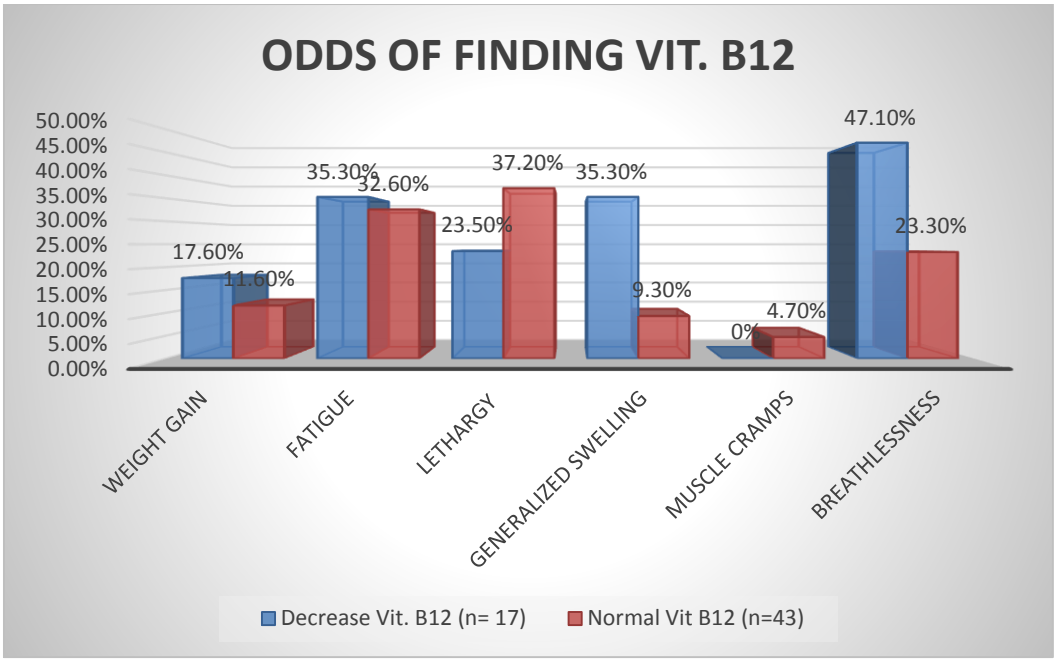


GRAPH 11: - GRAPH ODDS OF FINDING SYMPTOMS IN PATIENTS WITH INCREASE TSH VS. NORMAL TSH.

TABLE 9.2: ODDS OF FINDING SYMPTOMS IN PATIENTS WITH DECREASED VITAMIN B12 VS. NORMAL VITAMIN B12.

Exposure	Decrease Vit. B12 (n= 17)	Normal Vit. B12 (n=43)	p-value	Confidence interval	OR
Weight Gain	3(17.6)	5(11.6)	0.537	0.343-7.727	1.629
Fatigue	6(35.3)	14(32.6)	0.839	0.347-3.683	1.13
Lethargy	4(23.5)	16(37.2)	0.311	0.144-1.867	0.519
Generalized Swelling	6(35.3)	4(9.3)	0.015	1.271-22.250	5.318
Muscle Cramps	0(0)	2(4.7)	0.366	NA	NA
Breathlessness	8(47.1)	10(23.3)	0.07	0.896-9.608	2.933

There was >1.5 times chance of having **weight gain** in patients with decreased vitamin B12 level (odds ratio 1.629; 95% CI 0.343-7.727; p=0.537), 1.13 times chances of finding **fatigue** (odds ratio 1.130; 95% CI 0.347-3.683; p=0.839), >5 times significant chances of developing **generalized swelling** in patients with decreased b12 levels (odds ratio 5.318; 95% CI 1.271-22.250; p=0.015), >2 times chances of developing **breathlessness** (odds ratio 2.933; 95% CI 0.896-9.608; p=0.07) and only 0.5 times chances of developing **lethargy** (odds ratio 0.519; 95% CI 0.144-1.867; p=0.311). No patients with decrease vitamin B12 levels had muscle cramps and so the odds ratio was not calculated.

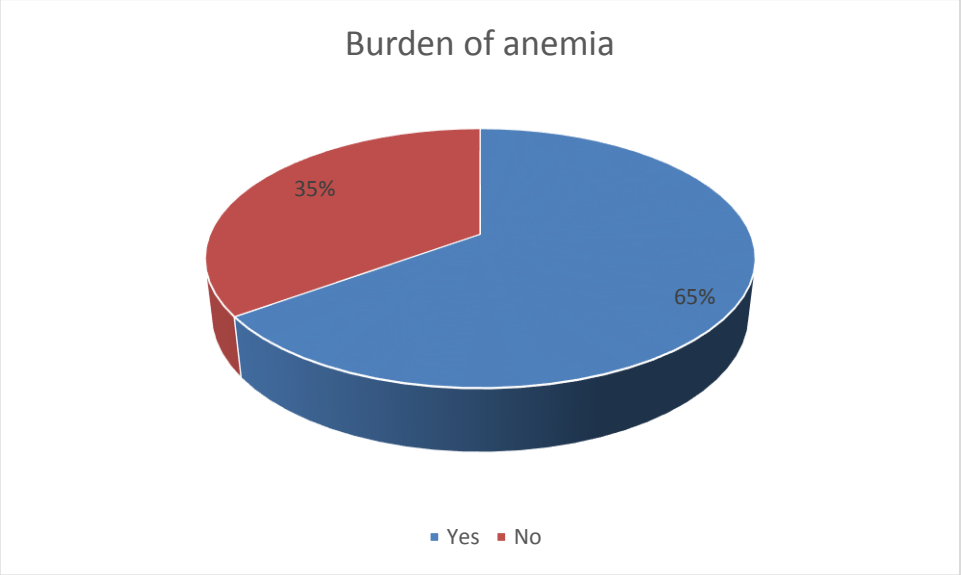


GRAPH 12: - GRAPH SHOWING ODDS OF FINDING SYMPTOMS IN PATIENTS WITH DECREASED VITAMIN B12 VS. NORMAL VITAMIN B12.

TABLE 10: BURDEN OF ANEMIA IN HYPOTHYROID PATIENTS

Anemia	Frequency	Percent
Yes	39	65
No	21	35
Total	60	100

	Anemia	N	Mean	Std. Deviation	t-value	p-value
TSH	yes	39	27.5906	33.78226	1.640	0.106
	no	21	13.8578	24.64939		
Vitamin B12	yes	39	497.1795	480.26650	1.142	0.258
	no	21	356.4476	404.00940		



GRAPH 13: - GRAPH SHOWING BURDEN OF ANEMIA

TABLE 11: CORRELATION OF SERUM TSH WITH VITAMIN B12 LEVELS.

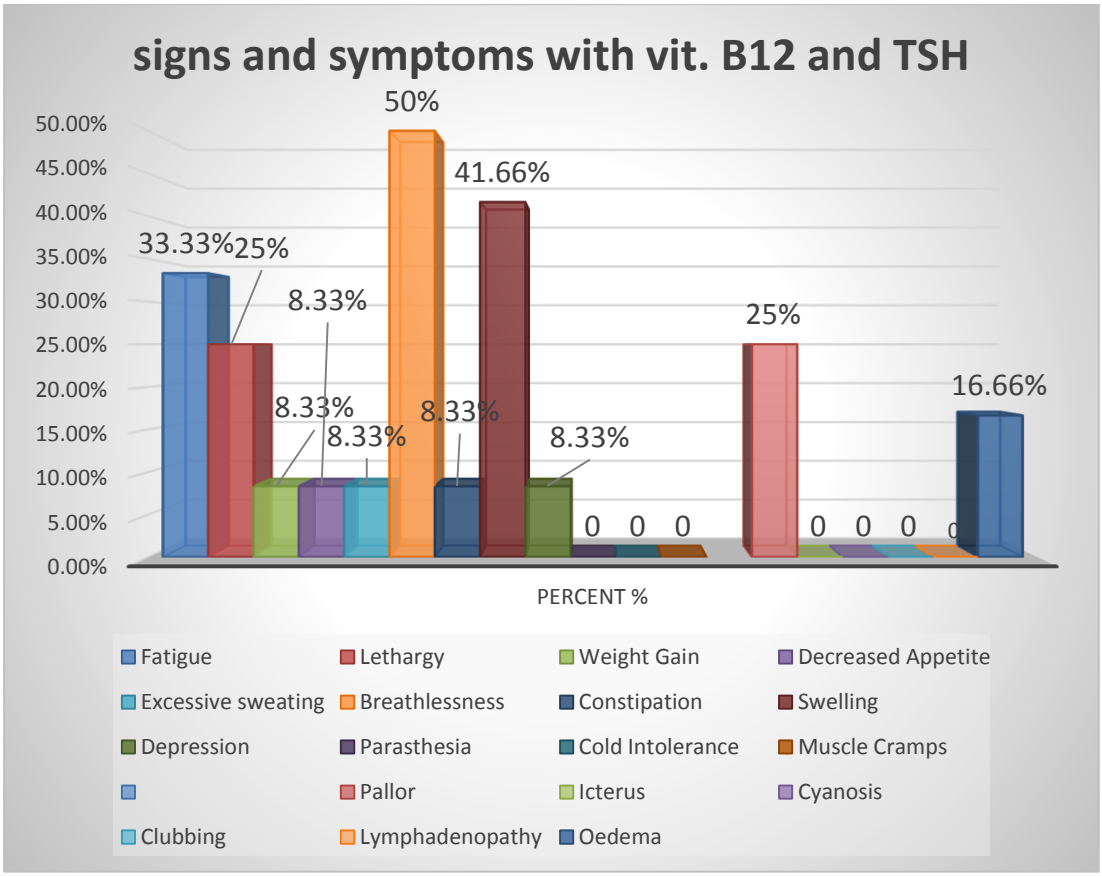
		Vitamin B12
S. TSH	Pearson Correlation	0.18
	p-value	0.168

There was no significant correlation between S. TSH and Vitamin B12 levels (r 0.180, p 0.168).

