LEAN BODY MASS BASED LEVOTHYROXINE SUPPLEMENT LESSENS DETERIORATION OF CARDIAC FUNCTION AND EXERCISE CAPACITY IN RADIOIODINE ABLATED DIFFERENTIATED THYROID CARCINOMA PATIENTS

by

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CANDIDATE'S DECLARATION

It is hereby declared that this thesis or any part of it has not been submitted elsewhere for the award of any degree or diploma

Signature of the Candidate

Fatima Begum

Dedication

To my late father A G Jinat Ali,

I always shed tears and remember my father's smiling face answering my each query during my childhood, which inspires me to struggle through hardships for my education

and to my mother Shahida Begum,

I would like to be a mother like my Ma who has taken so much pain to educate her children

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List of abbreviations

A	Late Diastolic Wave
AHA	American Heart Association
AJCA	American Joint Committee on Cancer
ATA	American Thyroid Association
Am	Late Diastolic Wave in myocardium (in tissue Doppler imaging)
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
BP	Blood Pressure
BMC	Bone Mineral Concentration
bpm	Beats per minute
BSA	Body Surface Area
cAMP	Cyclic Adenosine Mono Phosphate
cGy	Centi Gray
2D	Two Dimensional Mode
DBP	Diastolic Blood Pressure
Dct	Deceleration Time
DTC	Differentiated Thyroid Carcinoma
DXA	Dual Energy X-ray Absorptiometry
E	Early Diastolic Wave
Em	Early Diastolic Wave in myocardium (in tissue Doppler imaging)
ECG	Electrocardiogram
EF	Ejection Fraction
ET	Ejection Time
ETT	Exercise Tolerance Test
FT3	Free Triiodothyronine
FT4	Free Tetraiodothyronine/thyroxine

FS	Fraction Shortening
GBq	Giga Becquerel
HSD	Honestly Significant Difference
Ht	Height
HR	Heart rate
$^{131}\mathbf{I}$	Radioiodine-131
IVRT	Isovolumic Relaxation Time
IVST	Interventricular Septal Thickness
LT4	Levothyroxine
LBM	Lean Body Mass
LVIDD	Left Ventricular Internal Diameter During Diastole
LVIDS	Left Ventricular Internal Diameter During Systole
LVM	Left Ventricular Mass
LVMi	Left Ventricular Mass Index
m	Mean
m	Meter
MBq	Mega Becquerel
mci	Milli Curie
M-mode	Motion mode
mRNA	Messenger Ribonucleic Acid
MET	Metabolic Equivalent
MHC	Myosin Heavy Chain
µgm	Microgram
mVCFc	Heart rate adjusted mean velocity of circumferential fiber shortening
NCX	Sodium Calcium Exchanger
NIS	Sodium Iodide Symporter
PLB	Phopholamban
PWT	Posterior Wall Thickness

RAIUT	Radioiodine Uptake Test
RIT	Radioiodine Therapy
SBP	Systolic Blood Pressure
SD	Standard Deviation
SRS	Symptom Rating Scale
SVR	Systemic Vascular Resistance
T3	Triiodothyronine
T4	Tetraiodothyronine
TBW	Total Body Weight
TDI	Tissue Doppler Imaging
Tg	Thyroglobulin
TNM	Tumor, Node, Metastases
TR	Thyroid Receptor
TSH	Thyroid Stimulating Hormone
UICC	Union Internatinale Centre Cancer
UWW	Under Water Weighing
WBS	Whole Body Scan

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Abstract

Conventional supplement therapy of levothyroxine (LT4) for differentiated thyroid carcinoma (DTC) keeps the patient in subclinical hyperthyroid state, which affects the heart activity and lowers exercise capacity. Lean body mass (LBM) has been recently suggested as best determinant of LT4 supplement dosing in patients with DTC. The present study was done to optimize the dose of LT4 in low risk group (T1, N0, M0) of patients with DTC and thereby preventing the adverse cardiac effects and improve exercise capacity. The importance of dose adjustment of LT4 based on lean body mass has not been properly addressed before.

Sixty patients with differentiated (papillary) thyroid carcinoma (young age group) without any signs of metastases, previous cardiac problems and chronic disease were consecutively enrolled in the study. They were referred to Institute of Nuclear Medicine and Ultrasound, Dhaka during the year 2007-2009 from different district Hospitals of Bangladesh. All patients had undergone total thyroidectomy and then received about 100 mci radioiodine ablative therapy and subsequently 200 µgm LT4 daily for initial 2 months. Age, weight, height, body surface area, body mass index and life style matched 23 healthy euthyroid volunteers were also selected. All clinical, biochemical, echocardiographic and Exercise Tolerance Test (ETT) data of healthy adults control were obtained for comparison with patients at baseline study after two months of radioiodine ablative therapy and on LT4 replacement on conventional 200 µgm/day at first follow up visit. Then 60 patients were grouped as Group-I and Group-II, each group consisted of 30 patients. Thirty patients of Group-I had undergone dual energy X-ray absortiometry (DXA) investigation to estimate lean body mass and received optimized LT4 dose depending on lean body mass (about 131± 23 µgm/day, 3.5-4 µgm/kg/LBM/day). In Group-II, 30 patients continued the conventional fixed dose of LT4 (200 µgm/day). Patients of both groups were followed up clinically and hormone assay were done at 3 months interval. At 6-12 months of LT4 supplement (conventional and LBM based) all study parameters (Symptom Rating Score, hormone data, echocardiographic data and ETT) were reevaluated.

