"Correlation of TSH with BMI in Euthyroid and Subclinical Hypothyroid patient's"

Full term training report Submitted to

Lovely Professional University, Punjab

in partial fulfilment of the requirements

for the degree of

Master of Science in

Clinical Biochemistry

Submitted by

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(Reg. No. 11312544)

LOVELY SCHOOL OF PHYSIOTHERAPY AND PARAMEDICAL SCIENCES
LOVELY PROFESSIONAL UNIVERSITY, PUNJAB, INDIA
(2015)

DECLARATION

I, Anupam Sharma, student of M.Sc clinical biochemistry under department of paramedical sciences of Lovely Professional University, Punjab, hereby declare that work embodied in this Full term training was carried out by me under the direct supervision of Dr. Ekta Chitkara, Assistant Professor. This work has not been submitted in part or in full in any other university for any degree or diploma.

Place: LPU, Punjab — Anupam Sharma

Date- — Reg. No. 11312544

CERTIFICATE

This is to certify that the present full term training entitled **" Correlation of TSH with BMI in Euthyroid and Subclinical Hypothyroid patient's"** is the outcome of the original piece of work carried out by Mr. Anupam Sharma (Registration No: 11312544) himself under my guidance and the contents of his Full term training did not form a basis of the award of any previous degree to him and to the best of my knowledge to anybody also. The thesis has not been submitted by the candidate for any research degree in any other University.

The Full term training is fit for submission to the partial fulfillment of the conditions for the award of M.Sc. in Clinical Biochemistry. Further, certified that the candidate in habit and character is a fit and proper person for the award.

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THHCC/HR/2015

Dated: 30th April, 2015

To Whom It May Concern

This is to certify that Mr. Anupam Sharma has completed his Training in Department of Laboratory w.e.f 16th January, 2015 to 30th April, 2015.

During his stay with the organization, he was found to be sincere and hard working towards responsibilities entrusted to him.

We wish him success for future endeavors.

For Tagore Hospital & Heart Care Centre,

Prabhat Kumar

Hospital Administrator
THHCC, Jalandhar

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Anupam Sharma

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LIST OF ABBREVIATIONS

T3	**Triidothyronine**
T4	**Tetraidothyronine or Thyroxine**
TSH	**Thyroid Stimulating Hormones**
SH	**Subclinical Hypothyroidism**
LDL	**Low Density Lipoprotein**
CVD	**Cardiovascular disease**
TC	**Total Cholesterol**
LP (a)	**Lipoprotein (a)**
TG	**Triglyceride**
VLDL	**Very Low Density Lipoprotein**
BMI	**Body Mass Index**
W.H.O	**World Health Organization**
ng/ml	**Nano gram per millilitre**
ug/ml	**Microgram per millilitre**
uIU/ml	**Micro International unit per millilitre**
CLIA	**Chemiluminescence Immuno Assay**
C.N.S	**Central Nervous System**
r	**Correlation Coefficient**

Abstract

Thyroid hormones (T3 and T4) synthesized by thyroid gland and play essential role in normal body development and tissue metabolism. Iodine is essential factor that is required for synthesis of thyroid hormones. The secretion of thyroid hormones is regulated by Negative feedback mechanism. After reached in blood circulation the majority of T4 and T3 bound with carrier proteins -: thyroxine – binding proteins (TBG) having higher affinity for T4, thyroxine – binding prealbumin (transthyretin) and albumin for purpose of transportation. The common diseases related to thyroid hormones includes -: Hypothyroidism, Hyperthyroidism, Thyroiditis, Goiter, Nodes, and Tumors of thyroid glands (Benign and Malignant). Subclinical hypothyroidism also called mild thyroid failure is defined as normal thyroid hormones but mildly elevated TSH (5 – 10 uIU/ml) with no or mild sign and symptoms. The Prevalence of thyroid disorders commonly observes in females then males.

Obesity is defined by body mass index which is a reasonable indicator of body fat. Hypothyroidism is associated with obesity and various studies conducted to find out the relationship between TSH and BMI observed different finding in the particular study. In present study, a poor positive correlation between TSH and BMI was observed in total euthyroid subjects. A poor negative association between TSH and BMI in euthyroid Males and poor positive (r value – 0.21) relationship was observed in euthyroid females. In Subclinical hypothyroid patients (Total, Male and female), Poor negative correlation was observed between TSH and BMI. The conclusion of this study is, as TSH increased the BMI will also increased in (mostly females) euthyroid subjects. The Inverse or poor negative correlation was observed within TSH and BMI among euthyroid males and inverse correlation was noticed in patients with subclinical hypothyroidism.

INTRODUCTION

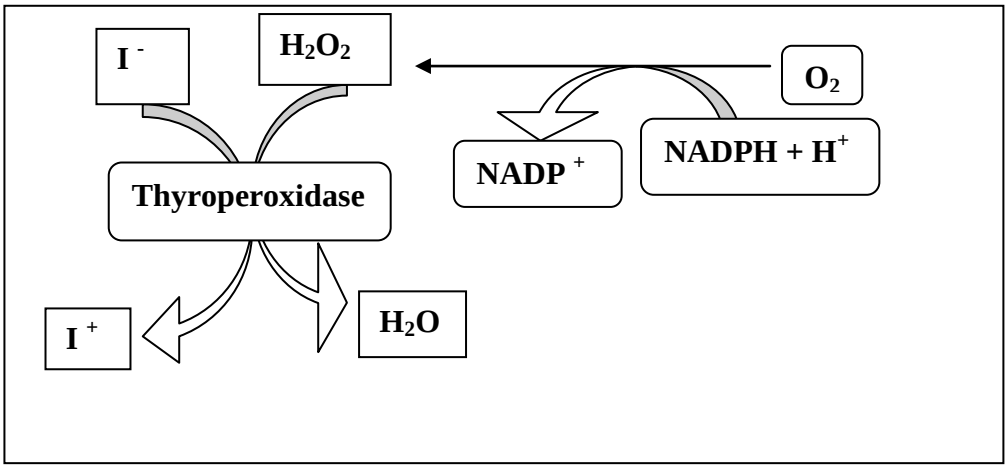
INTRODUCTION

The Thyroid is an endocrinal, butterfly shaped and biggest gland in neck which makes and stores hormones that helps in regulation of blood pressure, heart rate, body temperature and also helps in regulation of growth and rate of chemical reactions (metabolism) in the body. The normal weight of thyroid gland is 30 gm in adults, located just inferior to the larynx and composed of right and left lateral lobes on either side of the trachea [1]. Thyroid is a soft tissue, enough visible and moves up and down with Adam's apple during swallowing, also felt easily when a person head's tilted back.

Thyroid Hormones synthesis and Production

The thyroid follicles make up the most of the thyroid gland their cell wall primarily consists of follicular cells which produce two major hormones of the thyroid gland – T3 (Triidothyronine) and T4 (Tetraidothyronine or Thyroxine) and few parafollicular cells (C – cells) produce hormone called "Calcitonin" which helps in the regulation of calcium homeostasis [1]. Iodine is essential for the synthesis of thyroid hormones. Before the synthesis of T3 and T4, iodide (I^-) to iodine (I^+) conversion is essential and this reaction catalyzed by enzyme called Thyroperoxidase also require H_2O_2 [2].

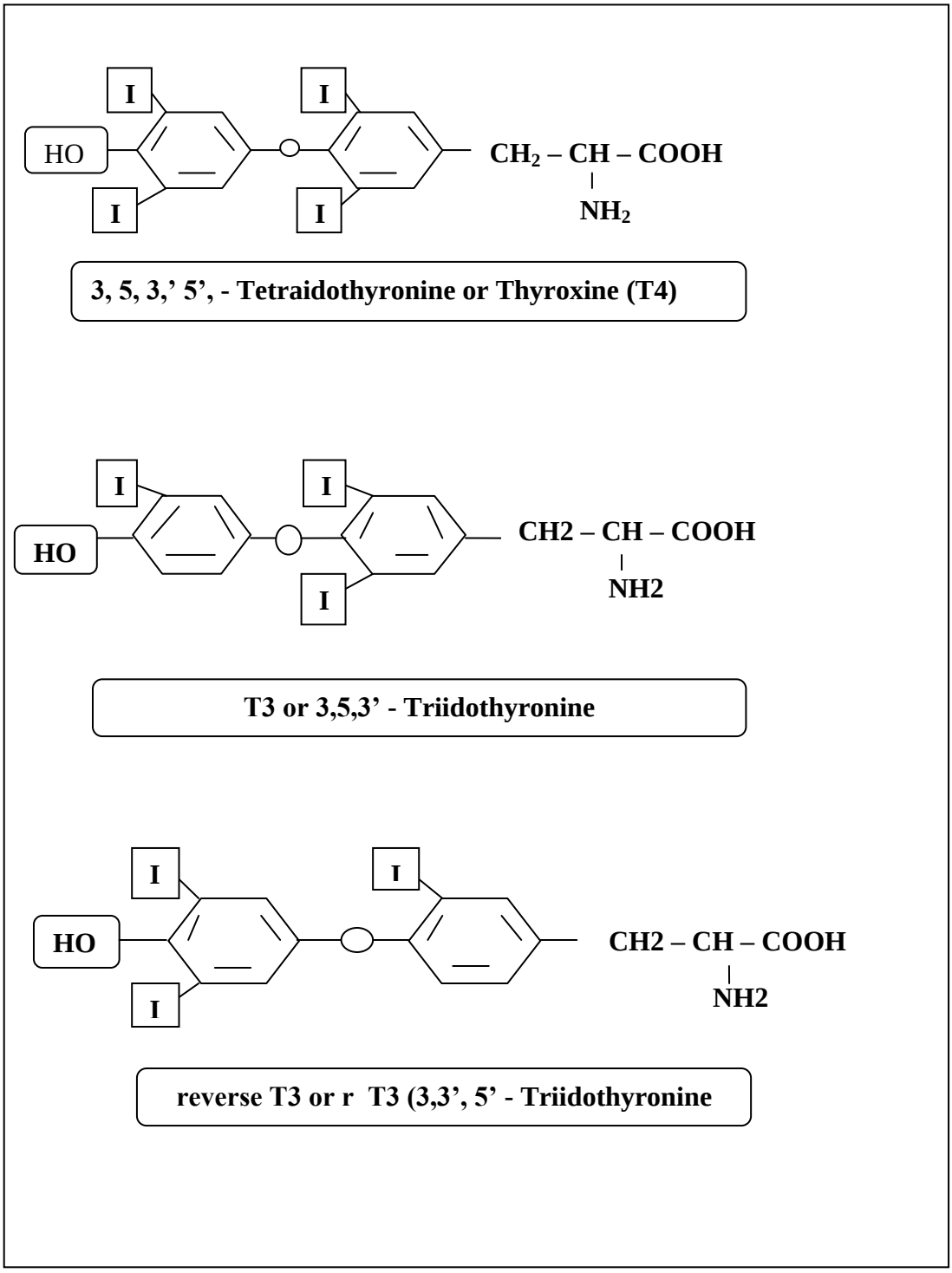
Fig. 1: Shows the conversion of Iodide (I^-) to Iodine (I^+) [86].