TABLE 12: DISTRIBUTION OF SIGNS AND SYMPTOMS IN PATIENTS WITH BOTH DECREASED VITAMIN B12 AND RAISED TSH.

SYMPTOMS & SIGNS	FREQUENCY n=12	PERCENT %
Fatigue	4	33.33%
Lethargy	3	25%
Weight Gain	1	8.33%
Decreased Appetite	1	8.33%
Excessive sweating	1	8.33%
Breathlessness	6	50%
Constipation	1	8.33%
Swelling	5	41.66%
Depression	1	8.33%
Paraesthesia	0	NA
Cold Intolerance	0	NA
Muscle Cramps	0	NA
Pallor	3	25%
Icterus	0	NA
Cyanosis	0	NA
Clubbing	0	NA
Lymphadenopathy	0	NA
Oedema	2	16.66%

12 patients had combined deficiency of Vitamin B12 and raised TSH. Out of 12 patients 50% of patient had complaint of breathlessness, 41.66% came with the complaint of swelling, 33.33% had complaint of fatigue, 25% came with complaint of lethargy and had pallor on examination, 16.66% had oedema on examination and 8.33% had weight gain, decrease appetite, excessive sweating, depression and constipation. Thus, with add-on Vit. B12 deficiency, many more patients presented with breathlessness, swelling and fatigue as compared to those with raised TSH but normal S. Vitamin B12.

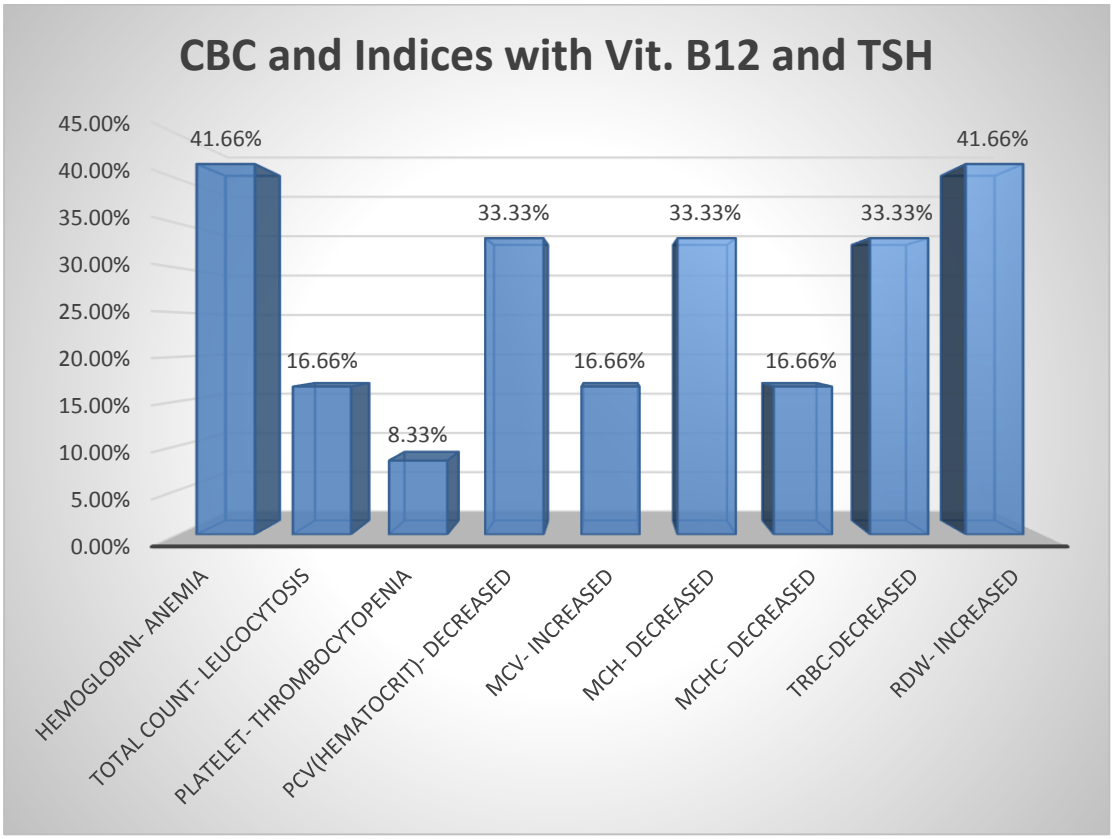


GRAPH 14: - GRAPH SHOWING DISTRIBUTION OF SIGNS AND SYMPTOMS IN PATIENTS WITH BOTH VITAMIN B12 DEFICIENCY AND RAISED TSH.

TABLE 13: DISTRIBUTION OF CBC AND BLOOD INDICES IN PATIENTS WITH BOTH DECREASED VITAMIN B12 AND RAISED TSH.

CBC and Blood Indices	Frequency (n=12)	Percent %
Haemoglobin		
Increased	0	NA
Decreased	5	41.66%
Total Count		
Increased	2	16.66%
Decreased	0	NA
Platelet		
Increased	0	NA
Decreased	1	8.33%
PCV (hematocrit)		
Increased	0	NA
Decreased	4	33.33%
MCV		
Increased	2	16.66%
Decreased	4	33.33%
MCH		
Increased	2	16.66%
Decreased	4	33.33%
MCHC		
Increased	0	NA
Decreased	2	16.66%
TRBC		
Increased	2	16.66%
Decreased	4	33.33%
RDW		
Increased	5	41.66%
Decreased	2	16.66%

On investigating, Anemia and red cell distribution width was found raised in 41.66% of patients, 33.33% of patients were found out to have decreased hematocrit (PCV), MCH and TRBC and only 16.66% had leucocytosis and raised MCV and decreased MCHC. However, only 8.33% of them had thrombocytopenia.



GRAPH 15: - GRAPH SHOWING DISTRIBUTION OF CBC AND BLOOD INDICES IN PATIENTS WITH BOTH VITAMIN B12 DEFICIENCY AND RAISED TSH.

DISCUSSION

In this observational study we included 60 hypothyroid patients during the study period. We observed that as compared to overt hypothyroidism, prevalence of subclinical hypothyroidism is higher, with higher frequency in older female population. 51-60 years was the most common age group in our patient population. Females made the majority of those affected. There are reports that there is an age-related shift towards higher thyroid-stimulating hormone (TSH) concentrations in older patients. It has therefore been proposed that if age-adjusted normal ranges are used, the prevalence may not increase with old age. As far as the gender is concerned, hypothyroidism has been reported to be five to eight times more common in women than men[44] as in our study. Additionally, it has been reported to be more common in women with small body size at birth and during childhood.

Hypertension was the most common past medical history found in 20% of our study patients which is similar to that reported in the previous studies. In previous studies, it was reported that in patients with total thyroidectomy or withdrawal of thyroxin for six weeks there is an increase in serum norepinephrine and aldosterone concentrations. This results in increase in blood pressure with a greater rise in diastolic pressure. [45] Studies have reported that approximately 20 to 40% of hypothyroid patients have hypertension (as in our study), even though cardiac output is reduced.[46]

Approximately 28% of the patients in our study had low serum vitamin B 12 levels. Previous studies have reported pernicious anemia to occur in about 10% of patients with hypothyroidism caused by chronic autoimmune thyroiditis. [47] Such patients are reported to present with a macrocytic anemia with marrow megaloblastosis. The mechanism is unclear and it may be multifactorial in some patients. However,

normocytic normochromic anemia was the most commonly seen RBC morphology in our study patients. In a previously published series of 202 patients with hypothyroidism, a small subset of patients had macrocytosis despite normal levels of vitamin B12, folate, and iron. [48] Of these anemic patients, 25% were treated with thyroxin alone. It has been suggested that patients with autoimmune hypothyroidism may have concomitant vitamin B12 deficiency caused by autoantibodies to gastric parietal cells. Studies have shown that in patients with iron deficiency anemia and hypothyroidism, combined therapy with levothyroxine and oral iron supplements results in correction of the anemia, which may have been refractory to treatment with iron alone.[49] Moreover, it has been seen that MCV is mildly increased in hypothyroidism, which may be due to concomitant defects that cause macrocytosis and microcytosis.[50] Therefore it is recommended to measure vitamin B12 level in patients with hypothyroidism who are anemic as well.

We found a strong significant correlation between hemoglobin, MCV values and TSH. Similar to this, Kawa et al reported that in hypothyroidism RBC and Hb. were decreased, while hematocrit was increased. [51] They also showed that MCH and MCHC were lower in patients with thyroid dysfunction and MCV was increased in two groups of hypothyroidism and hyperthyroidism. However, the dose of thyroxin and years of known diagnosis had no correlation with any blood indices in our study.