Serum FT3 (Group-I, 5.5±1.3 pmol/L; Group-II,10.1±1.3 pmol/L, *$p < 0.001$), FT4 (Group-I,17.9 ±1.9 pmol/L; Group-II, 27.4±0.94 pmol/L; *$p < 0.001$) were higher and TSH (Group-I, 0.1± 0.01 mIU/L; Group-II, 0.09± 0.05 mIU/L; *$p < 0.001$) was suppressed in patients with DTC at conventional LT4 dose (200 µgm/day) compared to healthy control and patients with optimized dose of LT4 (mean±SD, 131± 23 µgm/day) of Group-I at second visit. Symptom Rating Scale score (SRS, Group–I, 2±1, Group-II, 8±1, at second visit; *$p < 0.001$), heart rate (Group-I, 87±14 beats/min, Group-II, 100±20 bpm, at second visit; *$p < 0.003$). SBP (Group-I, 114± 7 mm Hg, Group-II, 119±8 mm Hg, at second visit), DBP (Group-I, 75±7 mm Hg, Group-II, 78±4 mm Hg, at second visit) were slightly higher in patients (Group-II) after receiving conventional LT4 suppressive dose but were not statistically significant. Left ventricular mass (LVM) (*$p<0.05$), left ventricular mass index (LVMi) (*$p<0.01$), fraction shortening (FS%)

(*$p<0.001$*) and heart rate adjusted mean velocity of circumferential fiber shortening (mVCFc) (*$p<0.001$*) were increased in patients of Group-II after exposure of conventional LT4 dose compared to patients received optimized dose (Group-I) at second visit. Ejection time was also decreased in patients of Group-II at second visit compared to patients of Group-I at first visit *$P<0.01$*. Mild degree of diastolic function abnormalities were also noted in Group-II patients at second visit compared to Group-I patients. Early (E) diastolic velocity of Group-II was significantly low at second visit compared to that of Group-I at first visit (*$p<0.005$*) and late (A) was comparatively high in group II compared to Group-I at second visit (A, Group-I, 51±8 cm /sec, Group-II, 58±8 cm /sec; *$p<0.01$*). Deceleration time (Dct) was significantly low in Group-II compared to patients in Group-I at two visits and patients of Group-II at first visit (Dct, Group-I, 155± 16 m sec, Group-II, 127± 18 m sec; *$p<0.001$*). Similarly in tissue Doppler imaging technique, late diastolic mitral annular velocity (Am) was higher in Group-II compared to Group-I at second visit (Am, Group-I, 15±3 cm /sec, Group-II, 19±6 cm / sec; *$p<0.003$*). Significantly high modified Tei index was also noted in patients of Group-II at second visit compared to their first visit value and patients of Group-I at different visits (Group-I, 0.34± 0.08; Group-II, 0.48± 0.06 at second visit *$p<0.001$*). Exercise capacity as evaluated by exercise tolerance test (ETT), showed significant difference (*$p<0.05$*) in metabolic equivalent (MET) between healthy volunteers and patients groups at first visit but no difference was found between two patient groups at different time points.

It is concluded that optimization of dose of LT4 based on lean body mass can avoid chronic exposure of mild excess of thyroid hormone in the body and improve quality of life in patients with low risk DTC by preventing and minimizing adverse cardiac effects.

Chapter I

Introduction

Chapter I

Introduction

1.1 Introduction

Thyroid carcinoma is the commonest endocrine malignant tumor (Jana S et al., 1999). In the United States, thyroid carcinoma accounts for 1.5% of all cancers and 20,700 new cases per year (Internet, Maitra A and Abbas AK et al., 2004). A female predominance has been noted in the early and middle years of life, perhaps related to expression of estrogen receptors on neoplastic thyroid epithelium (Internet, Maitra A and Abbas AK et al., 2004).

The thyroid carcinomas are mostly differentiated (papillary and follicular) having long life expectancy. Less than 10 % cases are undifferentiated (anaplastic and medullary) (Mazzaferri EL and Kloos RT, 2001; Maitra A and Abbas AK et al., 2004). Differentiated thyroid carcinomas are the most curable cancers. Properly treated patients with differentiated (papillary) carcinoma of thyroid gland have 10 years survival in about 95% cases (Jana S et al., 1999; Mazzaferri EL and Kloos RT, 2001; Sawka AM et al., 2009), almost normal life expectancy. Conventional mode of treatment of patient with differentiated thyroid carcinoma (DTC) is total thyroidectomy followed by radioiodine ablation therapy. Although there is controversy about the appropriate extent of surgery, most of the physicians strongly support total and near total thyroidectomy leaving no more than 2-3 gm of thyroid tissue to spare the blood supply to the parathyroid glands. Total and near total thyroidectomy results in lower recurrence rate (Jana S et al., 1999). Surgical removal of thyroid gland followed by destruction of residual normal thyroid tissue by radioiodine (^{131}I) ablative therapy has been strongly advocated to prevent regrowth of cancer and to decrease death rate (Mazzaferri EL and Kloos RT, 2001). Thereafter, patients receive life long levothyroxine (LT4) supplement as their thyroid glands have been totally destroyed by above mentioned procedures (Burmeister L et al., 1992; Toft AD, 1994 and Schlumberger M et al., 2004). LT4 is

given in a dose not only to treat hypothyroid state, but in thyroid stimulating hormone (TSH) suppressive dose. Suppression of pituitary secretion of TSH retards the growth and spread of cancer (Burmeister et al., 1992; Pujol P et al., 1996; Cooper DS et al., 2006). There are several recommendations for LT4 replacement therapy. Mostly preferred method of LT4 therapy is initial supplement based on total body weight (2.5±5 µ g m/kg / body weight) in case of patients with DTC (Burmeister et al., 1992), thereafter adjustment of dose at expected level depending on serum TSH level doing follow up blood hormone levels (FT3, TSH) at 6-12 months interval.

This LT4 supplement at TSH suppressive dose keeps the patient in subclinical hyperthyroid state. LT4 therapy at suppressive doses has certain cardiac disadvantages including increased heart rate, increased incidence of atrial arrythmias, enhanced left ventricular (LV) systolic function and increased LV mass (Minz G et al., 1991; Biondi B et al., 1993, Sawin CT et al., 1994; Biondi B et al., 2000, Klein I and Danzi S., 2007). Subclinical hyperthyroid state of patients also lowers the exercise capacity of patients (Mercuro G et al., 2000) and deteriorates existing cardiac problems (Shapiro LE et al., 1997). Furthermore, proper caution is required about the dose of levothyroxine supplement of patients with DTC who have already existing cardiac symptoms (Ladenson PW, 1990; Samuel AM, 1999).