Iodine takes by the follicular cells and combined with tyrosine to make two thyroid hormones precursors. A protein called Thyroglobulin is also required of T3, T4 synthesis.

When body require T3 (contain 3 iodine atom) and T4 (contain 4 iodine atom) released from thyroglobulin and comes into the blood circulation to perform their function [3]. In higher amount (80-95%) T4 is formed but it is biologically less active, T3 is found in less amount (about 5 – 20%) but it is biologically more active then T4 [4].

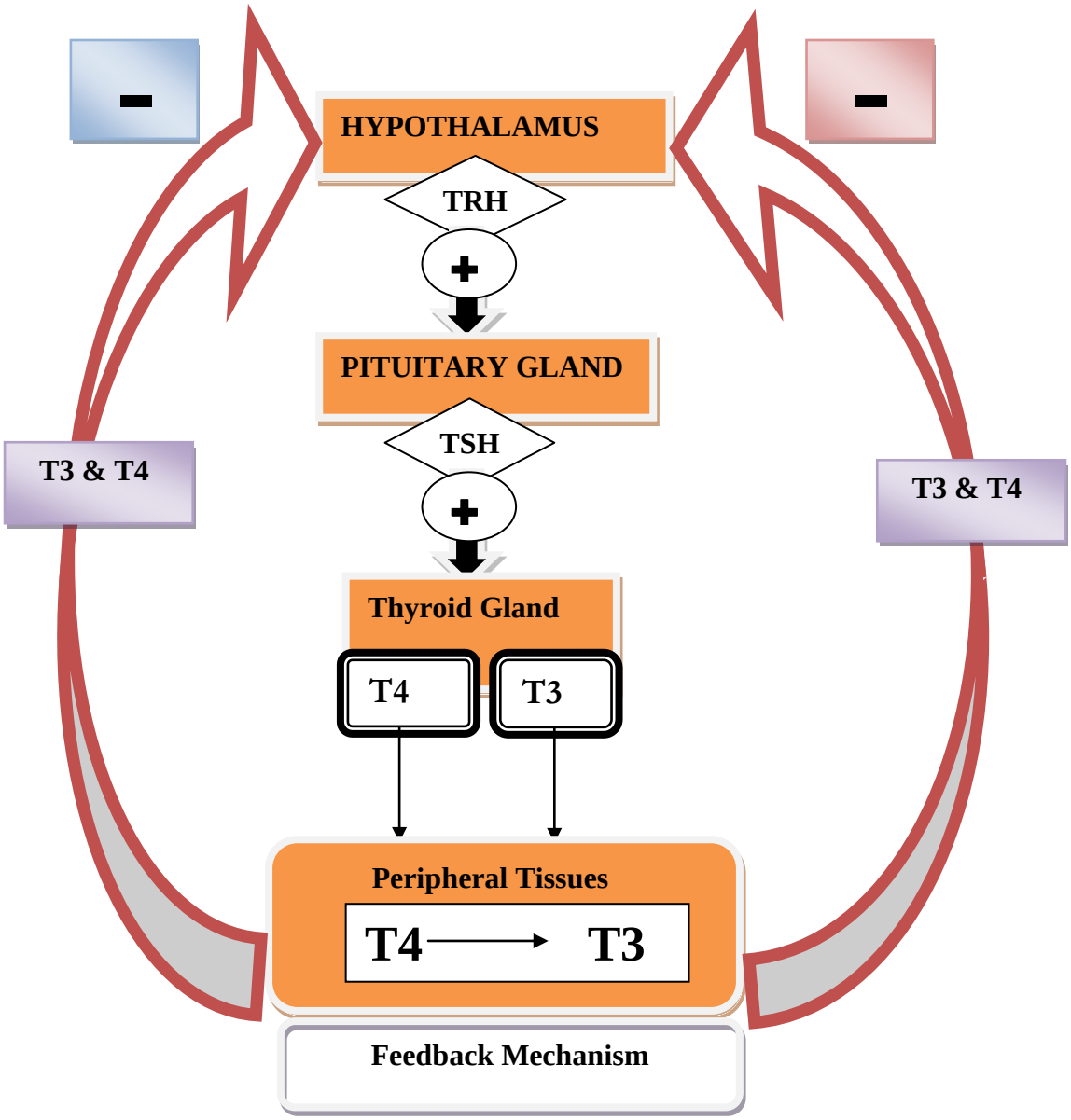
Fig. 2: Shows the structures of T3, T4 and r T3 [86].



Regulation of T3 and T4 synthesis

Hypothalamus (a portion of brain), which is responsible for production of various hormones is connected with anterior pituitary through the blood vessels. Firstly, hypothalamus release a chemical called Thyrotropin Releasing Hormone (TRH), when it reached to anterior pituitary it stimulate to synthesize and produce thyroid stimulating hormone (TSH) from the anterior pituitary then TSH stimulates to produce T3, T4 from thyroid gland. The secretion of thyroid hormones is decided by pituitary gland also known as "Master gland" located at the base of the brain [2].

Fig. 3: Shows the regulation of T3 and T4 [86].



Thyroid gland cells have receptor site, TSH (Thyroid Stimulating Hormones) secreted by anterior Pituitary linked with these receptors and the cells stimulated to produce and release thyroid hormones; If more T3 and T4 is required to the body then more amount of TSH is produced and if less T4 and T3 required then small amount of TSH produced by pituitary gland [5]. TSH regulates the iodide uptake by sodium/iodide symporters, the steps is necessary for normal thyroid hormone synthesis and secretion [6**].**

Transportation of T3 and T4

After reached in blood circulation the majority of T4 and T3 bound with carrier proteins -: Thyroxine – binding proteins (TBG) having higher affinity for T4, thyroxine – binding prealbumin (transthyretin) and albumin for purpose of transportation [7]. Only a small fraction remains unbound known as free T3 (fT3) and free t4 (fT4) in the circulation, when it reached in to the required tissue it enter inside cells by unique transport channels and cytoplasm is the site where conversions of T4 to T3 take place, mainly in liver, pituitary gland, kidney and peripheral tissue. Normally, about 0.03% T4 and 0.5% T3 were found in unbound form and only free form have the ability to bind with specific hormone receptor in peripheral tissue [8].

Table. 1: Action of T3 and T4 on different Processes in Body.

Basal metabolism	Stimulation of metabolic activities (about 60- 100%) above then the normal is one of the major effect of thyroid hormones. Also increase the O_2 utilization in most of the tissue excluding- testes, brain retina and lungs.
Carbohydrate Metabolism	Utilization and absorption of glucose by intestine stimulated by thyroid hormones, they boost the Gluconeogenesis and Glycogenolysis, overall increase the blood glucose level.
Protein Metabolism	The major effect of thyroid hormones on protein metabolism is to activate transcription process in the cell nucleus, result in the increase production of proteins.

Cardiovascular System	Thyroid hormones increase -: blood flow, cardiac output, and heart rate. They also increase the strength of heart muscle andt finally lead to changes in blood pressure.
Respiratory system	They increase the frequency and depth of breathing.
Digestive tract	They increase appetite, nutrient absorption and intestinal motility.
Central Nervous System	T3 and T4 are essential for the normal development of C.N.S. They speed up the brain.
Muscle function	Thyroid hormones stimulate the muscle function.
Sleep	The increased amount of thyroid hormones leads to insomnia and vice versa if reduced then leads to strong drowsiness.
Other endocrine glands	Stimulate the secretion of other glands [9, 10, 11, 12, 13, 14, and 15].

Common diseases related to thyroid gland

1. Hypothyroidism – occurs due to decreased functioning of the thyroid gland.
2. Hyperthyroidism – excess or hyper functioning of thyroid gland (Thyrotoxicosis).
3. Thyroiditis –due to inflammation in the thyroid gland.
4. Goiter– enlargement of thyroid gland (simple and multinodular– toxic or non-toxic).
5. Nodes – node appears in thyroid gland.
6. Tumors of thyroid glands (Benign and Malignant) [16].