Hypothyroidism in women has been shown to result in either oligomenorrhoea or hypermenorrhoea-menorrhagia. These menstrual changes result in decreased fertility. [52] In a small study of 171 premenopausal women with hypothyroidism, 16% had oligomenorhoea or amenorrhea. 5% of our study population had oligomenorrhoea.

Hypothyroid and vitamin B12 deficient patients often have common symptoms of weakness, lethargy, memory impairment, numbness and tingling. Muscle involvement in adults with hypothyroidism is common. Approximately, 33% of our patients reported symptoms of lethargy and fatigue and and 22% of our patient population had complaints of breathlessness. Shortness of breath on exertion and decreased exercise capacity have been suggested to be due to impaired respiratory function. Weakness of respiratory muscles and decreased pulmonary responses to hypoxia and hypercapnia can result in hypoventilation. [53] It has been seen that several patients, despite being on adequate thyroxin replacement, have persistence of symptoms and are subsequently found to be vitamin B12 deficient.

In a study of 116 hypothyroid patients 40% had low vitamin B12 levels and generalized weakness, impaired memory, depression, numbness and decreased reflexes were more frequently noted in B12 deficient patients. [8] On examining the correlation of increased or normal TSH levels with various symptoms, no statistically significant correlation was found. Similarly, decreased or normal vitamin B 12 levels had no effect on any physical symptom of the patients except generalized swelling.

Metabolism of homocystine and methyl-melonyl acid (MMA) require vitamin B 12, thus both MMA and homocystine levels increase in vitamin B12 deficiency. [54] When homocysteine levels are elevated other causes like co-exisiting folic acid deficiency, renal impairment and inadequate thyroid replacement need to be evaluated. We did not study homocysteine levels in our study, but this is an area of increasing interest. Studies have shown a relationship between hypothyroidism and hyperhomocysteinemia[55], which has also shown to improve with treatment of thyroid status. We also analyzed the correlation between serum TSH level and vitamin B12, which failed to reach statistical significance.

SUMMARY

Hypothyroidism is a condition caused due to decreased synthesis, metabolism or decreased action of thyroid hormone which can be due to various causes. Hypothyroidism is the most common of thyroid disorders in India, affecting one in ten adults. The prevalence of hypothyroidism is 11% in India, compared with U.K & U.S.A, which is only 2% and 4·6% respectively. Despite the known fact that anemia and thyroid dysfunction often occur simultaneously, the pathophysiology remains unclear. Hypothyroid patients often present with symptoms of numbness, paresthesia, poor memory and weakness, despite being on adequate replacement doses of thyroxin**.** Only few studies have been conducted to assess the cause of anemia and specifically role of Vitamin B12**.** So, we planned this study to see for prevalence of anemia in thyroid patients and to see if there is any association between vitamin B12 deficiency and anemia in patients with hypothyroidism either new or in already diagnosed cases that present to our hospital.

It was an observational study. It was carried out in the Department of Medicine, SBKS Medical Institute & Research Centre. All hypothyroid patients attending the medicine OPD or admitted to medicine wards were enrolled for the study. The patients already diagnosed as hypothyroid >18 years in age and those who give consent for participation in the study were included. Total 60 patients of hypothyroidism were included in the study. A detailed history was taken from all participants. All were subjected to CBC, thyroid function test, S. Vitamin B12. Sickling, Urine RM, renal function test, liver function test. S. ferritin, retic count was recorded only if required. Data was analysed to assess the burden of B12 deficiency in hypothyroidism and to find out any correlation between TSH level, anemia and vitamin B12 deficiency.

Majority of the patients of hypothyroidism belong to > 50 years' age group of 51 to 60 years. Females made more proportion of population of hypothyroidism as compared to the opposite gender. About one third of hypothyroidism had decreased vitamin B 12 levels. Fatigue and lethargy were the most commonly reported symptoms, followed by breathlessness and generalized swelling. TSH levels of our study population correlated well with hemoglobin levels and MCV values. However, no clinical symptom correlated with TSH levels. Similarly, no blood indices or physical symptom correlated with vitamin B12 levels. TSH levels itself did not correlate with vitamin B12 levels in our patients. However, 28% of the hypothyroid patients had vitamin b12 deficiency.

Our findings suggest that anemia is common among patients with hypothyroidism as is vitamin B12 deficiency, however we could not establish any significant correlation of TSH with vitamin B12 and anemia. However, we found that severity of symptoms was greater in patients with B12 deficiency also present with raised S.TSH. Data published previously demonstrates the role of thyroxin in anemia that could not be corrected by iron alone. Therefore, based on these results, we would recommend testing for TSH levels in anemic patients and testing for vitamin B12 anemia in hypothyroid patients. Further studies are required to understand the pathophysiology and mechanisms involved in hypothyroidism and vitamin B12 deficiency anemia. A multicentric randomized controlled study will help us in elucidating the role of TSH in vitamin B12 deficiency anemia and overall impact on the clinical outcome in these patients.

CONCLUSION

The results of our observational study showed that majority of the patients of hypothyroidism belong to > 50 years' age group of 51 to 60 years. Females are more prone to develop hypothyroidism as compared to the opposite gender. About one third of hypothyroidism had decreased vitamin B 12 levels. Fatigue and lethargy is the most commonly reported symptom, followed by breathlessness and generalized swelling. TSH levels of our study population correlated well with hemoglobin levels and MCV values. However, no clinical symptom correlated with increased or normal TSH levels. Similarly, no blood indices or physical symptom correlated with vitamin B12 levels. TSH levels itself did not correlate with vitamin B12 levels in our patients.

Our findings suggest that anemia is common among patients with hypothyroidism as is vitamin b12 deficiency, however we could not establish any significant correlation of TSH with vitamin B12. However, we found that severity of symptoms was greater in patients with B12 deficiency also present with raised S.TSH. Data published previously demonstrates the role of thyroxin in anemia that could not be corrected by iron alone. Therefore, based on these results, we would recommend testing for TSH levels in anemic patients and testing for vitamin B12 anemia in hypothyroid patients. Further studies are required to understand the pathophysiology and mechanisms involved in hypothyroidism and vitamin B12 deficiency anemia. A multicentric randomized controlled study will help us in elucidating the role of TSH in vitamin B12 deficiency anemia and overall impact on the clinical outcome in these patients.

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ANNEXURE I:

LIST OF ABBREVIATIONS

TSH	Thyroid stimulating hormone
T3	triiodothyronine
T4	thyroxine
fT3	Free triiodothyronine
fT4	Free thyroxine
AITD	Autoimmune thyroid disease
TTF	Thyroid transcription factor
PAX-8	Paired homeobox 8
Tg	Thyroglobulin
TPO	Thyroperoxidase
TSH-R	Thyroid stimulating hormone receptor
TRH	Thyroid releasing hormone
NIS	Sodium iodide symporter
hCG	Human chorionic gonadotropin
GIT	Gastrointestinal tract
ECF	Extracellular fluid
MIT	Monoiodotyrosine
DIT	diiodotyrosine
mRNA	Messenger ribonucleic acid
DNA	Deoxy ribonucleic acid
DUOX 1 and 2	Dual oxidase 1 and 2

cAMP	Cyclic adenosine monophosphate
TSI	Thyroid stimulating Immunoglobulin
IGF 1	Insulin like growth factor 1
TGF Beta	Transforming growth factor beta
GH	Growth Hormone
SCH	Subclinical hypothyroidism
Gs	Stimulating G protein
WHO	World Health Organisation
PCV	Packed cell volume
MCV	Mean corpuscular volume
MCH	Mean Corposcular haemoglobin
MCHC	Mean Corposcular haemoglobin concentration.
TRBC	Total Red blood cell
RDW	Red cell Distribution width
EPO	Erythropoetin
OPD	Out patient department
Hb	Haemoglobin
Tc	Total count
PMNs	Polymorphonuclear cells
Urine RM	Urine routine micro
IHD	Ischemic Heart disease
HTN	Hypertension
RBS	Random Blood Sugar

SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
K/C/O	Known case of
GERD	Gastro esophageal reflux disease
CVA	Cerebrovascular accident

ANNEXURE II:

PARTICIPANT INFORMATION SHEET

Study Title*:* A study of anemia in hypothyroidism with reference to vitamin B12 levels.

1. Introduction: Hypothyroidism is a common disease worldwide with varied frequency. It can affect erythropoiesis leading to anemia. Though it can produce all types of anemia we wish to co-relate vitamin B12 with thyroid disorder as the information regarding their relation in the available literature is inconclusive.

2. What is the purpose of this study?

   To see the burden of vitamin B12 in Hypothyroid patients and find if there is any correlation between the two.

3. Why have I been chosen?

   Having hypothyroidism, there is no history of any chronic disease or alcohol consumption or on vitamin B supplementation.

4. Do I have to take part?

   Yes. Only for few tests which has to be done.

5. How long will the study last?

   Study will last for 1½ to 2 years.

6. What will happen to me if I take part?

   You will be subjected to only some questions about and related to the symptoms and the necessary investigations. These will carry no harm in any way.

7. What do I have to do?

   Co-operate for giving real facts for questions and, allow investigator to complete the investigations needed.

8. What are the benefits of the study?

   This study will provide an insight regarding need of regular vitamin b12 supplementation to hypothyroid patients.

9. What happens when the study stops?

   When study stops data gathered during the study will be evaluated & inference would be made accordingly. Identity of any patient will not be revealed.

10. What if something goes wrong?

    There is as such no risk to any participant because it does not include any human or animal experimentation.