American Thyroid Association recommended initial thyrotropin (TSH) suppression to below 0.1 mIU/ml in high risk patients and maintenance of the TSH at or slightly below the lower limit of normal (0.1-0.5 mIU/L) is appropriate for low risk patients (Cooper DS et al., 2006; Polyzos SA et al., 2007).

There are several size descriptors to measure the dose of drugs such as, total body weight (TBW), body mass index (BMI), body surface area (BSA) and lean body mass (LBM). LBM is the precise predictor in dosing of the drugs which are hydrophilic (Green B and Duffull SB., 2004). In a recent study, it has been shown that individual requirement of LT4 supplement is mostly dependent on lean body mass rather than total body weight (Santini F et al., 2005). Lean body mass (LBM)

is a potentially useful predictor of the pharmacokinetic behavior of drugs which are highly water soluble. LT4 is water soluble and its pharmacokinetics is dependant on lean portion of body. LT4 is deiodinated to T3 (active form of hormone) in muscle, kidney and liver. T4 is deiodinated to rT3 (reverse T3, inactive form) in skin. Fatty tissue has no role in metabolism of LT4 (Santini F et al., 2005). Total body mass is calculated by Dual Energy X-ray Absoptiometry (DXA) as follows: Total body mass (TBW) = total bone mineral concentration (BMC) + total fat mass (FM) + total lean mass. Thereby, lean body mass (LBM) = the total body mass-(total fat mass + total BMC) (Stikkelbroeck NMML et al., 2003). DXA is the recent and precise method to measure the lean body mass. This method has higher efficacy to measure body composition, fat mass and lean body mass than the other methods such as under water weighing (UWW) method, bioelectrical impedance analysis (BIA) (Andreoli A et al., 2009; Green B and Duffull SB, 2004; Linda MB, 2001).

Young patients with DTC having low risk of recurrence and metastases (T1, N0, M0) should be given more attention in prescribing LT4 therapy, because they have long life expectancy. To prevent adverse cardiac effects due to long term administration of LT4 in supraphysiologic dose, physician should be cautious about dosing of LT4. Lean body mass based LT4 dosing is advocated recently in low risk group of patients with differentiated thyroid carcinoma to improve the quality of life by preserving good cardiac function and exercise capacity.

1.2 Hypothesis and objectives

Hypothesis: It is hypothesized that dose adjustment of levothyroxine on the basis of lean body mass would lessens the detrimental effects of levothyroxine on heart activity and exercise capacity of patient with differentiated thyroid carcinoma.

Objectives:

1. Optimization of levothyroxine supplement based on lean body mass in low risk group of patients with differentiated thyroid carcinoma.
2. To preserve the good cardiac function and exercise capacity of low risk group of patients with differentiated thyroid carcinoma.

Chapter II

Literature Review

Chapter II

Literature Review

2.1 Thyroid gland

The anatomist Thomas Whartson first identified thyroid gland in 1656 (Wikipedia, 2010). Thyroid gland is one of the largest endocrine glands in the body weighing about 25 grams in adults. The name 'thyroid' comes from Greek word ' thyreos' which means shield. This gland is located infront of neck below the thyroid cartilage, which is generally known as Adam's apple and at approximately the same level of cricoid cartilage. Thyroid gland is a butterfly-shaped organ having two lobes, right lobe and left lobe connected by a bridge like portion called isthmus.

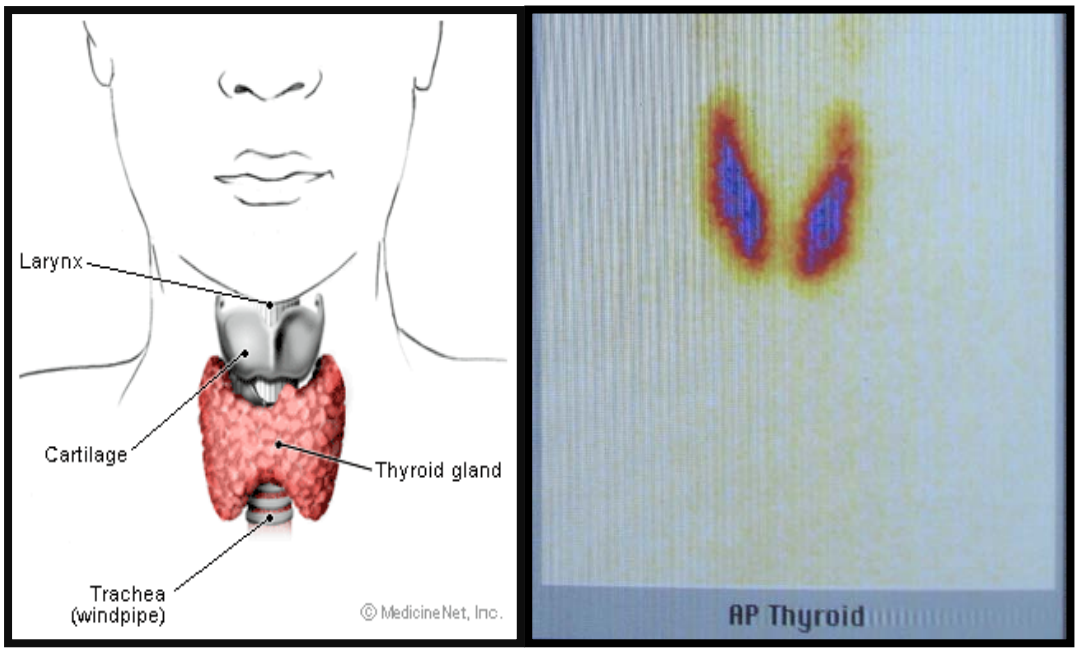

Fig. 1. Left: Anatomical location of thyroid gland (Medicine Net, Inc, accessed on 14 Aug, 2009). Right: ^{99m} Technetium scan of normal thyroid gland by Gamma camera (anterior – posterior view).