Hypothyroidism

Hypothyroidism is a clinical syndrome resulting from the deficiency of thyroid hormones which leads to slowing down the metabolic processes [17]. In general population, hypothyroidism is a common metabolic disorder and associated with many biochemical changes inside our body [18]. The cases of thyroid failure most commonly observed in Women's and incidence increased with age [19]. Autoimmune chronic lymphocytic thyroiditis is the most common cause of hypothyroidism in Australia. It is commonly seen in diabetic patients [20, 21]. It is obesity like pathological condition, associated with lipid metabolism disorders and leads to dislipidemia (one of the major risk factor of coronary diseases) [22]. Hypothyroidism is associated with cardiovascular risk factors and if remain untreated it can leads to atherosclerosis [23].

Clinical Features

1. Weight gain with poor appetite.
2. Dry and Cold Skin.
3. Cold Intolerance.
4. Hoarsening of voice.
5. Hair loss and Nail growth retarded.
6. Lethargy and tiredness.
7. Slow relaxation of muscle.
8. Weakness.
9. Other associated signs including-: Constipation, Anaemia, Dementia and Muscle stiffness [24].

Causes

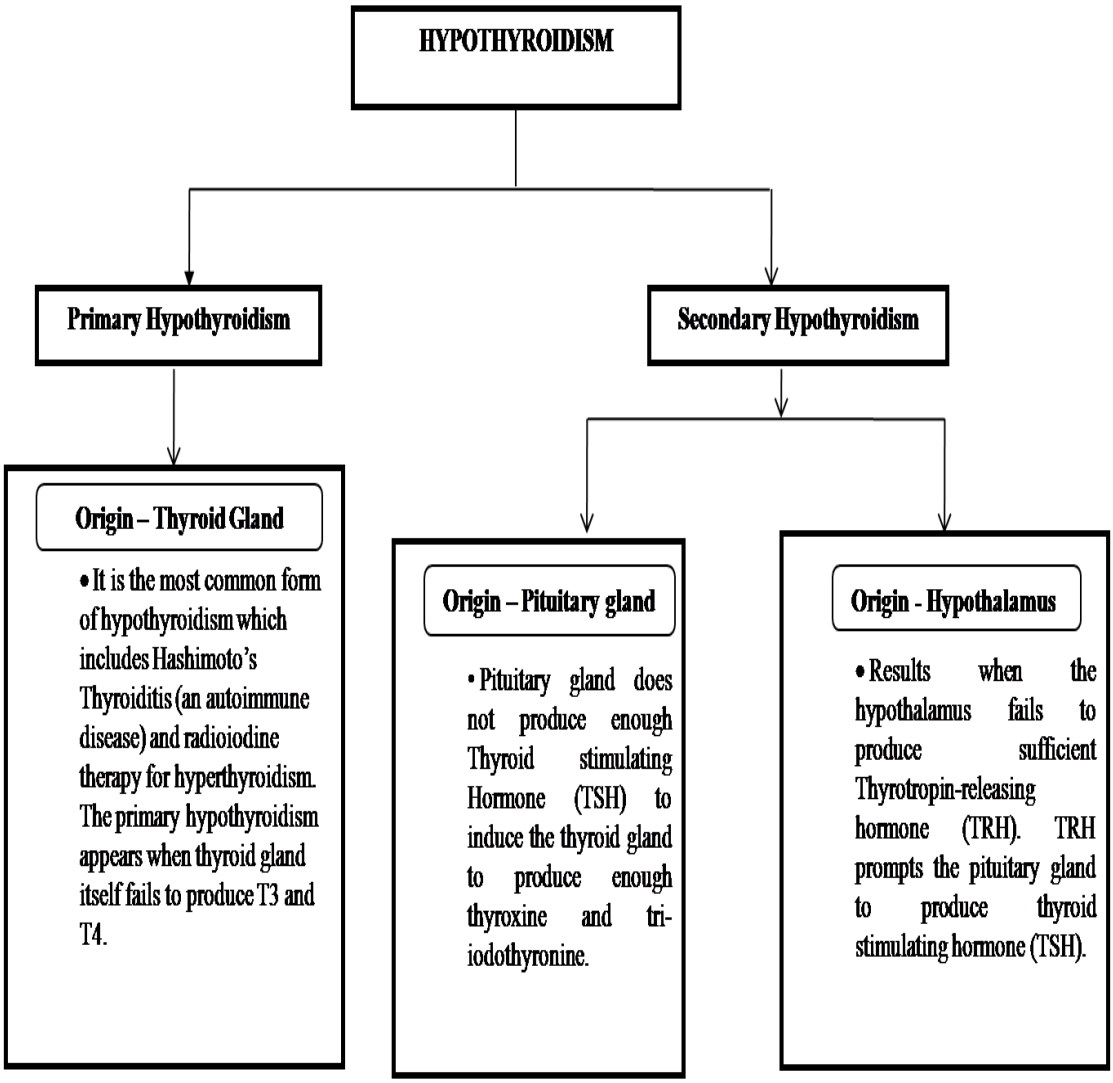
The main Causes of Hypothyroidism include-:

1. Hashimoto's disease (Autoimmune destruction of thyroid gland).
2. Surgical treatment of hyperthyroidism or radioiodine.
3. Severe Iodine deficiency.
4. Congenital defects, such as -: T3 and T4 biosynthesis blocks.
5. Thyroid Stimulating Hormone (TSH) deficiency.
6. Treatment with drugs such as -: Lithium Carbonate [25].

Classification

Hypothyroidism can be classified on the basis of aetiology into two groups.

Fig. 4: Shows classification of hypothyroidism.



Subclinical Hypothyroidism

SH is defined as abnormal condition which is appears with mild elevated TSH level (5 – 10 mIU/L), but normal thyroid hormones concentration with absence of clinical signs and symptoms [26]. It is estimated that the 4.3 – 9% of general population was affected with SH [25, 26]. It may progress to overt hypothyroidism, prevalence found

higher among women's and in old population [25, 27, and 28]. Effect of subclinical hypothyroidism is not well understood yet but various studies reported that it is associated with high levels of LDL and TC [27, 29]. The patients with subclinical hypothyroidism have elevated plasma Lp-PLA_2 (known CVD marker). SH have a serious effect on various other CVD risk factors [30]. Among the children's, autoimmune thyroiditis is the most common cause of SH and diagnosed by elevated levels of Serum Thyroid peroxidise, furthermore other causes includes iodine deficiency, some drugs effect or excess intake of drugs these are less common causes of SH [31– 32] .

Overt Hypothyroidism

Overt Hypothyroidism diagnosed by decreased serum fT4 with increased TSH levels [33]. The individual who have subclinical hypothyroidism is more prone to progress overt hypothyroidism. When the thyroid functions activity is decreased then activity of HMG-CoA reductase will also reduced [34, 35]. Overt hypothyroidism associated with hypercholesterolemia. Previous studies suggested that patients with overt hypothyroidism have more risk of developing atherosclerotic disease. The well documented features of overt hypothyroidism are high levels of apolipoprotein B, LDL cholesterol and total cholesterol [36]. Therefore, the catabolism of LDL and IDL is decreased because the activity of LDL receptors decreased [37, 38]. Overt hypothyroidism associated with changes in blood pressure, particularly diastolic values [39]. An elevated homocystein level is a risk factor for cardiovascular disease and its levels are reported to be increased in overt hypothyroidism [40, 41 and 42].

Hyperthyroidism

Hyperthyroidism also called thyrotoxicosis caused by the overproduction of thyroid hormones. Graves's disease (an autoimmune disorder) is one of the most common causes of hyperthyroidism [43]. The prevalence found more in women (2%) then men (0.2%) and 15% cases of hyperthyroidism occurs in patient older than 60 years [44]. In iodine sufficient areas, the prevalence of overt hyperthyroidism is 2 per 1000 and subclinical hyperthyroidism is 6 per 1000 [45]. In general population, the incidence of hyperthyroidism is lower (2.2%) as compared to hypothyroidism [46]. The activity of HMG – CoA reductase seen to be increased in hyperthyroid patients and level of TC, LDL-C, Apo B and Lp(a) were found decreased . The most common feature of

hyperthyroidism is increase heart rate [47]. Decreased levels of HDL – C with no changes in T.G and blood pressure have been found in hyperthyroid patients [48].

Clinical features

The symptoms of hyperthyroidism vary according to the Age, amount of T3 and T4 you have and how long your thyroid gland produce excess T3 and T4. It mainly appears with symptoms of sympathetic nervous system. Young patients may suffer with Anxiety, tremor and hyperactivity and older patients have more cardiovascular symptoms including-: dyspnea, atrial fibrillation and weight loss.

Table 2. Clinical features of Hyperthyroidism.

General	Weight loss.
Skin	Sweating and feel hot.
Cardiovascular System	Angina, atrial fibrillation, tachycardia, cardiac failure.
Neurological	Agitation and tremor.
Bones	Hypercalcaemia and Osteoporosis.
Muscles	Proximal myopathy.
Gastro intestinal	Diarrhoea.
Gynae.	Amenorrhoea.
	Hair loss.