11. Will my taking part be kept confidential?

    Yes. All data collected will be kept confidential.

12. What else should I know?

    Whole study is on voluntary basis, no adverse events are expected, and no extra financial burden would be levied on participant.

13. Who to call with questions?

    Dr. Palak Bhuta Mobile No. 9638466677

પરિશિષ્ટ – ૧

સુમનદિપ વિદ્યાપીઠ યુનિવર્સીટી, પીપરીયા, તા.વાઘોડીયા, જિ. વડોદરા.

પીન નં :૩૯૧૭૬૦

ડૉ. પલક ભુતા

<u>સહભાગીદારનું સહભાગી પત્રક</u>

અભ્યાસનું શીર્ષક :- હાઈપોથારોઈડિઝનમાં એનિમિયાનો વિટામીન B12 ના સંદર્ભે અભ્યાસ

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(૧) પ્રસ્તાવના :- હાઈપોથાઈરોડિઝન એ વિટામીન B_{12} માં જોવા મળતો એક સામાન્ય રોગ છે. તે અરીપ્રોપોએસિસને અસર કરે છે જેથી એનિમીયા થાય છે. તેનાથી દરેક પ્રકારના એનિમીયા થાય છે તેમ છતાં અમે તેને વિટામીન B_{12} ની સાથે થાઈરોઈડ ડિસઓર્ડર ની સાથે તેનો સંદર્ભ જોડીને અભ્યાસ કરવા માંગીએ છે કેમકે, ઉપલબ્ધ તબીબી સાહિત્યમાં તેઓના સંબંધ વિશે કોઈ ચોક્કસ નિર્ણય પર આવી શક્યું નથી.

(૨) અભ્યાસનો હેતુ શું છે ? હાઈપોથાઈરોઈસ દર્દીઓમાં વિટામીન B_{12} નું પ્રમાણ જોવું અને આ બંનેની વચ્ચે કોઈ સંબંધ છે કે કેમ તે તપાસવો.

(૩) મારી પસંદગી શા માટે થઈ છે ? તમને હાઈપોથાઈરોડિઝમ છે તેમજ તમને કોઈ કાયમી રોગ નથી કે તમે મદ્યપાન નથી કરતાં કે કોઈ વિટામીન B ના પૂરકો લેતાં નથી.

(૪) મારે ભાગ લેવાનો છે ?હા, માત્ર થોડાક જ ટેસ્ટ કરાવવા માટે.

(૫) અભ્યાસ કેટલો સમય ચાલશે ? ડોઢથી બે વર્ષ સુધી ચાલશે.

(૬) જો હું ભાગ લઈશ તો મારી સાથે શું થશે ? તમારે માત્ર થોડા પ્રશ્નોના જવાબ જ આપવાના છે, તેથી તમારી સાથે કશું થાય તેવી શક્યતા જ નથી. અને આ પ્રશ્નો પણ તમને જે તકલીફ થાય છે તે સંદર્ભે જ પૂછવામાં આવશે તેથી તમને કોઈ તકલીફ થશે નહીં.

(૭) મારે શું કરવાનું રહેશે ? કે પ્રશ્નો પૂછવામાં આવ્યા છે તેના જવાબો સાચા અને વિસ્તારપૂર્વક આપવાના રહેશે. તેમજ સંશોધકને સંશોધન પૂર્ણ કરવામાં સહયોગ આપવાનો રહેશે.

(૮) આ અભ્યાસથી શું થશે ? હાઈપોથાઈરોઈડના દર્દીઅપમાં નિયમિતપણે જરૂર પડતા વિટામીન B_{12} ની કેટલી જરૂર છે તેમજ તે વિશેની બીજી ઝીણવટભરી માહિતી પણ મળશે.

(૯) અભ્યાસ પૂર્ણ થયેથી શું થશે ? અભ્યાસ પૂર્ણ થયેથી જે પણ માહિતી એકત્ર કરવામાં આવેલી છે તેનું વિશ્લેષણ થશે તેમજ તેને ધ્યાનમાં રાખી યોગ્ય નિષ્કર્ષ પર આવીશું. આ પ્રક્રિયા દરમિયાન દર્દીની ઓળક ક્યાંય, કોઈ પણ રીતે છતી નહીં થાય તેની ખાતરી રાખશો.

(૧૦) જો કંઈક અજૂગતું કે ખોટું થશે તો ? આ અભ્યાસ દરમિયાન વ્યક્તિ કે પ્રાની કોઈની પર પણ કોઈ પ્રકારનો પ્રયોગ કે અખતરો કરવાનો નથી તેથી કંઈપણ અજૂગતું કે ખોટું થવાની શક્યતા નથી.

(૧૧) હું આ અભ્યાસમાં ભાગ લઉં છું તે ગોપનીય રખાશે ? હા, તમારી ઓળખ છતી નહી થાય તેમજ તમારી માહિતી પણ ગોપનીય રખાશે.

(૧૨) મારે બીજું શું જાણવાની જરૂર છે ? આ સંપૂર્ણ અભ્યાસ સ્વૈચ્છીક છે, તેમાં કોઈપણ પ્રકારે, કશું પણ ખોટું નથી થવાનું, અને કોઈપણ પ્રકારનો આર્થિક ખર્ચ સહભાગીએ ઉપાડવાનો નથી રહેતો.

(૧૩) કોઈપણ મૂંઝવણ કે પ્રશ્ન હોય તો કોનો સંપર્ક કરવો ?

ડૉ. પલક ભુતા, મો.નં. ૯૬૩૬૪૬૬૬૭૭

परिशिष्ट – ३

सुमनदिप विद्यापीठ, पीपरीया, तहसिल :वाघोडीया, जिला : बडौदा. पीन नं : ३९१७६०

सहभागी का जानकारी पत्रक

अभ्यास का शीर्षक :– हाइपोथाइरोडिझम में एनिमिया का विटामीन B_{12} के संदर्भ में अभ्यास.

(१) प्रस्ताविक :– हाइपोथाइरोडिझम के मरिझ आज विश्वभरमें देखे जा सकते है, यह एक आम बात है। हाइपोथाइरोडिझम एरिपथ्रोपोएसिस पर अपना प्रभाव छोडता है और उसीसे एनीमीया होता है। इसी से सभी प्रकार के एनीमीया भी होते है। फीरभी हम उसे B_{12} के साथ थाइरोइड डिसओर्डर को साथमें रखकर उसका संदर्भ जोडकर अभ्यास करना चाहते हैं, क्योकि, उपलब्ध दाक्तरी साहित्यमें इनके संबंधके बारे में कीसीभी निर्णय पर नहीं आ पाए हैं।

(२) अभ्यास का उद्देश्य क्या है ? हाइपोथाइरोइड के मरीजो मे ं B_{12} का प्रमाण देखना व इन बीच कोई संबंध है या उसकी जाँच करना।

(३) मेरा ही चयन क्यो ? आपको थाइरोडिझम है ओर आपको और कोई पर्णकालीन रोग नहीं है या आप मद्यपान नहीं करते या B_{12} की आपूर्ति के लिए अन्य कोई दवाईर्यां नही लेते।

(४) मुझे हिस्सा लेना है ? हा, आपको सिर्फ कुछ टेस्ट करानेके लीए ही हिस्सा लेना है।

(५) अभ्यास कीतने समय तक चलेगा ? अभ्यास डेढ साल से लेकर दो साल तक चलेगा।

(६) में अगर हिस्सा लेता हुँ तो मेरे साथ क्या होगा ? अपको सिर्फ कुछ चंद सवालों के जवाब दने हैं। वह भी विस्तार से और जो भी है वह सच सच बताना है। इसमें आपको कोई तकलीफ नहीं होगी।द्र

(७) मुझे क्या करना होगा ? आपको जोभी पूछा जाए उसका सही सही, विस्तारपूर्वक जवाब दने होंगे और अभ्यासमें संशोधनकर्ता को सहयोग देना होगा।

(८) इस अभ्यास में क्या फायदा होगा? हाइपोथाइरोइड के मरीजों में आए कीतनी मात्रा मे B_{12} की जरुरत पडेगी व उससे जडी हुई अन्य जानकारीयाँ भी प्राप्त होगी, जीससे मरीजों के इलाज में सहायता होगी।

(९) अभ्यास खत्म होने के बाद क्या होगा? अभ्यास खत्म होने पर उपलब्ध सभी जानकारीओं का विश्लेषण कीया जाएगा और उचित निष्कर्ष निकाला जाएगा। इस पूर्ण प्रक्रिया क दौरान कहीं पर भी मरीज की पहचान सार्वजनीक होगी।

(१०) अगर कुछ गलत हुआ तो? अभ्यास के अंतर्गत कोई भी दवाई का या उपचार का , कीसी भी प्राणी या मनुष्य पर कोई प्रयोग नहीं कीया जाएगा और इसीलीए कुछ गलत होने की संभावना ही नहीं हैं।

(११) जों हीस्सा ले रहा है इस बात को गोपनीय रखा जाएगा? हा, आपकी व आपकी या आपसे मीली हुई जानकारी पुर्ण रुपसे गोपनीय रखी जाएगी।

(१२) मुझे और क्या जानना है? कुभ भी नहीं, फिर भी आपकी जानकारी के लीए, इस अभ्यास में हिस्सा लेना पूर्णरुपसे स्वैच्छीक है, कोई भी अपेक्षित या अनपक्षित घटना होने वाली नहीं है, और आपको कीसी भी प्रकार का खर्च नहीं उठाना हैं।

(१३) अगर कोई दिक्कत हो तो किसका संपर्क करे ?