Thyroid gland is made up of multiple follicles. Each follicle is surrounded by a single layer of cells and filled with proteinaceous material called colloid (Ganong WF, 2005). In the fetus, at 3-4 weeks of gestation, the thyroid gland appears as an epithelial proliferation in the floor of pharynx at the base of the tongue. The fetus starts making its own thyroid-stimulating hormone (TSH) by week 8, and the follicles of the thyroid begin to make colloid and thyroxine by the 10th week of fetal life (Wikipedia, 2010).

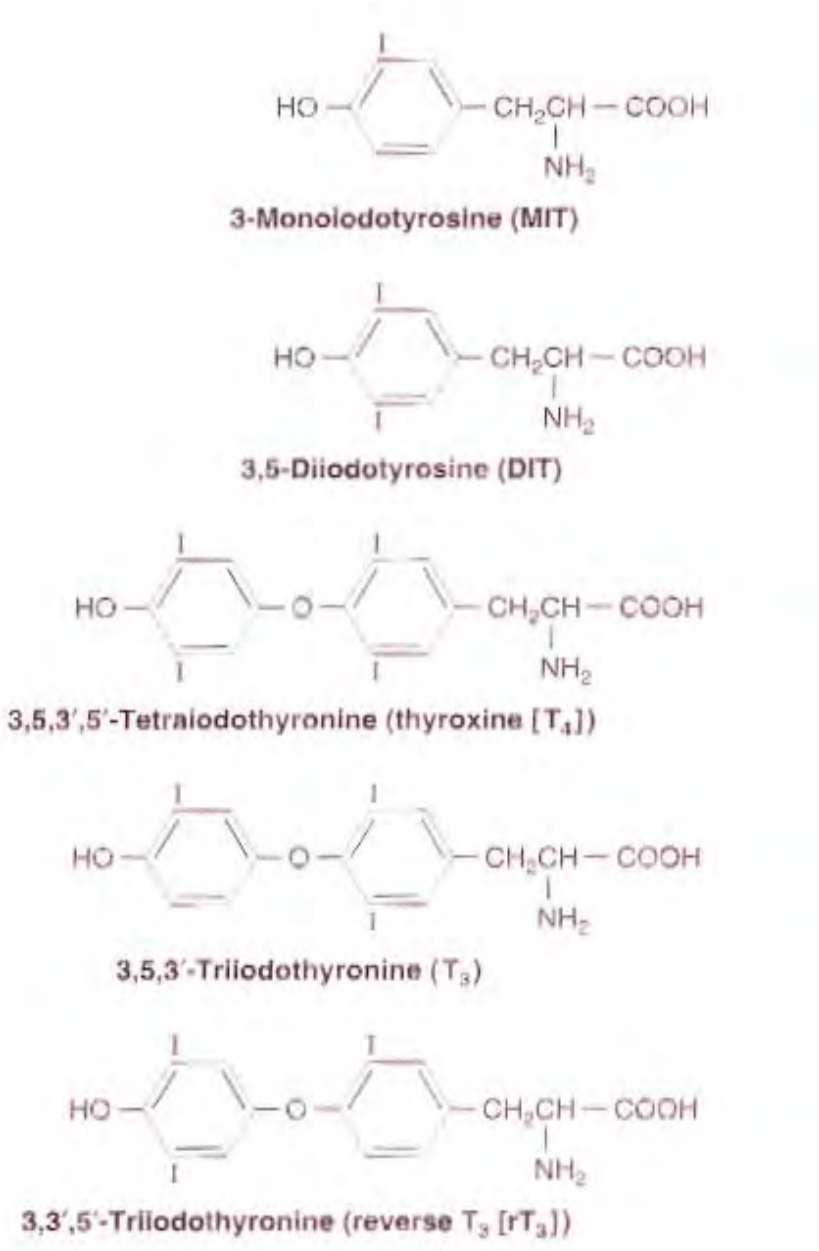

Fig. 2. Structure of thyroid hormones and related compounds. (Ganong WF, 2005).

LT_4 (Levothyroxine) and T_3 (triiodothyronine) are synthesized by the thyroid gland in response to TSH (Thyroid stimulating hormone) liberated from anterior pituitary gland. T4 and T3 are synthesized in the thyroid by combining iodine with amino acid tyrosine (Fig. 2.) and are secreted into the blood complexed with plasma globulin. The thyroid gland primarily secretes T_4 (~ 85%), which is converted to T_3 by 5'-monodeiodination in the liver, kidney, and skeletal muscle (Ganong WF, 2005; Klein I and Danzi S et al., 2007). Very small portion of T4 and T3 remains unbound to plasma protein which portion is called free (F), these FT3 (free triiodothyronine) and FT4 (free thyroxine) are active hormone which act in cellular level (Ganong WF, 2005; Granner DK, 2005). Thyroxine was first isolated in 1919 by American biochemist Edward Calvin Kendall and was synthesized in 1927 by British biochemist Charles Harington (1897-1972) (Wikipedia, 2010).

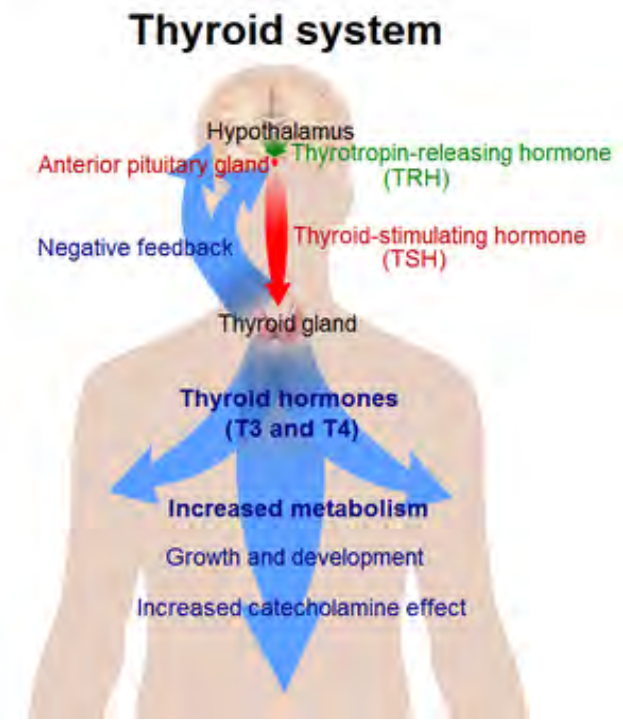

Fig. 3. Feedback mechanism of thyroid hormone secretion with stimulation of TSH by pituitary gland (Wikipedia, 2010)