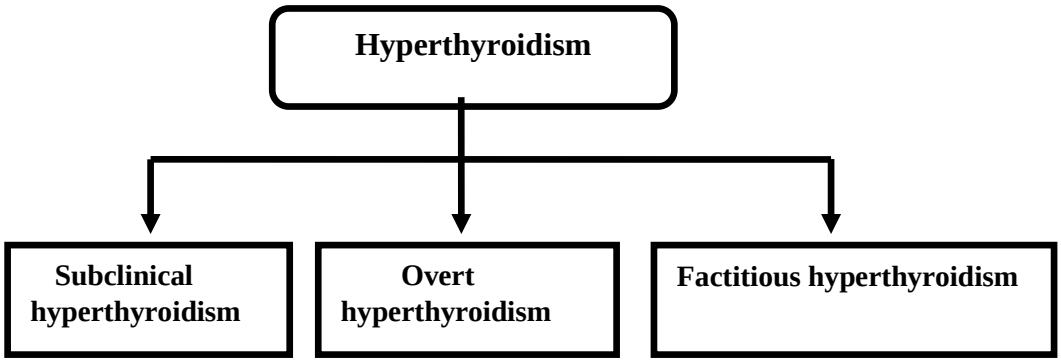
Causes of Hyperthyroidism

The main causes of hyperthyroidism are

1. Graves Disease.
2. Toxic multinodular Goiter.
3. Adenoma (autonomously functioning single thyroid nodule.
4. TSH – secreting pituitary tumour.
5. Thyroiditis.
6. Excess thyroid hormones ingestion.
7. Follicular carcinoma.
8. Fetal and neonatal hyperthyroidism.
9. Side effect of certain medicine.

Classification

Hyperthyroidism can be classified into 3 groups they are -:



Subclinical Hyperthyroidism

Subclinical hyperthyroidism is defined as an abnormal condition that is characterized by decrease TSH level but normal T3 and T4 levels. The TSH suppression is acute in this stage that's why it is differ from overt hyperthyroidism [49]. It can be caused by endogenous or exogenous factors. The endogenous factors include-: Graves disease, Multinodular goiter or autonomously functioning thyroid adenoma [50] and exogenous factors are – TSH suppressive therapy with L – thyroxine or differentiated thyroid carcinoma [51]. Previous data documented that patients above 60 year age with subclinical hyperthyroidism have higher risk of Atrial arrhythmia and in postmenopausal women it is associated with loss of bone mineral density [52]. Either endogenous or exogenous cause both have clinical features including -: less concentration, anxiety, nervousness, sweating, fear, palpitation, heat intolerance and tremors [53 – 54]. Various studies found that the patients with subclinical hyperthyroidism have greater risk of developing dementia and Alzheimer's disease [55].

Overt Hyperthyroidism

The term “overt” refer to more severe condition. Overt hyperthyroidism is defined as increased T3 and T4 level but decreased TSH level. The subclinical hyperthyroidism may progress to overt hyperthyroidism and associated with visible physical symptoms. Graves’s disease is the major risk factor for overt hyperthyroidism. It is clearly known that the overt hyperthyroidism associated with weight loss and its prevalence more found among the women’s than men’s [56]. Thyroid hormones have profound effect on bone metabolism, the patients with overt hyperthyroidism has higher risk of osteoporosis and fractures whether in subclinical it remain controversial [57].

Factitious hyperthyroidism

This type of hyperthyroidism occurs due to the excessive ingestion of thyroid hormones. It is a very severe condition and associated with weakness, cardiac failure, weight loss and Arrhythmia [58]. In this condition, the level of thyroid hormones are seen to be increased and due to the T4 ingestion the level of free T4 will also increased but when T3 is injected the level of free T4 is suppressed. It is mostly seen in patients who are taking excessive thyroid hormones medications. Uncommonly, it can be caused by eating meat contaminated with thyroid gland. It is diagnosed by the elevated level of free T4 and total T3, T4 with decreased radioactive iodine uptake. If it remains untreatable it may cause atrial fibrillation, bone mass loss, heavy pain in chest, heart attack and abnormal heart rhythm.

Body Mass Index (BMI)

BMI is a reasonable indicator of body mass and calculated by weight in kilograms and height in meter square (kg/m^2) [59]. It is an easy, non – invasive and less expensive method that is used for screening body fat routinely in research and clinical areas. It is not an accurate tool because it does not differentiate overweight due to access fat mass from overweight due to excess lean mass. It is mostly use to measure the obesity in adult population [60]. Other methods are more accurate but they cannot use for studying or screening large population. Some factors including -: Age, Sex, ethnicity and muscle mass can impact the link between BMI and body fat. In children and adolescence, it varies with age and sex. Whereas in adults the cut points that define obesity and overweight are not linked with age or not different for females and

males for example -: a 6 year old boy BMI 21 kg/ m^2 consider as over fat but a 16 year old boy BMI with 21kg/m^2 is consider to be lean [61] .

Obesity and BMI

In simple words "obesity" is defined as an excess of body fat and a state of being overweight. WHO define obesity or overweight as abnormal or excessive body fat accumulation that leads to the various serious problems related to health. Obesity is defined by body mass index more then 24.9 and according to WHO an Asian adult with BMI value of $\geq$ 23.0 is consider as obese [62]. Various studies found that the obesity is associated with abnormal lipids parameters which clear that the prevalence of cardiovascular diseases is higher in obese patients [63]. In obese person have higher risk of developing diabetes mellitus and many types of cancer including uterine, colon, esophageal and other endocrinal disorders.

Table. 3: WHO classification of adults underweight, overweight and obese according to BMI.

Classification	**BMI (kg/m^2)**
Underweight	**< 18.5**
Normal Weight	**18.5 to 24.9**
Over Weight	**$\geq$25.0**
Obese	**$\geq$30.0**
Obese class I	**30.0 – 34.9**
Obese class II	**35.0 – 39.9**
Obese class III	**$\geq$40.0**

REVIEW OF LITERATURE

Review of literature

A comparative study conducted by **A Nyrnes and R. Jordan et. al.** in 2006 on 10491 subjects to find the association between serum TSH and BMI in both male and females (age – 29 -89) concluded that the serum TSH was positively and significantly associated with BMI in non smokers. They didn't find any statistically significant relation between TSH and BMI among smokers. In both males and females and smokers and non smokers the Serum TSH levels increased with age [64].

Smoking can affect the relationship between TSH and BMI. A population based study conducted by **L. Mehan and A. Amouzegar et al**. (2012) on 1581 subjects (age $\leq$ 20) for evaluate the association between TSH concentration and BMI in Euthyroid observed a significant positive correlation ($P < 0.004$) within TSH and BMI in Euthyroid non smokers and no correlation was found within BMI and TSH in smokers. They reported that the every 1 uU/ml unit raised TSH appeared with 0.31 kg / m^2 increased BMI [65].

Working on 1572 Euthyroid women's, a negative correlation was reported between free T4 and BMI by **Ho Sang Shon et al.** (2008). In this cross sectional study they observed that free thyroxine was negatively correlated with Triglyceride and also suggest that the decreased free thyroxine level appeared with obesity in Euthyroid subjects [66].

N. Knudsen et al. (2005) noticed a positive correlation ($P< 0.01$) within TSH and BMI and a negative ($P < 0.001$) association between BMI and free T4. No relation was observed between serum free triidothyrorine values and BMI. The results of this study are that the increased TSH values in serum are linked with increased incidence of obesity and suggested that the weight loss appeared with decreased levels of T3 and TSH [67].

Dipankar s.p et al. (2012) found significantly ($P<0.05$) increased BMI value in hypothyroid and significantly decreased BMI value in hyperthyroid patients as compared to control group. Conclusion of this study was – there is a correlation existed between abnormal lipids profile (dyslipidemia) and body composition in thyroid dysfunction [68].

A noble work done by **A. Solanki et al.** (2013), to find out the association between TSH and BMI in healthy adults conclude that there was a significant association within TSH and BMI. The observation shows a significant variation in TSH ($P < 0.001$) with increasing BMI, as TSH increased the BMI will also increased [69].

A Correlational analyses performed by **T. M. Natahl et al.** (2013) on 56 healthy peoples, was recognized a positive correlation between T3 and BMI in healthy females (28) and a definite relationship among TSH with BMI in healthy males. The results of this study suggested that thyroid hormones particularly T3 regulate the Basal metabolic rate and abnormal thyroid functions directly linked with alterations in lipid parameters and body weight which can lead to obesity [70].

Many observations show the therapy for hyperthyroidism leads to weight gain. **J. Burnunova et al.** (2003) design a study to determine the degree of weight gain in patients after treatment with hyperthyroidism therapy, observed a median weight gain within 6 months 5.0 kg, after 1 year 9.0 and 12 kg was after 2 years [71].

Poplawaska – Kita A et al. (2014) reported that patients with Hashimoto thyroiditis (which is the most common cause of hypothyroidism) had increased BMI as compared with control group. Furthermore, the observations of this study suggested that as compared to normal healthy subjects the individuals with Hashimoto thyroiditis has high BMI [72].

S.A Giakar et al. (2011) included 400 subjects into their study to assess the thyroid function and Bmi in normal population and observed no relation between BMI and T3, T4 but there was a positive relation noticed between BMI and TSH levels. The results obtained from this study suggested that a little increase in serum TSH associated with increase the occupancy of obesity [73].

Documented by various studies that patients with SH are more prone to develop cardiovascular diseases. **B. Kiliçaslan et al.** (2013) conducted a study with the aim "to determine the impact of obesity on cardiac functions and association with SH in healthy women's" observed the high TSH values in obese females, a positive correlation within TSH and BMI, others parameters including LVM, LAV and waist circumference were also show positive correlation with TSH. The outcomes of this study was cardiac anatomical and physiological abnormalities may be associated with Subclinical Hypothyroidism in obese subjects [74].