डॉ. पलक भुता, दूरभाष संपर्क : 9638466677

ANNEXURE III:

INFORMED CONSENT FORM

Informed Consent Form (ICF) for Participants in Research Programs involving studies on human beings

Study Title: -

Please initial box
(Subject)

(i) I confirm that I have read and understood the information sheet dated ……....….for the above study and have had the opportunity to ask questions. ☐

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, ☐

Even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. ☐

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) ☐

(v) I agree to take part in the above study. ☐

P.T.O

Signature/Thumb impression of the participant _____

Legally acceptable representative _____

Signatory's Name _____ Date _____

Signature of the investigator _____ Date _____

Study Investigator's Name _____ Date _____

Signature of the impartial witness _____Date _____

Name of the witness _____

ANNEXURE-D

સંમતિ સૂચન

અભ્યાસ શીર્ષક : હાઈપોથારોઈડિઝનમાં એનિમિયાનો વિટામીન B12 ના સંદર્ભે અભ્યાસ

સહભાગીનું મિતાક્ષરી : ..... સહભાગીનું નામ : .....

જન્મ તારીખ / ઉંમર : .....

સહયોગીનું સરનામું : .....

લાયકાત : .....

વ્યવસાય : વિદ્યાર્થી/સ્વરોજગાર/નોકરી/ગૃહિણી/અન્ય
(યોગ્ય વિકલ્પ પર નિશાની કરો)

અભ્યાસ પાત્રની વાર્ષિક આવક : .....

વારસદાર(રો)ની વિગત

વારસદારનું નામ : .....

વારસદારનું સરનામું : .....

અભ્યાસપાત્ર / સહયોગી સાથે સંબંધ : .....

કૃપા કરી માં હકો જવાબ આપો.

૧. હું ખાતરી આપુ છું કે આ અભ્યાસનું ..... તારીખની માહિતી પત્રક મે વાંચ્યું છે અને સમજ્યો છું તેમજ મને પ્રશ્નો પૂછવાની તક મળેલ છે.

૨. હું સમજું છું કે આ અભ્યાસમાં માન અધ્યોગિતા સ્વૈચ્છિક છે અને હું કોઇ પણ સમયે કારણ દર્શાવ, વિના જ મુક્તિ થઇ શકુ છું તેથી મારી તબીબી ચિકિત્સા કે કાયદાકીય હક્કો પર કોઇ પ્રભાવ પડશે નહીં.

૩. હું સમજુ છું કે અભ્યાસના અન્વેષક, તંબ્બોના વતી કાર્ય કરનાર હિતરક્ષક સમિતિ અને નિયામક સતાઓને જાણ વર્તમાન કે ભાવિ સંશોધન જે મારી સહભાગિતા પછી મૈત્રી લીધા પછી પણ જાનનો બંને કિસ્સામાં મારી સ્વાસ્થ્ય માટેની જોવા મારી પરવાનગીની આવશ્યકતા નથી. હું તેના ઉધ્ઘોપક લેવામાં સહમત છું જો કે

હું સમજૂ છું કે માહિત વ્યક્તિ કે પ્રકાશન દ્વારા મારી ઓળખ રજૂ કરવામાં આવશે નહીં.

૪. હું કોઇ પણ માહિતી કે પરિણામ જે માપ આવા વૈજ્ઞાનિક હેતુસર ઉપલબ્ધ કરાવાય છે તેના ઉપયોગમાં અવરોધ ન કરવા માટે સંમત છું.

૫. હું ઉપયોગ અભ્યાસમાં સહભાગી થવા સંમત છું.

અભ્યાસપાત્રની સહી / અંગૂઠાનું નિશાન .....

તારીખ : .....

સહી કરનારનું નામ : .....

અન્વેષકની સહી : .....

તારીખ : .....

અભ્યાસ અન્વેષકનું નામ : .....

સાક્ષીની સહી : .....

તારીખ : .....

સાક્ષીનું નામ : .....

દર્દી માહિતી પત્રક અને ભરેલું, માહિતી સંમતિ પત્ર અભ્યાસ સમાન કે તેની આપેલ વ્યક્તિ વ્યક્તિ આપવું.

प्रतियोगी

अभ्यासमे सहभागी होते समयका

अनुमति– संमति पत्र

अभ्यास का नाम : **विटामिन बी–१२ की कमी के संदर्भ में हाइपोथायरायडिज्म में एनीमिया का अध्ययन**

अभ्यास क्रमांक दिनांक

प्रतियोगी की जन्मतारीख / आयु

१) में सत्यापित करता हुं की ता..... से..... उपरोकत अभ्यास के विषयमें जानकारी पढने की एवं प्रश्न करने के अवसर प्रदान किये गये है ।

२) में जानती/ जानता हुं की इस अभ्यासमें सहभागीता करना मेरे लिये स्वैच्छि है, और कोइ भी कारण प्रद्धति किये बिना किसी भी समय इस में से मुक्त होने की स्वतंत्रता है, ऐसा करने से मेरे दाकतरी हस्सो से उपर कोई प्रभाव नहीं होगा ।

३) मे जानती/ जानता हुं कि यह अभ्यासकर्ता, उनसे सहयोगी और जुथ और उनकी उमरीयों से मेरे स्वास्थ्य संबंधी किसी भी जानकारी प्राप्त करने में मेरी अनुमति की आवश्यकता नहीं है, भले ही मे उस अभ्यास से मुक्त हो गई हुँ । मे जानती/ जानता हुं कि मेरी इस प्रसार की जानकारी अन्य किसी भी प्रसार से प्रसाशित नहीं की जाएगी ।

४) इस अभ्यास के दौरान अथवा उसके प्राप्त जानकारी विज्ञानकयोग के हेतु उपयोग करने स्वतंत्र है ।

५) में इस अभ्यासमें जूडने / सहभागी होने के लिये सहमत हुं ।

अभ्यासने सहयोगी की सही या अंगुठे का निशान

तारीख .....

कानुनी अन्वेष्कके सही .....तारीख .....

अन्वे का नाम .....

साक्षी / गवाह की सही ..... तारीख .....

गवाह / साक्षी का नाम .....

ANNEXURE IV:

PROFORMA:

Name:

Age / Sex / Weight:

Address:

OPD number:

IPD number:

Education:

Occupation:

Socio – economic status:

Smoker:

Alcoholic:

HISTORY

A. CHIEF COMPLAINTS:

- Weight Gain
- Cold intolerance
- Fatigue
- Lethargy
- Muscle Cramps
- Decrease Appetite
- Depression
- Swelling
- Breathlessness
- Paresthesia
- Excessive sweating
- Constipation

B.HISTORY OF PRESENTING ILLNESS:

PAST HISTORY-

H/O Similar complaints / DM / HTN / TB/ IHD/ EPILEPSY/ BRONCHIAL ASTHAMA/ HYPOTHYROIDISM

FAMILY HISTORY

PERSONAL HISTORY

OBSTETRIC & MENSTRUAL HISTORY-

GENERAL EXAMINATION

- Temperature
- Pulse
- B.P
- Respiratory Rate
- Pallor / Icterus / Cyanosis / Clubbing / Edema / Lymphadenopathy

SYSTEMIC EXAMINATION

- Respiratory system:
  - Breath sound-Any foreign sound- Yes/No
  - If yes- crepts/rhonchi/other
- Respiratory rate :
- Cardiovascular system:
  - S1- S2/Murmur
  - Heart rate
- Central nervous system:
  - GCS Score
- Per Abdomen :
  - soft/ hard
  - Tender/ Non tender
  - organomegaly

LAB INVESTIGATION

- CBC
- RBC Indices
- Peripheral smear
- Reticulocyte count
- Sickling
- S.TSH:
- Free T3
- FreeT4
- Urine RM
- Vitamin B12
- RBS
- Urea
- Creatinine
- Bilirubin

RADIOLOGICAL INVESTIGATION

ECG

Chest Xray

USG Abdomen

ANNEXURE V:

MASTER CHART

KEY TO MASTER CHART

SR NO	:	SERIAL NO
WT	:	WEIGHT
ADD	:	ADDRESS
WEIGHT GAIN	:	1 : NO
		2 YES
FATIGUE 1	:	1- NO
		2- YES
LETHARGY1	:	1-NO
		2- YES
DECREASED APETITE	:	1-NO
		2- YES
GENERALISED SWELLING	:	1-NO
		2- YES
COLD INTOLERANCE	:	1-NO
		2- YES
MUSCLE CRAMPS	:	1-NO
		2- YES
DEPRESSION	:	1-NO
		2- YES
BREATHLESSNESS	:	1- NO BREATHLESSNESS,
		2- PRESENT

OTHER PAST HISTORY

PERSONAL HISTORY	:	1-none, 2-tobacco chewer, 3-alcoholic, 4-smoker
PAST HISTORY	:	(k/c/o hypothyroidism: 1-NO, 2-YES)
OBS & MENS	:	OBSTETRICS & MENSTRUAL HISTORY Normal-1, oligomenorrhoea- 2, polymennorhoea-3, Pregnant-4
TEMP	:	TEMPERATURE
BP	:	BLOOD PRESSURE
RESP.RATE	:	RESPIRATORY RATE
PALLOR	:	1-ABSENT, 2-PRESENT
ICTERUS	:	1-ABSENT, 2-PRESENT
CYANOSIS	:	1-ABSENT, 2-PRESENT
CLUBBING	:	1-ABSENT, 2-PRESENT
LE	:	LYMPHADENOPATHY 1-ABSENT, 2-PRESENT
OEDEMA	:	1-ABSENT, 2-PRESENT ,non-pitting, 3-present, pitting
RS-RESPIRATORY SYSTEM	:	1-NORMAL, 2-ABNORMALITY PRESENT