Thyroid stimulating hormone (TSH) secreted by anterior pituitary gland regulates the synthesis and secretion of thyroid hormones. In turn, secretion of TSH is dependent on thyroid hormones named as 'feedback mechanism' (Fig. 3.). When increased thyroid hormones are present in plasma, this situation inhibits pituitary glands to secret TSH, so its level becomes suppressed (below normal). On the other hand, decreased thyroid hormone levels stimulate pituitary gland to secret TSH. Above mentioned mechanism works in hyperthyroidism, where FT3, FT4 levels are high and TSH becomes suppressed. In hypothyroid state, FT3, FT4 hormones are low and then pituitary gland is stimulated to secret TSH and subsequently its level become high. Thyroid hormones act in cellular level of all system of the body. These hormones increase O_2 consumption of cells, help in growth and development, lipid metabolism and increase carbohydrate absorption from intestine (Ganong WF, 2005)

2.2 Thyroid carcinoma

The incidence of thyroid cancer is rising in United States, Canada and United Kingdom. (Mazzaferri EL and Kloos RT, 2001; Sawka AM et al., 2009). In the United States, the incidence of thyroid cancer has increased from 3.6 per 100,000 persons in 1973 to 8.7 per 100,000 in 2002, representing 2-4 fold increase. In the United Kingdom, age-standardized incidence rates for thyroid cancer have nearly doubled from 1.4 to 2.6 per 100,000 persons between 1973 and 2005. The fatality rate of thyroid carcinoma is low, as the annual number of deaths due to thyroid cancer is approximately 5 % of the annual number of newly diagnosed cases in the United States (Sawka A M et al., 2009). Most thyroid carcinomas are well-differentiated lesions. The major subtypes of thyroid carcinoma and their relative frequencies include the following:

- Papillary carcinoma (75%-85 % of cases)
- Follicular carcinoma (10 to 20 % of cases)
- Medullary carcinoma (5 % of cases)
- Anaplastic carcinoma (< 5 % of cases) (Kebebew E and Clark OH, 2000)

Papillary and follicular thyroid carcinomas are differentiated thyroid carcinoma and are usually curable when diagnosed at an early stage (Mazzaferri EL and Kloos RT., 2001; Schlumberger M et al., 2004). Differentiation refers to the extent to which neoplastic cells resemble comparable normal cells, both morphologically and functionally (Kumar V et al., 2004; Luster M et al., 2008). Lack of differentiation is called anaplasia (Kumar V et al., 2004). Medullary carcinoma of thyroid is derived from parafollicular cells or C cells of thyroid-they are neuroendocrine neoplasm. Anaplastic carcinoma of thyroid is undifferentiated tumor of thyroid follicular epithelium and very much aggressive tumor with mortality rate nearly 100% (Maitra A and Abbas AK., 2004).

2.2.1 TNM classification of differentiated thyroid carcinoma

The staging of cancers is based on the size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of blood-borne metastases. Two major systems are currently in use, one developed by the Union Internationale Centre Cancer (UICC) and the other by the American Joint Committee (AJC) on Cancer Staging. The UICC formed a classification called the TNM system- T for the primary tumor, N for regional lymph node involvement and M for metastases. The TNM staging varies for each specific form of cancer, but there are some general principles. With increasing size, the primary lesion is characterized as T1 to T4. T0 indicates in situ lesion. N0 indicates no nodal involvement, whereas N1 to N3 denotes involvement of an increasing number and range of nodes. M0 signifies no distant metastases, whereas M1 or sometimes M2 indicates the presence of blood-borne metastases and some judgment as to their number. The AJC employs a somewhat different nomenclature and divide all cancers into stages 0 to IV, including within each of these stages the size of primary lesion as well as the presence of nodal spread and metastases. The TNM system remains to be the most applicable and consistent staging system for papillary thyroid carcinoma (PTC) (Kumar V et al., 2004; Lang BH., 2007).

2.2.2 Pathogenesis of thyroid carcinoma

There are several factors implicated in the pathogenesis of thyroid carcinoma – genetic and environmental.

Environmental factor: The major risk factor is ionizing radiation particularly when one is exposed to it in his/her first two decades of life. Radiation was used liberally for head & neck lesions (tonsillar enlargement, acne, tinea capitis) in the past. Up to 9% of people who received such treatment during childhood period had subsequently developed thyroid malignancies. Exposure to ionizing radiation in different areas of radiation accident and bombing and nuclear testing has increased the incidence of thyroid cancer in children (Maitra A and Abbas A K., 2004). Longstanding multinodular goiter has been considered as predisposing factor also. Endemic goiter due to iodine deficiency have a higher incidence of follicular carcinomas (Maitra A and Abbas AK., 2004)

2.2.3 Papillary Carcinoma:

Papillay carcinoma of thyroid gland is the most common differentiated carcinoma (DTC). It occurs most commonly in the second to fifth decades of life.

Pathogenesis: Majority of thyroid carcinomas associated with previous exposure to ionizing radiation. Papillary carcinomas appear to arise by multiple distinct, non overlapping molecular pathways. One pathway involves rearrangements of the tyrosine kinase receptors RET or NTRK1 (neurotropic tyrosine kinase receptor 1) and another involves activating mutations in the BRAF oncogene. A third pathway involves RAS mutations (Maitra A and Abbas AK, 2004).

Morphology: Lesions of papillary carcinoma may be solitary or multiple. Some are well-circumscribed and encapsulated. Others may have ill defined margins and may infiltrate surrounding tissue. Fibrosis and calcifications are sometimes noted in lesions and some are often cystic. On cut surface they may appear as granular and sometimes they contain well-defined papillary foci.