Suganty et al. (2011) were reported that there was a significant positive correlation between serum TSH and BMI in Euthyroid females. The study was design to evaluate the association between TSH and BMI in female euthyroid subjects [75].

J.J.Deiz et al. In 2011 also noticed a significant correlation between TSH and BMI in Euthyroid subjects. They conclude that TSH level significantly increased with weight [76].

AIMS AND OBJECTIVES

Aims and Objectives

- **To find out the relationship of Thyroid Stimulating Hormone with Body Mass Index in Euthyroid subjects (both males and females).**

- **To find out the relationship of TSH with BMI in Subclinical Hypothyroid patients (both males and females).**

.

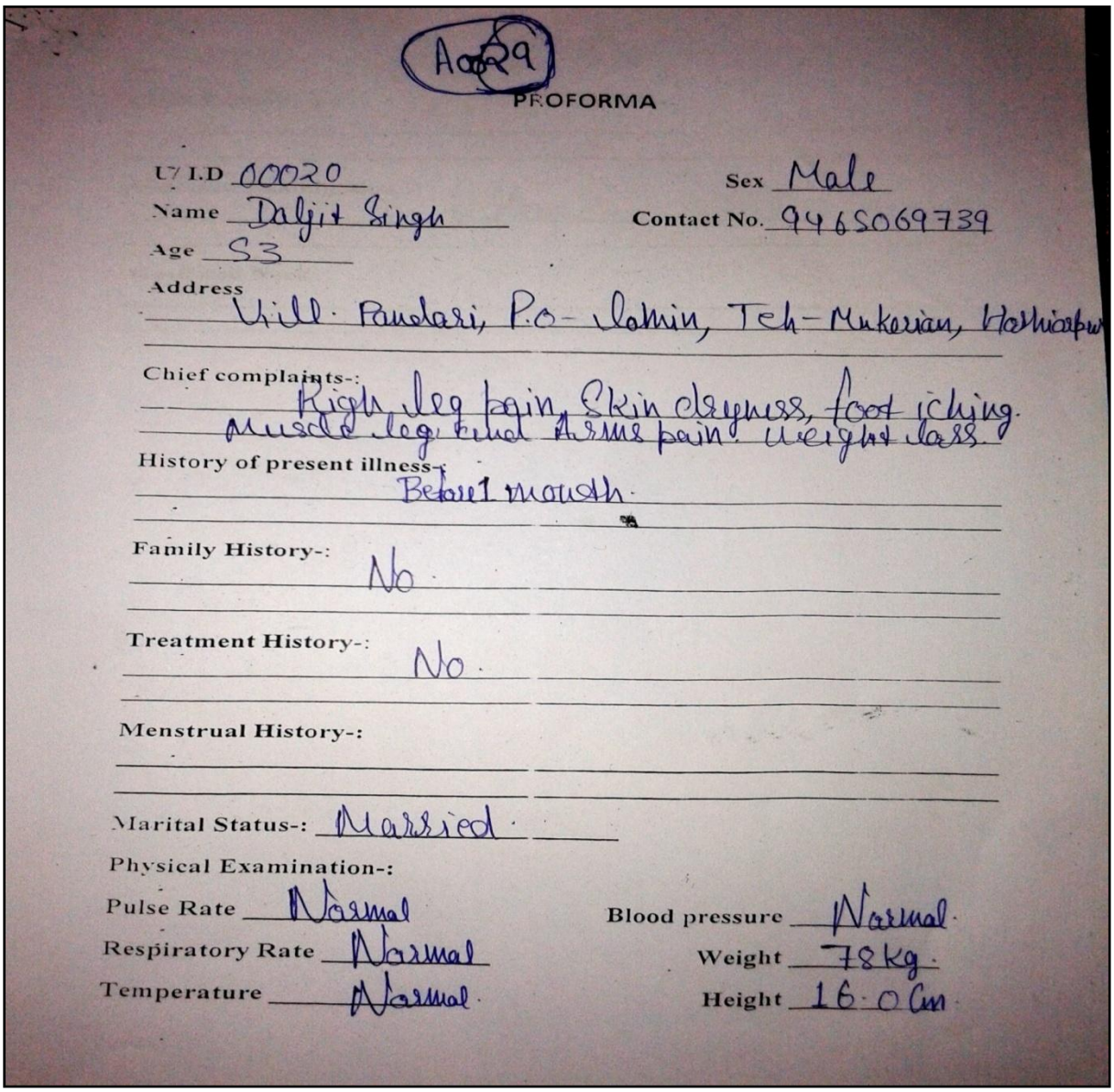
METHODS AND MATERIALS

Methods and Materials

Subjects

The present study was carried out in Tagore Hospital and Heart Care Centre (Jalandhar). Total 90 volunteers both males and females the age between 17 to 85 years were included in this study. An informed consent was taken from all the participants. Age in years, height (cm), weight (kg) and History (including -: Chief complaints, family thyroid history, blood pressure, Temperature and head and neck examination) from the subjects were collected.

Fig.5: Shows proforma with participant information.



A029

PROFORMA

U/ I.D 00020 Sex Male

Name Daljit Singh Contact No. 9465069739

Age 53

Address Vill. Pandori, P.O- Lohsin, Teh- Mukerian, Hoshiarpur

Chief complaints-: Right leg pain, Skin dryness, foot itching. Muscle leg and Arms pain. Weight loss.

History of present illness-: Before 1 month.

Family History-: No.

Treatment History-: No.

Menstrual History-:

Marital Status-: Married.

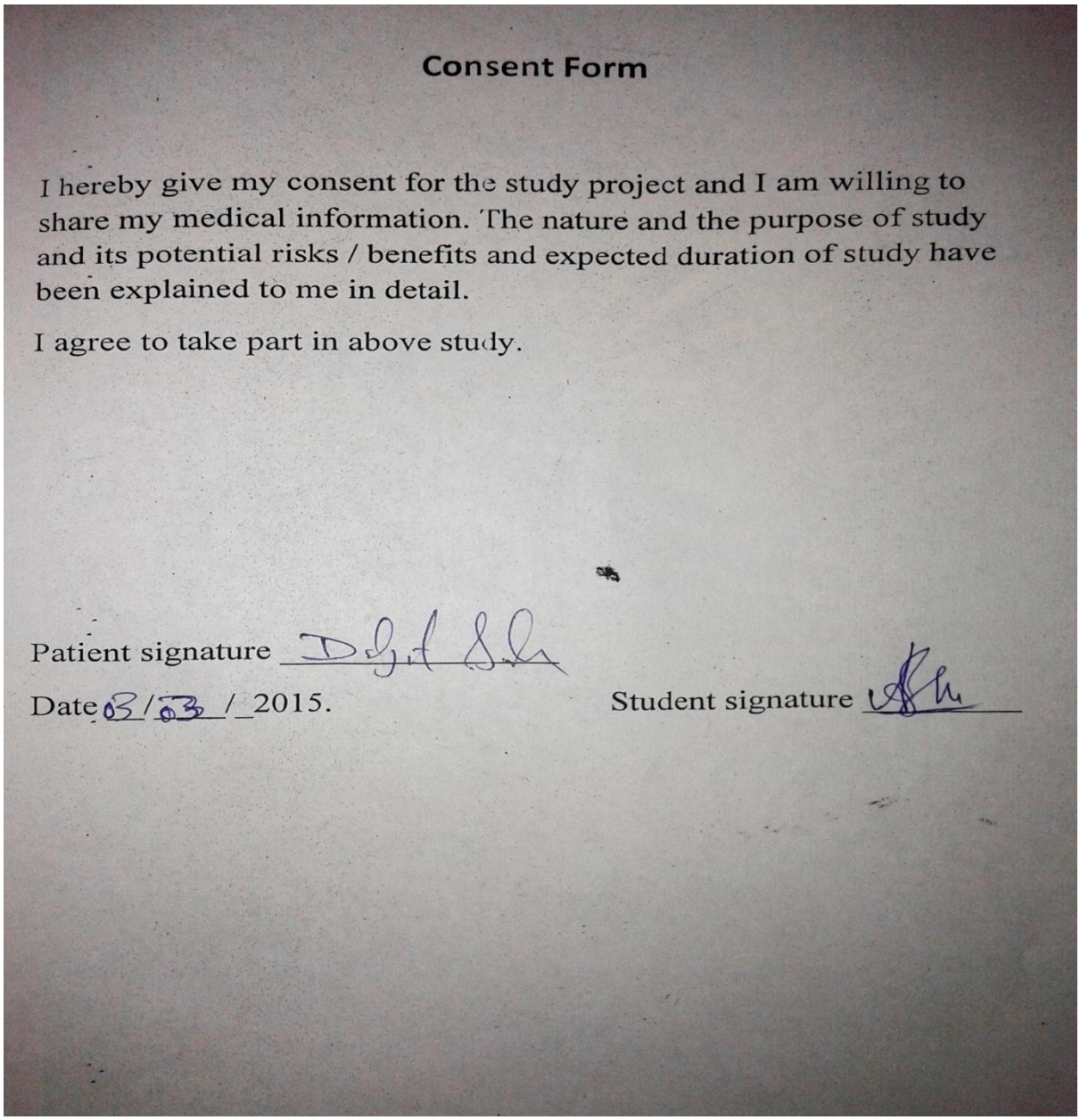
Physical Examination-:

Pulse Rate Normal Blood pressure Normal.