CVS	:	CARDIO VASCULAR SYSTEM 1-NORMAL, 2-ABNORMALITY PRESENT
CNS	:	CENTRAL NERVOUS SYSTEM 1-NORMAL, 2-ABNORMALITY PRESENT
PA	:	PERABDOMEN 1-NO ORGANOMEGALY, 2-ORGANOMEGALY PRESENT
HB	:	HEMOGLOBIN in mg/dL
TC	:	TOTAL COUNT
DC	:	DIFFERENTIAL COUNT
PC	:	PLATLET COUNT in lacs
MCV	:	MEAN CORPUSCULAR VOLUME
MCH	:	MEAN CORPUSCULAR HEMOGLOBIN
MCHC	:	MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION
TOTAL RBC	:	TOTAL RED BLOOD CELL COUNT
RDW	:	RED CELL WIDTH
RBS	:	RANDOM BLOOD SUGAR
ECG,	:	(WNL-WITHIN NORMAL LIMIT- 1, BRADYCARDIA- 2, OTHER ABNORMALITY-
SICKLING	:	(1-ABSENT, 2-PRESENT)
Trait / Disease		1- sickle trait 2- sickle disease

URINE-RM	:	1-normal, 2-abnormal
CHEST X RAY	:	1-normal, 2-abnormal
USG ABDOMEN	:	(WNL-WITHIN NORMAL LIMITS , ABNORMALITY-2)

MASTER CHART

PRIMARY DATA			SYMPTOMATOLOGY											HISTORY									GENERAL EXAMINATION														COMPLETE BLOOD COUNT				RBC INDICES						PERIPHERAL SMEAR				SICKLING										RFT		LFT							
SR NO	AGE	SEX	WEIGHT GAIN	FATIGUE	LETHARGY	DECREASE APETITE	GENERALISED SWELLING	MUSCLE CRAMPS	COLD INTOLERANCE	DEPRESSION	BREATHLESSNESS	EXCESSIVE SWEATING	CONSTIPATION	PARESTHESIA	PAST HISTORY	K/C/O since YEARS	DOSE OF THYROXINE	DIAGNOSIS/REMARKS	OTHER PAST HISTORY	PERSONAL	OBS & MENS	FAMILY	TEMP	PULSE	BP	PALLOR	ICTERUS	CYANOSIS	CLUBBING	LE	OEDEMA	RS	CVS	CNS	PA	REMARKS	Hb	TC	DC	PC	HEMATOCRIT	MCV	MCH	MCHC	TOTAL RBC	RDW	RBC MORPHOLOGY	WBC MORPHOLOGY	PLATELET MORPHOLOGY	BLOOD PARASITE	SICKLING	TRAIT/DISEASE	RETIC COUNT	TSH	FREE T3	TOTAL T3	FREE T4	TOTAL T4	VITAMIN B12	RBS	UREA	CREATININE	BILIRUBIN	SGPT	SGOT	URINE RM	ECG	C-XRAY	USG ABDOMEN	OTHER
1	20	M	1	2	2	1	1	1	1	1	1	2	1	1	1					1	1	1	Afebrile	80	114/70	1	1	1	1	1	1	1	1	1	1		14.8	5400	52,39,4,5	1.75	44.4	87.9	29.7	33.3	5.05	12.5					1			12.229					165.9	97							1	1	1	
2	47	F	1	1	2	1	1	1	1	1	2	1	1	1	2	1 year	25 mcg			1	1	1	Afebrile	76	110/66	1	1	1	1	1	2	1	1	1	1		10.5	6700	71,22,3,4	1.84	31.4	81.3	27.2	33.4	3.86	13.4					1			3.24					1968	153	33	0.9					3	2	1	
3	60	F	1	1	1	1	1	1	1	1	1	1	1	1	2	1 yr	50 mcg			1	1	1	Afebrile	88	130/84	1	1	1	1	1	1	1	1	1	1		12.5	10,600	63,29,4,4	2.86	36.7	86.2	29.3	34.1	4.26	14.8					1			1.57		0.95		10.2	248	116	45	1.3	0.9	22	20		1	1	1	
4	40	F	1	1	1	1	1	1	1	1	2	1	1	1	2	6 months	50 mcg			1	1	1	Afebrile	84	122/80	1	1	1	1	1	1	1	1	1	1		13	7100	60,32,4,4	1.81	40.4	87.5	28.2	32.3	4.62	15.1	normocytic,normochromic	normal	adequate	absent	1			12.04	2.8		1.12		647	98	31	1					1	1	1	
5	35	F	1	1	1	1	1	1	1	1	1	1	1	1	2	1 yr	100 mcg		Cardiac tamponade	1	1	1	Afebrile	80	124/80	2	1	1	1	1	1	1	1	1	1		9.1	4800	55,36,4,5	2	34.6	94	27.3	28.7	3.59	20.1	sickle cells+				2		0.50%	9.49					447								2	1	2	
6	37	F	1	2	2	1	2	1	1	1	1	1	1	2	2	5 yrs- left treatment since 1 year	100 mcg	defaulter- started from 1 month		1	1	1	Afebrile	74	124/72	1	1	1	1	1	2	1	1	1	1	non-pitting	10.4	5600	69,24,3,4	2.93	35.2	71.3	21.1	29.5	4.94	19.5					1			100	2.1		0.46		826		20	1				1	1-low voltage	1	1	
7	40	F	1	1	2	1	1	2	1	1	1	1	1	1	2	2 yrs	200mcg		HTN	1	1	1	Afebrile	80	100/70	1	1	1	1	1	1	1	2	1	1	Mid diastolic murmur in mitral area	14.9	9700	67,24,4,5	1.92	44.5	75.7	25.3	33.5	5.88	17.3					1		1%	0.14	3.7		1.81		496	100	15	0.9				1	3	2	1	
8	38	F	2	1	2	1	1	1	1	1	1	1	1	1	1					1	1	1	Afebrile	80	120/70	2	1	1	1	1	1	1	1	1	1		7.6	7900	70.21,4,3	3.97	25.5	60.1	17.9	29.8	4.24	15.8	microcytic, hypochromic	normal	adequate	absent	1		1.50%	6.081		1.39		9.6	299	73						1				
9	46	F	1	1	1	1	1	1	1	1	1	1	1	1	2	3 yrs	75mcg			1	1	1	Afebrile	88	94/60	1	1	1	1	1	1	1	1	1	1		13.6	7900	46,45,4,5	2.92	40	88.2	29.9	33.9	4.54	18.3								8.06	2.3		0.12		88.7	91	23	0.8				2	1	1	1	
10	35	F	1	1	1	1	2	1	1	1	2	1	2	1	1				HTN	1	1	1	Afebrile	76	150/100	1	1	1	1	1	1	1	1	1	1		11.7	6200	64.28,4,4	3	34.6	57.9	19	33.8	5.97	14.2					1			10.373	2		0.76		204	144		1					1	1		
11	55	F	1	1	1	1	1	1	1	1	1	1	1	1	2	2 yrs	25 mcg		HTN, IHD	1	1	1	Afebrile	56	90/66	1	1	1	1	1	1	1	1	1	1		13.4	6600	62,29,4,5	3.47	41	69.7	22.8	32.7	5.88	13.6	mild anisopoikilocytosis	normal	adequate	absent	1		1%	8.56	2.5		0.6		125	103	12	1.2		33		1	1	1		
12	55	M	1	1	1	1	1	1	1	1	1	1	1	1	2	3 months	50 mcg		CVA- recovered	1	1	1	Afebrile	102	112/78	1	1	1	1	1	1	1	1	1	1		12	11000	53,38,4,5	2.26	37.2	65.1	21	32.3	5.71	18.6								66.91	1		0.06		353.7		18	0.7					1			