Histopathologic examination offers the definitive diagnosis.

The characteristic microscopic hallmarks of papillary carcinomas are the following:

- Papillary carcinoma may have papillae containing fibromuscular stalk covered by single or multiple layers of cuboidal epithelial cells.
- The nuclei of papillary carcinoma cells contain finely dispersed chromatin which gives optically clear or empty appearance giving ground glass or Orphan Annie eye nuclei. Cytoplasm of cells may produce the appearance of intranuclear grooves/inclusions. Diagnosis of carcinoma may be done on the basis of intranuclear inclusions (Maitra A and Abbas AK, 2004).
- Concentrically calcified structures termed psammoma bodies are often seen within the core of papillae. This is strong indication of papillary carcinoma and not found in follicular and medullary carcinoma. A hidden carcinoma is considered when psammoma body is found in a lymph node and perithyroidal tissue.
- Metastases to adjacent lymph nodes occur in half of the cases. Vascular spreading is relatively uncommon.

There are variant forms of papillary carcinoma – the encapsulated variant is usually confined to thyroid gland and account for 10% of all carcinomas. The follicular variant has typical nuclear feature of papillary carcinoma but has an almost follicular architecture. The tall cell variant is characterized by tall columnar cells lining the papillary structure. An unusual diffuse sclerosing variant of papillary carcinoma is found in young and children. There is diffuse fibrosis throughout the thyroid gland. Nodal metastases are present in almost all cases (Maitra A and Abbas AK, 2004)

Clinical course: Asymptomatic thyroid nodule is the usual presentation in most of the cases. In some cases, enlargement of cervical lymphnode may be the first manifestation. Single nodule with carcinoma may move freely like benign lesion. Hoarseness, dysphagia, cough or dyspnoea are the features of advanced disease.

Prognosis: Papillary thyroid cancers have excellent prognosis with 10 years survival rate in excess of 95 %. Local metastases are seen in 5% -20 % and distant metastases are seen in 10-15 % (Kebebew E and Clark OH, 2000). Prognosis also depends on age of the patient (age above 40 is less favourable), presence of local and distant metastases (Mazzaferri EL and Kloos RT, 2001).

2.3 Management of thyroid carcinoma

The proper management of thyroid carcinoma remains mainly on the hands of referring physician, surgeons and nuclear medicine specialist. It is a disease with relatively good prognosis, with a large group of patients who are at low risk of death. In this situation it is crucial to balance the possible side effects of treatment against possible benefits gained by more conservative or more aggressive treatment (Jana S et al., 1999, Polyzos SA et al., 2007).

2.3.1 Surgical management

Surgery is the prime mode of management of thyroid carcinoma (Podnos YD et al., 2007). There is still debate about extent of surgery, whether lobectomy (partial thyroidectomy) or total thyroidectomy (Kebebew E and Clark OH, 2000; Mazzaferri EL and Kloos RT., 2001; Polyzos SA et al., 2007). One group of conservative physicians supports the partial thyroidectomy. Majority of the physicians and world wide Institutes support total thyroidectomy (Mazzaferri EL and Kloos RT, 2001). Total thyroidectomy is chosen method for following reasons- (1) microscopic foci could be present in contralateral lobe, (2) total thyroidectomy is prerequisite for radioiodine ablation treatment, (3) metastatic lesion could be visualized in whole body scan after total thyroidectomy, (4) decreases the risk of recurrence (De Groot LJ et al., 1990). The disadvantages of total thyroidectomy is its morbidity viz, (1) recurrent laryngeal nerve injury, (2) hypoparathyroidism and (3) hypothyroidism. In the hands of experienced surgeons, there is only a 1%-2% risk of recurrent laryngeal nerve injury or hypoparathyroidism after total thyroidectomy (Jana S et al., 1999).

2.3.2 Radioiodine therapy

Dr. Joshep G Hamilton and John Lawrence treated hyperthyroidism by ^{131}I on October 12, 1941 (Sawin CT, 1997). This achievement formed the basis of one of the most successful areas of therapeutic Nuclear Medicine. Ablation of residual thyroid tissue by radioiodine is a widely practiced procedure after total thyroidectomy. Its advantages are-firstly, ^{131}I destroys residual thyroid tissue and microscopic thyroid carcinoma which is difficult to detect clinically. Secondly, its use greatly simplifies the follow up evaluation for secondaries especially using serum thyroglobulin (Tg) as tumor marker. In the presence of large remnant thyroid tissue, secondaries may remain undetected on whole body scan (WBS) (Reynolds JC and Robbins J 1997; Mazzaferri EL and Kloos RT., 2001). Papillary carcinoma of the thyroid may be bilateral, microscopically multicentric, metastasizes to regional lymph nodes and has a higher incidence of persistent or recurrent disease. These observations are more evident with incomplete thyroidectomy. Both papillary and follicular cancers have a tendency to be invasive and locally infiltrative leading to a high probability of recurrence. This invasiveness is often missed on histology if not looked for carefully. All these features are strong argument in favour of ablation of residual thyroid tissue.

In a retrospective analysis of 1597 patients of differentiated thyroid carcinoma, it was observed that ^{131}I was the single most important prognostic indicator by the Cox proportional hazards regression model for prolonging "disease free survival". In this study, treatment with ^{131}I improved the outcome in both 'low risk' and high risk patients. The incidence of recurrence was reduced by 50 % in 'low risk' patients given ^{131}I therapy for ablation of residual tissue. Even the incidence of pulmonary metastases was reduced by more than 50% when subtotal thyroidectomy was supplemented by ^{131}I treatment (Samuel AM, 1999).