Respiratory Rate Normal Weight 78 kg.

Temperature Normal. Height 160 Cm.

Fig. 6: Shows the consent form with participant signature.



Consent Form

I hereby give my consent for the study project and I am willing to share my medical information. The nature and the purpose of study and its potential risks / benefits and expected duration of study have been explained to me in detail.

I agree to take part in above study.

Patient signature

Date 03/03/2015.

Student signature

Exclusion criteria include -: Smokers and Alcoholic.

Inclusion criteria -: Both male and female age between 17- 85 years.

Blood Sample collection

From all the subjects who came for determination of thyroid profile the blood samples with record of age and sex were collected. By venipuncture method, approximately 5ml blood was collected in plain vial from all subjects and after centrifugation the serum sample was analyzed for quantitative estimation of T3, T4 and TSH levels. The estimation of T3, T4 and TSH in human Serum was done by auto analyzer named as "ADVIA Centaur$^{@}$CP Immunoassay System" (SIEMENS) based on "Sandwich principle".

Reference Range -: T3 - 0.60 - 1.81 ng/ml.

T4 – 3.20 – 12.6 ug/ml.

TSH – 0.35 – 5.0 uIU/ml.

Anthropometrical measurements -: An instrument named as standiometer was used to measure Height (m) and standard weighing machine used for weight. The Body mass index (BMI) was calculated by using formula –

$$\textbf{BMI} = \frac{\textbf{Weight in kg}}{\textbf{Height in m}^2}$$

BMI classified as - <18.5 – underweight, 18.5 to 24.9 – normal weights, ≥25.0 – overweight, ≥30.0 – overweight, 30.0 – 34.9 – obese class I, 35.0 – 39.9 – obese class II and ≥40.0 – obese class III (according to WHO).

Biochemical Analysis -:

Thyroid Profile Assay (T3, T4 and TSH) performed by using Instrument - ADVIA Centaur$^{@}$CP Immunoassay System (SIEMENS)

Fig. 7: Instrument - ADVIA Centaur$^{@}$CP Immunoassay System (SIEMENS).

Principle of ADVIA Centaur$^{@}$CP Immunoassay System (SIEMENS)

Chemiluminescence is a chemical reaction that emits energy in the form of light, when used with immunoassay technique the light produced by the reaction indicates the amount of analyte in a sample.

In CLIA, Microplate luminometers are used that gives a sensitive, easy and alternative to conventional colorimetric methods (ELISA). The technique (ELISA) is based on colorimetric reactions of chromogenic substrates (example - TMB) and label enzymes. CLIA provides high sensitivity over the conventional colorimetric methods advantages are less incubation time requires and the addition of stopping reagents. The CLIA involve a horseradish peroxidase (HRP) labeled antibody or antigen and a mixture of chemiluminescent substrate, hydrogen peroxide, and enhancers. CLIA Kits are designed to detect chemiluminescent reactions. The method is highly sensitive for T3, T4 and TSH estimation.

Principle of T3 immunoassay

In the T3 CLIA, a certain amount of anti-T3 antibody is coated on microtiter wells. A measured amount of patient serum, and a constant amount of T3 conjugated with horseradish peroxidase are added to the microtiter wells. During incubation, T3 in the samples and conjugated T3 compete for the limited binding sites on the anti-T3 antibody of the wells. After 60 minutes incubation at room temperature, the wells are washed 5 times by wash solution to remove unbound T3 conjugate. A solution of chemiluminescent substrate is then added and read relative light units (RLU) in a Luminometer. The intensity of the emitting light is proportional to the amount of enzyme present and is inversely related to the amount of unlabeled T3 in the sample. By reference to a series of T3 standards assayed in the same way, the concentration of T3 in the unknown sample is quantified.

Principle of T4 immunoassay

In the T4 (Human) CLIA Kit, a certain amount of anti-T4 antibody is coated on microtiter wells. A measured amount of patient serum, and a constant amount of T4 conjugated with horseradish peroxidase are added to the microtiter wells. During incubation, the anti-T4 antibody is bound to the second antibody on the wells, and T4 and conjugated T4 compete for the limited binding sites on the anti-T4 antibody. After 60 minutes incubation at room temperature, the wells are washed 5 times by wash solution to remove unbound T4 conjugate. A solution of chemiluminescent substrate is then added and read relative light units in a Luminometer. The intensity of the emitting light is proportional to the amount of enzyme present and is inversely related to the amount of unlabeled T4 in the sample. By reference to a series of T4 standards assayed in the same way, the concentration of T4 in the unknown sample is quantified.

Principle of TSH immunoassay

The TSH (Human) CLIA kit test utilizes a unique monoclonal antibody directed against a distinct antigenic determinant on the intact TSH molecule. Mouse monoclonal anti-TSH antibody is used for solid phase (microtiter wells) immobilization and a goat anti-TSH antibody is in the antibody-enzyme (horseradish peroxidase) conjugate solution. The test sample is allowed to react simultaneously with the two antibodies, resulting in the TSH molecules being sandwiched between the solid phase and enzyme-linked antibodies. After 60 minutes incubation at room temperature, the wells are washed 5 times by wash solution to remove unbound anti-TSH conjugate. A solution of chemiluminescent substrate is then added and read relative light units in a Luminometers. The intensity of the emitting light is proportional to the amount of enzyme present and is directly related to the amount of TSH in the sample. By reference to a series of TSH standards assayed in the same way, the concentration of TSH in the unknown sample is quantified.

Procedure -:

- Firstly, separate the serum sample in tube and check sample volume to make sure that there is sufficient quantity to perform testing.
- Load sample into the sample rack and make sure there are no bubbles formation.
- Manually entered the sample I.D and load the rack into the instrument.
- Select the appropriate or required test which you want to perform (examples. T3, T4 and TSH).
- After test selection, the instrument will automatically starts pipetting and diluting the sample.
- The delay time for getting results, for T3 – 30 minutes, for T4 – 30 minutes and for TSH 45 minutes.
- Then, remove the serum specimen after finish.

RESULTS

Results

The present study was conducted on total 90 individuals. Both males and females age between 17 – 81 years were included in this study. Firstly, the total data was divided into 3 groups named as: Subclinical Hypothyroid (n= 30), Euthyroid (n=57) and Hyperthyroid include only 3 patients and according to Age, weight (kg), Height (m^2) and BMI the mean ± S.D values were calculated.

Table.4: Shows the general data with Values (mean ± S.D) of Age, weight (kg), Height (m^2) and BMI in 3 groups.

Parameters	**Subclinical Hypothyroid (n = 30)**	**Euthyroid (n = 57)**	**Hyperthyroid (n = 3)**
Age (Years)	48.6 ± 15.8	52.0 ± 12.5	47.3 ± 11.0
Weight (kg)	74.3 ± 16.7	70.4 ± 11.5	73.3 ± 2.8
Height (m^2)	2.67 ± 0.2	2.68 ± 0.3	2.72 ± 0.2
BMI (kg/m^2)	27.7 ± 5.8	26.3 ± 4.6	27.0 ± 2.9

The values (mean ± S.D) of various parameters including thyroid profile, BMI and weight were distributed according to the age groups.

Table. 5: Showing the Status of various parameters including – Thyroid profile (T3, T4 and TSH), BMI and Weight according to different age groups.

Age groups	**n**	**T3 (ng/ml)**	**T4 (ug/ml)**	**TSH (uIU/ml)**	**BMI (kg/m^2)**	**Weight (kg)**
17 – 30	7	1.13 ± 0.37	7.31 ± 2.66	5.28 ± 3.36	24.32 ± 4.83	65.71±11.94
31 – 40	13	1.24 ± 1.06	8.96 ±4.46	4.40 ± 3.07	26.8 ± 4.68	70.46 ± 16.09
41 – 50	25	1.05 ± 0.34	8.77 ± 2.77	3.66 ± 2.77	28.81 ± 5.72	75.6 ± 14.73
51 – 60	23	1.11 ± 0.31	9.58 ± 2.89	3.20 ± 2.04	26.27 ± 4.63	72.21 ± 13.29
61 – 70	18	1.04 ± 0.34	8.35 ±2.27	3.79 ± 2.76	26.51 ± 4.94	69.72 ± 10.51
>70	4	0.97 ± 0.20	9.45 ± 1.87	7.59 ± 2.29	23.8 ± 0.96	70.5 ± 7.72

The Minimum, Maximum, Average (mean) and S.D values of T3, T4 and TSH were calculated for all 3 groups (S.H, Euthyroid and Hyperthyroid) and placed into the tables.

Table. 6: Shows the minimum, maximum, average and S.D values of Thyroid profile (T3, T4 and TSH) in SH patients.

Subclinical Hypothyroidism (n = 30)			
	Parameters		
	T3 (ng/ml)	**T4 (ug/ml)**	**TSH (uIU/ml)**
Min.	0.66	4.1	5.03
Max.	1.63	12.5	9.9
Mean	0.97	7.7	7.39
S. D	0.25	2.56	1.58

Table. 7: Shows the values (minimum, maximum, mean and S.D) of T3, T4 and TSH in Euthyroid group.

Euthyroid (n = 57)			
	Parameters		
	T3 (ng/ml)	**T4 (ug/ml)**	**TSH (uIU/ml)**
Min.	0.60	4.4	0.54
Max.	1.86	12.5	4.94
Mean	1.07	8.89	2.39
S.D	0.29	2.14	1.15

Table. 8: Shows the Minimum, maximum, mean and S.D values of Thyroid profile in hyperthyroid patients.