13	47	F	2	2	2	1	1	1	1	1	1	1	1	1	2	1 yr	125 mcg			1	1	1	Afebrile	68	104/66	2	1	1	1	1	1	1	1	1	1		10.5	6900	57,39,1,3	3.94	33.6	76.5	23.9	31.25	4.39	14.4	microcytic, hypochromic	normal	adequate	absent	1			0.09		1.54		12.5	163	70		0.7		17		1				
14	42	M	2	2	1	1	1	1	1	1	1	1	2	2	1					1	1	1	Afebrile	84	116/64	1	1	1	1	1	1	1	1	1	1		16.2	9100	60,31,4,5	2.63	46.6	79.8	27.7	34.8	5.84	12.9								7.8		1.2		11.5	421		16	0.7				1	1			
15	30	F	1	1	1	1	1	1	1	1	2	1	1	1	2	2.5 yrs	25 mcg			1	1	1	Afebrile	72	110/80	1	1	1	1	1	1	1	1	1	1		14.9	6300	56,36,4,4	1.4	46.5	95	30.5	32.1	4.89	14.4								2.64	2.7		1.12		202	88						1				
16	51	M	1	1	1	1	1	1	1	1	1	1	1	1	1					2	1	1	Afebrile	82	110/70	1	1	1	1	1	1	1	1	1	1		11.5	5800	67,27,3,3	3.1	37.8	60.4	18.4	30.4	4.26	17.5								5.41	2.8		1.18		508.7	99	28	1					1	1	1	
17	58	M	1	1	1	1	1	1	1	1	1	1	1	1	2	4 yrs	100 mcg		HTN	1	1	1	Afebrile	68	116/74	1	1	1	1	1	1	1	1	1	1		13.4	5700	60,31,4,5	4.05	38	85.6	30.2	35.3	4.44	12.5								4.635	2		1.08		94.2	111	30	1.1				1	1	1		
18	70	M	1	1	2	1	1	1	1	1	2	1	1	1	1			IHD		4	1	1	Afebrile	82	128/74	2	1	1	1	1	2	2	1	1	1	Bilateraly pitting pedal oedema	5.2	4000	48,44,4,4	50,000	10.2	86.12	26.75	33	1.89	15.14	moderate anisopoikilocytosis	normal	decreased	absent	1		1%	81.54	0.5		3		836.8							1	1	2	2	
19	22	F	1	2	1	1	2	1	1	1	1	1	1	1	1					1	2	1	Afebrile	88	110/80	1	1	1	1	1	1	1	1	1	1		13.1	8900	60,31,4,5	4.5	38.6	102.8	34.9	33.9	3.75	14.9								6.11	3.3		1.24		136							1	1	1	1	
20	52	F	1	2	2	1	1	1	1	1	2	1	1	1	1			IHD		1	1	1	Afebrile	58	130/80	1	1	1	1	1	1	1	1	1	1		11.4	7000	60,30,4,4	2.7	34	88	29	32	3.9	12.3								>100	2.1		0.4		341		21	0.7	0.5	24	34	1	2,3	1	1	echo- IW hypokinesia, ef-45%, mild TR, Mild PAH
21	44	M	1	1	1	1	1	1	1	1	1	1	1	1	2	1 yr	50 mcg		HTN	2	1	1	Afebrile	68	146/94	1	1	1	1	1	1	1	1	1	1		12.7	6900	60,72,4,4	2.8	39.2	83.8	27.1	32.4	4.68	12.3								12.01	2.8		0.55		991.2	80		0.7	0.8	28	20	1				
22	48	F	1	1	1	1	1	1	1	1	1	1	1	1	2	6 yrs	88 mcg		HTN	1	1	1	Afebrile	100	110/60	1	1	1	1	1	1	1	1	1	1		13.1	9800	64,27,4,5	2.47	40.2	76.6	25	32.6	5.25	13.7	mild anisopoikilocytosis	normal	adequate	absent				14.7	2.8		0.92		508.1								1			
23	55	F	1	2	2	2	1	1	1	1	1	1	1	1	1					1	1	1	Afebrile	84	100/64	2	1	1	1	1	1	1	1	1	1		9	9600	80,13,3,4	2.88	29.8	67.1	20	29.9	4.44	15.7	moderate anisopoikilocytosis	normal	adequate	absent	1		1.50%	23.39	2.1		0.83		>2000	92	40	1								
24	41	F	1	1	1	1	1	1	1	1	1	1	1	1	2	7yrs	100 mcg			1	1	1	Afebrile	68	106/66	1	1	1	1	1	1	1	1	1	1		11.1	6800	66,20,4,5	2.74	28.4	74.2	22	32.1	5.4	14.6								14.18	2.2		0.91		450								low voltage			
25	60	F	1	1	1	1	2	1	1	1	2	1	1	1	2	30 yrs	50 mcg		GERD	1	1	1	Afebrile	68	140/80	1	1	1	1	1	2	1	1	1		Bilateraly non pitting pedal oedema, tenderness +	12.2	7600	66,24,3,4	2.12	26.4	72.6	24	29.2	5.6	16.4								0.68	2.7		1.48		198	111	36	0.6								B/L l.L doppler: no evidence of DVT, bilateral L.L subcutaneous oedema +, few subcentric non-necrotic enlarged L.N in inguinal area
26	40	F	1	1	2	1	2	1	1	1	1	1	1	1	1					1	1	1	Afebrile	80	120/70	1	1	1	1	1	2	1	1	1	1	non-pitting	12.5	9300	61,30,4,5	2.72	39.3	95.8	30.4	31.7	4.11	13.2								8.69	3.5		1.5		238	105	22	0.6		38			1		2- choledocholithiasis	
27	50	F	1	1	1	1	2	1	1	1	2	1	1	1	2	4 yrs	100 mcg		HTN, Dyslipedmia	1	1	1	Afebrile	78	140/76	2	1	1	1	1	2	1	1	1	1	Bilateraly pitting pedal oedema	7.6	6600	71,20,4,5	1.2	25.2	63.3	19.1	30.2	3.93	21.4	severe anisopoikilocytosis	normal	decreased	absent	1		3%	8.75	2.4		1.74		209	106	15	1	2.1	21	30	1	1	2	2	
28	56	F	1	1	1	1	2	1	1	1	2	1	1	1	1				HTN	a smo	1	1	Afebrile	100	130/90	1	1	1	1	1	2	2	1	1	1	Bilateraly pitting pedal oedema	11.8	7400	57,34,4,5	1.98	40.2	67.4	19.8	29.4	5.96	18.2	mild anisopoikilocytosis, sickle cells +	normal	adequate	absent	2	1	1.50%	25.17		0.73		4.9	228	140			1.1	21	38	1	3	2	2	ECHO: ? Ischemic DCM, Ef: 15-20%
29	38	M	1	2	1	1	1	1	1	1	1	1	2	1	1					1	1	1	Afebrile	80	108/60	1	1	1	1	1	1	1	1	1	1		12.2	6300	55,36,4,5	1.97	36.9	87.9	29	33.1	4.2	13.8								>100	2.4		0.04		412	102	42	1.3	0.8	21	43	1	1		1	
30	35	M	1	1	2	1	2	1	1	2	2	1	1	1	1				Bipolar mood disorder	2	1	1	Afebrile	88	124/86	1	1	1	1	1	1	1	1	1	1		13	9500	70,22,4,4	1.92	40.6	93.3	29.9	32	4.35	12.8								11.02					164	91									2	