Options/ methods of ablation of residual/ remnant thyroid tissue:

The ablation of residual thyroid tissue can be achieved in 3 ways -viz with low doses of ^{131}I, a high dose of ^{131}I and calculated dose of ^{131}I. In low dosage approach,

doses of ^{131}I are administered to outpatients less than 33 mci (Kebebew E and Clark OH., 2000) . The major advantages of low doses ablation are avoidance of hospitalization and reduced radiation exposure to the whole body in general and extrathyroidal tissues like bone marrow in particular (Mazzaferri EL and Kloos RT, 2001). The varying results of ablation therapy and the inadequate information regarding the effectiveness of low dosage ablation in preventing recurrences raises doubts in one's mind as to its usefulness. Disadvantages include low efficacy, costly approach necessitating significant time investment on the patient's part, multiple cycles of hypothyroidism, discomfort to the patient and 'stunning' of thyroid tissue may further make low dosage ablation less likely to succeed.

High dosage ablation: The second approach is the administration of high ^{131}I dose varying from 75-200 mci of ^{131}I as an inpatient therapy. The proponents of high dosage ablation suggest that higher dosages may actually be considered as an adjuvant radiation therapy for occult metastases not detected on diagnostic ^{131}I imaging studies. The studies show that, residual thyroid tissue can be successfully ablated with 100-200 mci in about 87% of patient and no significant increase of efficacy could be achieved by giving higher dosages. The dosages of ^{131}I needed for ablation of normal thyroid tissue with high ^{131}I uptakes are generally higher and these are more difficult to ablate. The usual practice in treating thyroid carcinoma is to give standard amount of ^{131}I to all patients. Most centers use dosages between 100-200 mci (3.7-7.4 GBq) and dosages upto 200 mci (7.4 GBq) are generally without any serious complications (Samuel AM, 1999, Mazzaferri EL and Kloos RT., 2001).

Calculated dosages ablation: The third approach is of radioiodine ablation is based on the radiation dose delivered rather than empirical administration of a fixed amount or varying amounts of ^{131}I. This approach advocates individualized treatment so that each patient receives a maximum "safe" dose, which maintain less than 2 Gy to the blood and not more than 120 mci (4.44 GBq) of ^{131}I retained in the whole body, 48 hours after treatment (Luster M, 2008). Average dosages of 309 mci (11.4 GBq) (75-659 mci, 2.78-24.4 GBq) have been administered without

permanent bone marrow suppression, leukaemia and pulmonary fibrosis (Samuel AM, 1999). The dosimetric calculations require determination of whole blood ^{131}I concentration and whole body retention for 4 days administration of tracer dosages. Whole body retention may be calculated from urinary excretion or by counting the patient at a suitable distance from an uncollimated scintillation crystal. The results indicate that 100 -200 mci (3.7-7.4 M Bq) usually eradicates uptake in iodine concentrating tissue in the thyroid bed or cervical lymphnodes. On the basis of radiation dosimetry, it was estimated that the minimal dose required to ablate a normal thyroid gland is between 30-40,000 cgy, at times may be as high as 50,000 cGy and requires about one mci (37 M Bq) of ^{131}I per estimated gram of thyroid tissue.

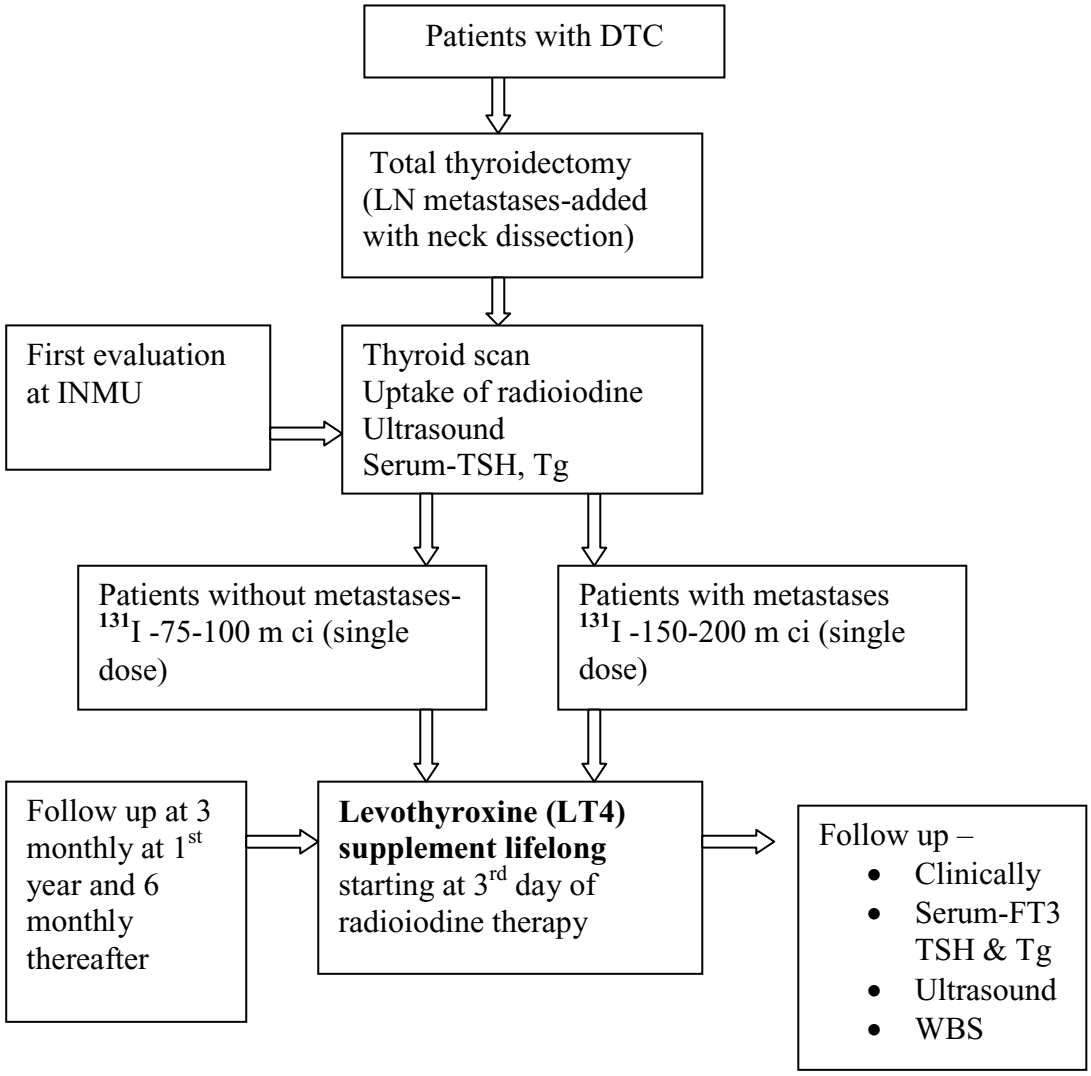

Fig. 4. Simplified fl ow c hart o f management o f p atients w ith d ifferentiated th yroid carcinoma at Institute of Nuclear Medicine and Ultrasound (INMU), Dhaka. WBS- whole body scan.