Hyperthyroid			
	T3 (ng/ml)	**T4 (ug/ml)**	**TSH (uIU/ml)**
Min.	1.99	15.1	0.01
Max.	4.7	22.1	0.11
Mean	2.92	18.46	0.04
S.D	1.53	3.50	0.05

As comparison between 3 groups, minimum values of T3 (0.60) in Euthyroid, T4 (4.1) in S.H and TSH (0.01) in hyperthyroid were observed. Maximum values of T3 (4.7) and T4 (22.1) in hyperthyroid and TSH (9.9) in SH group were found. The high mean values of T3 (2.92) and T4 (18.46) in hyperthyroid and TSH (29.1) in SH group were observed. Low mean values of T3 (0.97) and T4 (7.7) in SH and low mean TSH (0.04) in hypothyroid group were noticed.

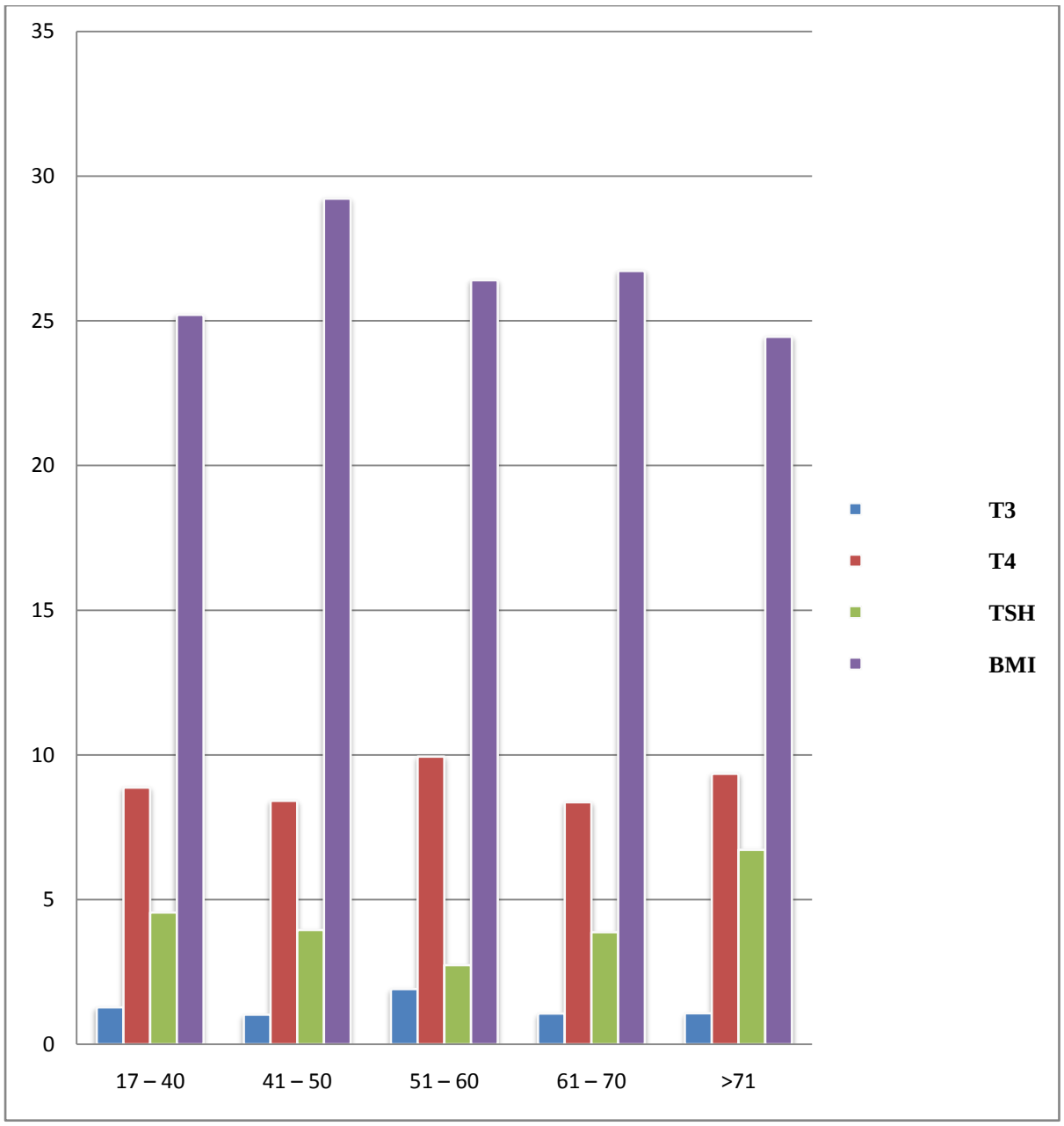
Total data was separated according to BMI and Thyroid hormones status in different age groups of female's population. The minimum age was 17 and maximum was 81 years. Mean and S.D values were calculated for all parameters (Thyroid profile and BMI) and placed into the table.

Table . 9: Showing the status of thyroid hormones and BMI in Females.

Age Group		**Parameters**			
	n	**T3 (ng/ml)**	**T4 (ug/ml)**	**TSH (uIU/ml)**	**BMI (kg/m^2)**
17 – 40	16	1.28 ± 0.96	8.87 ± 4.19	4.55 ± 3.1	25.2 ± 4.92
41 – 50	21	1.02 ± 0.29	8.41 ± 1.97	3.95 ± 2.85	29.22 ±5.96
51 – 60	15	1.91 ± 0.28	9.94 ± 2.86	2.74 ± 1.84	26.4 ± 5.23
61 – 70	12	1.06 ± 0.30	8.36 ± 2.51	3.87 ± 2.64	26.72 ± 4.87
>71	2	1.07 ± 0.27	9.35 ± 3.18	6.72 ± 2.93	24.45 ± 1.06

Below graph Shows, comparison with other age groups the high values of T3 and T4 in age group 51 – 60, TSH in >71 and high BMI in 41 – 50 were found. Lower values of T3 41 -50, T4 in 61 – 70, TSH in 51 – 60 and BMI in >71 groups were observed.

Fig. 8: Thyroid Hormones and BMI status of female's population in different age groups.



Among male's population, thyroid hormones and BMI values (mean ± S.D) were distributed according to age groups in Table.7. The mean and std. dev. values were calculated and placed

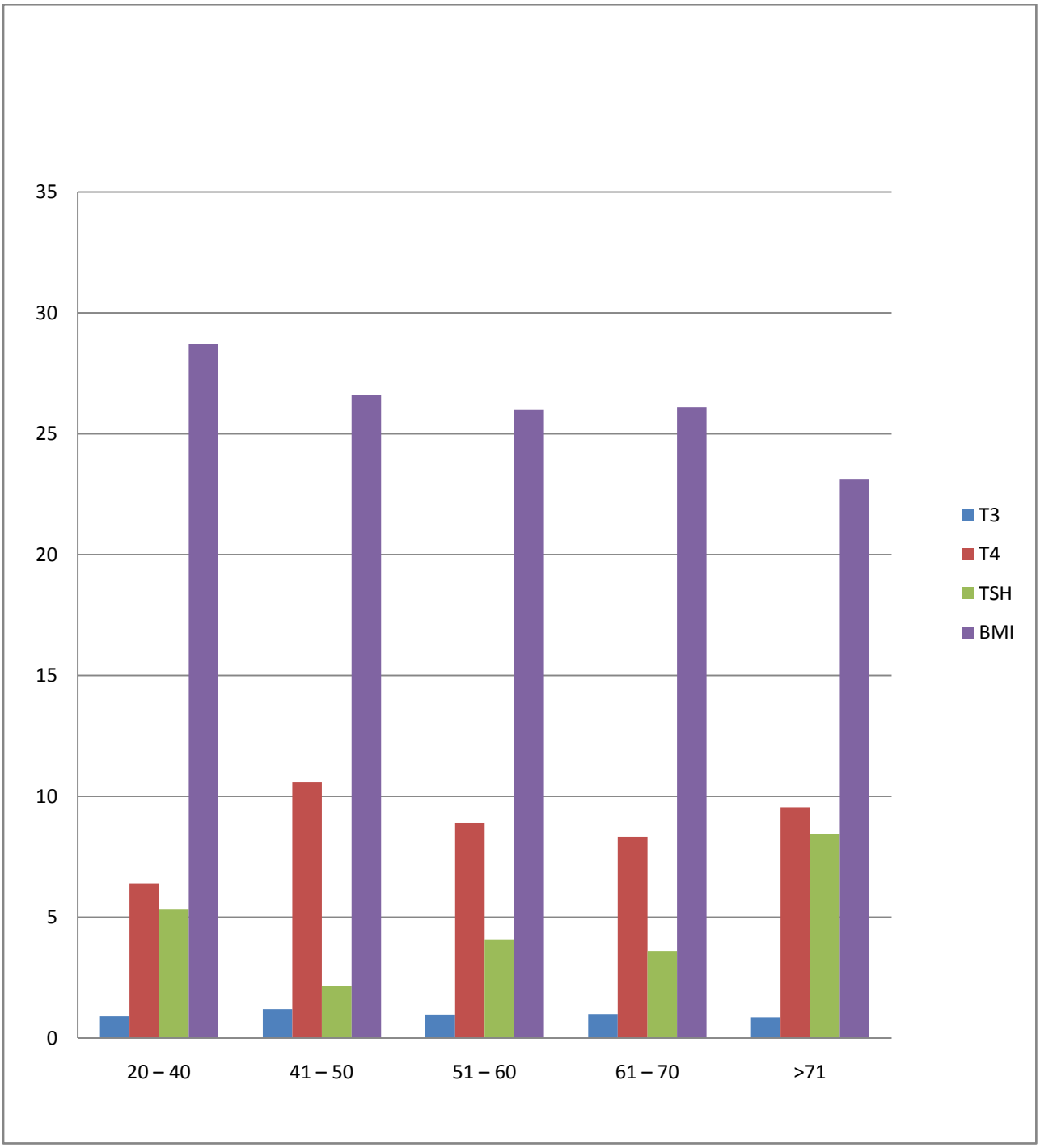
into the table. Total 24 males were included with minimum age 29 and maximum 78 years.