MASTER CHART

PRIMARY DATA			SYMPTOMATOLOGY												HISTORY						GENERAL EXAMINATION																			COMPLETE BLOOD COUNT				RBC INDICES						PERIPHERAL SMEAR				SICKLING																	
SR NO	AGE	SEX	WEIGHT GAIN	FATIGUE	LETHARGY	DECREASE APETITE	GENERALISED SWELLING	MUSCLE CRAMPS	COLD INTOLERANCE	DEPRESSION	BREATHLESSNESS	EXCESSIVE SWEATING	CONSTIPATION	PARESTHESIA	PAST HISTORY	K/C/O since YEARS	DOSE OF THYROXINE	DIAGNOSIS/REMARKS	OTHER PAST HISTORY	PERSONAL	OBS & MENS	FAMILY	TEMP	PULSE	BP	PALLOR	ICTERUS	CYANOSIS	CLUBBING	LE	OEDEMA	RS	CVS	CNS	PA	REMARKS	Hb	TC	DC	PC	HEMATOCRIT	MCV	MCH	MCHC	TOTAL RBC	RDW	RBC MORPHOLOGY	WBC MORPHOLOGY	PLATELET MORPHOLOGY	BLOOD PARASITE	SICKLING	TRAIT/DISEASE	RETIC COUNT	TSH	FREE T3	TOTAL T3	FREE T4	TOTAL T4	VITAMIN B12	RBS	UREA	CREATININE	BILIRUBIN	SGPT	SGOT	URINE RM	ECG	C-XRAY	USG ABDOMEN	OTHER
31	60	F	1	2	2	2	1	1	1	1	2	1	1	1	1				HTN	1	1	1	Afebrile	108	104/62	2	1	1	1	1	1	1	2	1		5.2	15000	53,38,4,5	3.1	10	83.8	27.2	32.5	1.91	13.5	predominantly microcytic	leucocytosis	clumps	absent	1		4%	8.39	3		1.33		198	90	102	0.7					1	1	1	iron-29, tibc-389, ferritin, 75,stool Ob-neg
32	36	F	1	1	1	1	1	1	1	1	2	1	1	1	1					1	1	1	Afebrile	96	104/66	1	1	1	1	1	1	1	1	1		8.8	4000	51,40,4,5	2.88	27.4	83.8	26.9	32.8	3.27	15.1	normocytic,normochromic	normal	adequate	absent				8.8	0.6		3.5		351	90	28	0.7	0.6	10	16	1	low voltage	1	1	echo: Moderate pericardial effusion
33	55	F	2	2	2	1	1	1	1	1	1	2	1	1						1	1	1	Afebrile	82	160/100	1	1	1	1	1	1	1	1	1		12.7	7900	61/30/4/5	1.99	37	83.5	27.1	32.4	4.43	12.5	normocytic normochromic	normal	adequate	absent				89	2.1		0.95		>2000	104	15	1	0.6	48	30	1	low voltage	1	1	
34	34	M	1	2	2	1	1	1	1	1	2	2	1	1						1	1	1	Afebrile	88	124/70	1	1	1	1	1	1	1	1	1		12.6	8600	54/36/4/5	2.25	36.4	84.2	28.1	32.6	3.24	15.2								6.47	2.8		0.16		231											
35	45	f	2	2	1	1	2	1	1	1	1	1	1	1	1					1	1	1	Afebrile	66	106/60	1	1	1	1	1	2	1	1	1		9	6,800	90/5/2/3	2.01	26.5	112.4	37	33	2.36	18.1								19.8					186											
36	60	F	1	1	2	2	1	1	1	1	1	1	2	1	1					1	1	1	Afebrile	70	112/64	1	1	1	1	1	1	1	1	1		11.6	14,000	73,18,4,4	4.02	31.4	82.4	30.4	36.9	3.81	16.4								25.76					228											
37	55	F	1	2	2	2	1	1	1	1	2	1	1	1	1			Pericardial effusion		1	1	1	Afebrile	64	110/62	2	1	1	1	1	1	1	1	1		7.1	6000	60/31/4/5	3.46	23.2	66.8	20.6	30.8	3.47	20.1							3	83.06	<0.5		<0.1		248	92	27	1	0.3	52	90	1	low voltage	2	1	echo- mild-mod pericardial effusion
38	45	F	1	2	1	1	1	1	1	1	2	1	1	1	1					1	2	1	Afebrile	88	112/70	2	1	1	1	1	1	1	1	1		5.8	9400	66/27/3/4	3.54	22.1	63.3	16.6	26.2	3.49	16.5	moderate anisopoikilocytosis	normal	adequate	absent			2	52.67	0.7		2.9		321.5	112	16	0.6	0.4	11	13	1	1	1	1	iron- 45, tibc- 135, ferritin-110
39	36	F	1	2	2	1	1	1	1	1	1	1	1	1	1			Pericardial effusion		1	1	1	Afebrile	74	98/64	2	1	1	1	1	1	1	1	1		6.4	3000	56/35/4/5	1.5	20.2	96.2	30.5	31.7	2.1	19.5	moderate anisocytosis	leukopenia	decreased	absent	1		1	88.2	<0.1		0.24		835.6	106	37	1.1	0.4	40	62	1	Sinus tachycardia, low voltage	1	multiple liver hemangioma, cholelithiasis	echo- mild pericardial effusion; iron- 41, tibc- 373, ferritin-207; stool ob-positive
40	45	F	1	1	1	1	mb s	1	1	1	1	1	1	1	2	8 yrs	50 mcg			1	1	1	Afebrile	82	128/80	1	1	1	1	1	2	1	1	1	bilatral lowelimb pitting	13	7900	60/33/3/4	2.65	40.3	83.5	26.9	32.2	4.82	13.3								1.13		1.23		5.7	311										
41	34	M	1	2	1	1	1	1	1	1	1	1	1	1	1					1	1	1	Afebrile	64	104/60	1	1	1	1	1	1	1	1	1		11.9	10,600	69/22/4/5	2.74	34.5	70.3	24.32	34.5	4.91	14.9								7.5					480.4											
42	26	F	1	1	1	1	1	1	1	1	1	1	1	1	2	10 months	150 mcg			1	1	1	Afebrile	88	126/74	1	1	1	1	1	1	1	1	1		9.3	11,200	85/10/2/3	3.53	28.7	87.7	28.3	32.3	3.28	15								0.1					507.3											
43	54	F	1	1	1	1	1	1	1	1	1	1	1	2	2	4.5 yrs	25 &50 mcg alternate day		HTN, Dyslipedmia	1	1	1	Afebrile	78	134/76	1	1	1	1	1	1	1	1	1		13.1	9300	60/34/2/4	2.53	41.6	85.8	27	31.5	4.85	14.6	normocytic normochromic	normal	adequate	absent				2.3					185	93										lipid profile: chol- 140, trig-162, hdl-50. ldl-58,vldl-32
44	55	F	2	1	1	1	1	1	1	1	1	1	1	1	1				DM on mixtard	1	1	1	Afebrile	78	136/90	2	1	1	1	1	1	1	1	1		10.1	7600	55/36/4/5	2.3	29.3	66.7	23.7	35.5	4.39	18.2								6.86		0.74		8.4	221											
45	56	F	1	1	1	1	1	1	1	1	1	1	1	1	1				HTN	1	1	1	Afebrile	70	110/60	1	1	1	1	1	1	1	1	1		11.4	8300	68/23/4/5	2.82	36.5	67.5	21	31.1	5.41	13.4								13.55					314	148										
46	50	f	1	1	1	1	1	1	1	1	1	1	1	1	2	4 yrs	88 mcg			1	1	1	Afebrile	78	126/74	1	1	1	1	1	1	1	1	1		11.7	7300	77/14/4/5	1.5	35.1	83	27.7	33.3	4.23	12.9								5.1	2.6		1.36		412											
47	22	F	1	1	1	1	1	1	1	1	1	1	1	1	2	20 yrs	125 mcg			1	1	1	Afebrile	80	124/78	1	1	1	1	1	1	1	1	1		12.5	10500	88/07/2/3	2.23	49.6	73	22.4	30.6	6.79	14								0.05	4.7		3.35		354											
48	30	F	1	1	1	1	1	1	1	1	1	1	1	1	2	1.5 yrs	75mcg			1	1	1	Afebrile	68	120/66	1	1	1	1	1	1	1	1	1		11.6	5600	58/33/4/5	2.4	46.6	76	24	31.3	5.12	15.6								17.96					256											
49	25	F	1	2	2	1	1	1	1	1	2	1	1	1	1					1	1	1	Afebrile	74	112/70	1	1	1	1	1	1	1	1	1		12.3	6700	59/32/4/5	3.17	36.2	80.3	27.3	34	4.51	15								11.87					323											
50	60	F	1	2	1	1	1	2	1	1	1	1	1	2	1					1	1	1	Afebrile	76	130/68	1	1	1	1	1	1	1	1	1		11.9	6500	51/40/4/5	2.49	36.2	83.4	27.5	33	4.33	14.6								8.39					230											
51	30	F	1	1	1	1	1	1	1	1	1	1	1	1	2	2 months	25 mcg		Migraine	1	1	1	Afebrile	80	118/70	2	1	1	1	1	1	1	1	1		8.9	4700	59/36/2/3	2.65	29.7	66.3	19.9	30	4.48	17.1								9.46	6.5		4.8		543											Anti TPO>1300
52	41	F	1	1	1	1	1	1	1	1	1	1	2	2	2	2 yrs	50 mcg			1	1	1	Afebrile	80	122/76	2	1	1	1	1	2	1	1	1		9	9100	71/20/4/5	3.48	31.8	69.7	19.7	28.3	4.56	13.7								7.59		85		9	361			0.53								iron–40.5, TIBC-406, ferritin-9.98
53	48	F	1	1	2	1	1	1	1	1	1	1	1	1	2	2 yrs	50 mcg			1	1	1	Afebrile	102	118/72	2	1	1	1	1	1	1	1	1		9.7	24,800	86/6/4/4	3.11	29	79.3	28.6	32.5	2.76	14.7								8.4		0.67		6.2	>2000	151	78	3.6								
54	30	F	2	1	1	1	1	1	1	1	1	1	1	1	2	1 year 7 months	50 mcg			1	1	1	Afebrile	82	122/80	1	1	1	1	1	1	1	1	1		11.1	7200	51,40,4,5	2.98	34.2	82	27	32.5	4.18	15.6	normocytic normochromic	normal	adequate					17.4					247											
55	30	F	1	1	1	1	1	1	1	1	1	1	1	1	2	1 yr	125 mcg			1	1	1	Afebrile	88	110/70	1	1	1	1	1	1	1	1	1		11.9	5100	50/41/4/5	2.74	33.8	81	27.6	34.1	4.31	12.1								0.17		2.5		1.95	365.8											
56	50	F	1	1	1	1	1	1	1	1	2	1	1	1	1					1	1	1	Afebrile	92	124/78	1	1	1	1	1	1	1	1	1		12.6	7300	61/30/4/5	3.47	37.3	82.3	27.8	33.8	4.53	13.5					1			12.03	3		1.19		207.9											
57	52	M	1	1	1	1	1	1	1	1	1	1	1	1	2	2 yrs	25 mcg		Obstructive apnea Disease	1	1	1	Afebrile	78	112/64	2	1	1	1	1	2	1	1	1		7.8	7700	70/22/4/5	2.77	29.1	73.7	21.3	28.9	3.95	18.6								>100	2.2		0.53		184	106	39	1.7								
58	36	F	2	2	1	1	1	1	1	1	2	1	1	2	1					4	1	1	Afebrile	76	128/84	1	1	1	1	1	1	1	1	1		12.7	14200	63/28/4/5	2.18	39.6	84.1	27	32.1	4.71	13.5								84.33	2.6		0.35		204	88	27	0.8								
59	63	F	1	1	1	1	1	1	1	1	1	1	1	2	2	10 yrs	100 mcg		HTN/IHD	1	1	1	Afebrile	80	160/100	1	1	1	1	1	2	1	1	1		12.6	11200	62/33/2/3	2.7	38.8	78.4	25.4	32.4	4.95	13.6								2.45					332.6											
60	35	F	1	2	2	1	1	1	1	1	2	1	1	1	2	1 yr	50 mcg		Blood transfusion 1 yr back	1	2	1	Afebrile	74	100/60	2	1	1	1	1	1	1	1	1		10.9	7500	58/36/3/3	1.54	32.4	83.3	28	33.6	3.89	13.4					1			2.75		1.3		0.64	268											