Table. 10: Showing the status of Thyroid hormones and BMI among the Males population.

Age Groups	**N**	**T3 (ng/ml)**	**T4 (ug/ml)**	**TSH (uIU/ml)**	**BMI (kg/m^2)**
20 – 40	4	0.9 ± 0.19	6.4 ± 1.83	5.34 ± 3.56	28.7 ± 2.97
41 – 50	4	1.2 ± 0.56	10.6 ± 5.48	2.14 ± 1.93	26.6 ± 4.22
51 – 60	8	0.97 ± 0.33	8.9 ± 3.03	4.06 ± 2.26	26.0 ± 3.55
61 – 70	6	1.00 ±0.44	8.33 ± 1.90	3.61 ± 3.01	26.08 ± 5.52
>71	2	0.86 ± 0.07	9.55 ±0.63	8.46 ± 1.78	23.1 ±0.07

Below graph shows the high level of T3 and T4 are observe in age 41 – 50, similarly TSH in > 71and BMI in 20 – 40. Low levels of T3 and BMI is noticed in age >70, T4 in 20 – 40, TSH in 41 – 50.

Fig. 9: Thyroid Profile and BMI status among males according to age groups.



For correlation analysis, according to Total, male and female population in euthyroid group the mean and std. dev. values of TSH and BMI were calculated and placed into the table. Correlation coefficient (r value) for total, male and female were calculated in Microsoft Office Excel Worksheet using (Data Analysis) correlation formula. The correlation coefficient (r – value) lies from -1 to +1.

Table. 11: Interpretation of r – value

1.0	**Perfect Correlation**
0 to 1	**Two variables increase or decrease together.**
0.0	**Two variables do not vary together at all.**
-1 to 0	**One variable increases as the other decreases.**
-1.0	**Perfect negative (inverse) correlation.**

Table .12: Shows the correlation of TSH with BMI in Euthyroid subjects.

	n	TSH (uIU/ml)	BMI (kg/m^2)	r value	Correlation
Total	57	2.39 ± 1.51	26.37 ± 4.67	0.14	Poor Positive
Male	14	2.48 ± 1.35	26.01 4.29	-0.05	Poor Negative
Females	43	2.36 ± 1.09	26.48 ± 4.82	0.21	Poor Positive

Table. 13: Shows the correlation of TSH with BMI in Subclinical Hypothyroid patients.

	n	TSH (uIU/ml)	BMI (kg/m^2)	r value	Correlation
Total	30	7.39 ± 1.58	27.71 ± 5.86	- 0.05	Poor Negative
Male	9	7.36 ± 1.64	26.95 ± 3.90	- 0.27	Poor Negative
Female	21	7.40 ± 1.54	28.04 ± 6.58	- 0.01	Poor Negative

Above tables (12, 13) shows poor Positive relationship between TSH and BMI in euthyroid (Total) that means if one variable increases the other variable also increases or if one decreases and other will also decreases. In males, poor negative correlation (means one variable increases and other variable decreases or vice versa) and in females poor positive relation was observed in Euthyroid group. In S.H group, poor negative correlation were found in Total, males and females population.

DISCUSSION

DISCUSSION

The present study was undertaken to find out the association between TSH and BMI in Subclinical hypothyroid patients and Euthyroid individuals. This study includes total 90 individuals that categorized in three groups (as Euthyroid, Subclinical Hypothyroid and Hyperthyroid) according to their T3, T4 and TSH levels. The normal range for thyroid profile is -: T3 - 0.60 – 1.80 ng/ml.

T4 – 3.20 – 12.6 ug/ml.

TSH – 0.35 – 5.0.

The total 57 numbers of Euthyroid subjects, Subclinical Hypothyroid include 30 and hyperthyroid include only 3 patients. In our study we found high prevalence of thyroid diseases in females (n = 66%) than males (n =24%). Various previous studies observed that thyroid hormones can affect the body weight by alter the B.M.R. Some studies shows decreased thyroid functions associated with weight gain or obesity and other analysis shows no relation with this regard. The link between body weight and TSH level is especially attractive [77].

In previous studies it was found that association between TSH and BMI could be altered by smoking but in recent studies a positive correlation within BMI and TSH was observed in smokers. A study conducted by Knudsen et al. (2005) noticed that little changes in thyroid function are associated with alteration in BMI but the exact mechanism about this association are not clear [78]. The obesity is defined by BMI (>25) and most of the patients was found to obese who came for assessment of thyroid functions in the hospital.

Obesity is appeared with alterations in lipids parameters which further leads to C.V.D. The decrease functions of thyroid gland are related to obesity and it was suggested that there must be association lies between lipid profile and thyroid hormones. Various studies conducted to find out the relationship between TSH and lipid profile but yet they do not observed any clear relationship [79 – 80].

A recent study performed by B.A. Laway et al. in 2014 was to evaluate the variations in lipid parameters between Subclinical Hypothyroid and normal individuals were observed the

elevated levels of TC, TG and VLDL in patient's withSH. No relationship was observed between HDL and TSH [81].

In present study, the poor positive correlation (r value - 0.14) between TSH and BMI was observed in total Euthyroid subjects. A poor negative association between TSH and BMI in Males and poor positive (r value – 0.21) relationship was observed in Euthyroid females (shows in table. 8). Suganty et al. (2011) were reported that there was a significant positive correlation between serum TSH and BMI in Euthyroid females (75). J.J.Deiz et al. also noticed a significant correlation between TSH and BMI in Euthyroid subjects. They conclude that TSH level significantly increased with weight (76).

In SH patients (Total, Male and female), Poor negative correlation was observed between TSH and BMI (table 9). This indicates the vice versa relationship lies between TSH and BMI in SH patients. The SH also called mild thyroid failure is defined as a normal thyroid hormones but mildly elevated TSH (5 – 10 uIU/ml) with no or mild sign and symptoms. The mild symptoms includes – weight gain, memory problems and cold intolerance. In present study the prevalence of weight gain, less sleep and joint pain observed more in SH patients. Patients with SH have higher risk of CVD then euthyroid. Occurrence of SH were found significantly higher in female population. The information about "correlation between TSH and BMI in SH patients" is very less or not well understood.

Anjanya Prasad V, et al. in 2013 observed a statistically significant difference between male and female patients with SH. They conclude that the TSH levels were significantly higher in morbidly obese female's patients than in males [82].

The exact mechanism behind the increased TSH in obese person not clears properly and it is more difficult to find mild thyroid failure in obese persons. In obese adults and children's, elevated TSH appeared with enlargement of thyroid gland and hypoechogeneity. Diagnosis of hypothyroidism not only evaluated by ultrasound, the proper diagnosis requires blood test with physical examinations [83 – 84].

The hypothyroidism is associated with weight gain or obesity and which is the major risk factor for diabetes. Found by various researches that patients with diabetes may have abnormal thyroid functions. A study shows prevalence 18.3% of SH in patients with Type 2 diabetes mellitus. The prevalence was found more in patients with age more than 50 years [85].

SUMMARY AND CONCLUSION

Summary and conclusion

The thyroid hormones play various essential roles in our body and they are essential for normal body functions. They were required to normal regulation of myocardial infarction, pulmonary ventilation, energy homoeostasis, vascular tone, water and electrolyte balance also helps in normal function of the C.N.S.

Various studies were performed to find out the association between TSH and BMI and each study give a different finding in their study. Based on the data analysis it can interpreted that a poor positive correlation between TSH and BMI and poor negative correlation between TSH and BMI is associated in euthyroid subjects. It indicates that when TSH increases the BMI will also be increased in total and females euthyroid subjects. Inverse or poor negative correlation was observed within TSH and BMI in patients with Subclinical Hypothyroidism. In the future, further studies regarding to "correlation between BMI and TSH" will defiantly add account in previous study. Therefore, from the literature available and statistical analysis of the data, it is accepted and state as, there is a positive correlation associated between BMI and TSH in Euthyroid subjects (Total and females).

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PROFORMA

U/ I.D _____ **Sex _____**

Name _____ **Contact No._____**

Age _____

Address

_____

_____

Chief complaints-:

_____

_____

History of present illness-:

_____

_____

Family History-:

_____

_____

Treatment History-:

_____

_____

Menstrual History-:

_____

_____

Marital Status-: _____

Physical Examination-:

Pulse Rate _____ **Blood pressure _____**

Respiratory Rate _____ **Weight _____**

Temperature _____ **Height _____**

Chest Examination

_____

_____

Abdomen Examination

_____

_____

Head and Neck

_____

_____

Consent Form

I hereby give my consent for the study project and I am willing to share my medical information. The nature and the purpose of study and its potential risks / benefits and expected duration of study have been explained to me in detail.

I agree to take part in above study.