Ablation criteria:

Ablation of the thyroid remnant was considered to be complete when radioiodine uptake (RAIU) was less than 0.1% , there was no visual evidence of ^{131}I concentration on the 1:1 dot scan and serum Tg level was less than 10 ng/ml. The criterion for partial ablation was the visualization of discrete concentration of ^{131}I in the thyroid bed even though the uptake was less than 0.1% (Cooper DS et al, 2006; Luster M et al., 2008).

2.3.3 TSH suppression therapy of levothyroxine (LT4)

Historically, Von Eiselberg in 1894 described the necessity of thyroid hormone replacement in a woman having thyroid carcinoma who had developed hypothyroid state after thyroidectomy. He observed she became euthyroid sometime later when her sternal metastasis began to grow indicating presence of functioning tissue that produced thyroid hormones. Sir Thomas Dunhill in 1937 diagnosed two children with thyroid carcinoma who subsequently developed recurrence. Those metastases large growths disappeared with the treatment of large dose of thyroxine. Presently also, patients of thyroid carcinoma treated with surgery and subsequent radioiodine ablative therapy receive thyroxine supplement life long starting from 3 days after radioiodine therapy. Suppression of TSH using supraphysiologic doses of LT4 is used commonly to treat patients with thyroid cancer in an effort to decrease the risk of recurrence (Anthony D and Toft MD; Cooper DS et al., 2006; Schlumberger M et al., 2004). Differentiated thyroid cancer expresses the thyrotropin receptor on the cell membrane. Response to TSH stimulation acts by increasing adenylate cyclase activity, leading to cAMP production, the expression of several thyroid- specific proteins (thyroglobulin, sodium iodide symporter) and by increasing the rates of cell growth (Derwahl M et al., 1999; Pujol P et al., 1996). Retrospective studies demonstrated that TSH suppression to below 0.1 mU/ml may improves outcomes in high-risk patients with thyroid cancer, although no such evidence of benefit has been documented in low- risk patients (Derwahl M et al., 1999; Green WL., 2005; Pujol P et al., 1996) . Adverse effects of TSH suppression may include the known consequences of subclinical thyrotoxicosis, including exacerbation of angina in

patients with ischaemic heart disease, increased risk for atrial fibrillation and increased risk of osteoporosis in postmenopausal women (Ladenson P W, 1991; Pujol P et al., 1996).

American Thyroid Association recommended initial thyrotropin (TSH) suppression to below 0.1 mIU/ml in high risk patients and maintenance of the TSH at or slightly below the lower limit of normal (0.1-0.5 mIU/L) is appropriate for low risk patients (Cooper DS et al., 2006, Derwahl M et al., 1999; Polyzos SA et al., 2007). There are several recommendations for dosing of LT4 replacement. Mostly preferred method of LT4 dosing is the initial supplement based on total body weight (2.5±5 µ gm/kg /total body weight) in case of patients with DTC (Burmeister L et al., 1992), thereafter adjustment of TSH at expected level doing follow up blood hormone levels at 6-12 months interval. This chosen method was not effective to maintain expected TSH level in 33% patients who were taking LT4 as evaluated by National Health and Nutrition Examination Survey of United States of America (Green WL, 2005). Santini F et al (2005) have shown in their study that LT4 dose is greatly dependent on lean body mass. Age and sex related differences in LT4 needs reflect different proportions of lean mass over total body weight. LT4 dosing on LBM could be used to achieve target level of hormone replacement quickly particularly in obese patients who have high fat mass. The obesity is reaching epidemic proportions, with the USA, UK and Australia recording a prevalence of 20% in adult population (Green B and Duffull SB, 2004). In developing country like Bangladesh the obesity is becoming more prevalent in urban population compared to rural population. Obesity is to be counted in calculating dose. On the other hand, athletes have high lean body mass, so they need more dose of LT4 than persons having same total body weight (Santini F et al, 2005, Green B and Duffull SB, 2004). Mild increment of LT4 dose may cause the fall of TSH level mildly to subnormal level, conversely a decrease in dose by 25 µ gm caused the rise of the TSH level in almost in all subjects to above normal range (Green WL, 2005). A physician should not be overzealous to prescribe any drug strictly following the single method for dosing. Physician should think other influencing factors on the pharmacokinetics of the drug. There are several known factors that may change the dose of LT4. Absorption

of L T4 may b e i nterfered by certain drugs s uch as chl estipol, cholestyramine, ferrous sulfate, aluminum hydroxide antacids and calcium salts. In that case taking LT4 a nd the abov e mentioned dr ugs a t di fferent t ime a nd r eadjustment of dos age may solve the problem. Soya protein and high fiber diet may inhibit its absorption. Other drugs, such as phenobarbital, phenytoin and carbamazepine and antitubercular agent rifampicin may accelerate the metabolism of LT4, in case of celiac sprue and malabsorption dose of LT4 are to be increased (Green WL, 2005).

2.4 Cardiovascular effects of thyroid hormone

Cardiovascular manifestations of hyperthyroidism were observed in first mentioned thyrotoxicosis patient. Caleb Hillier Parry described his first case, he saw in 1786, was a woman with goiter and palpitations. He noted "each systole shook the whole thorax" (Ladenson PW, 1990). Later Robert James Graves described palpitation and enlargement of thyroid gland in 1835 (Ching CW, 1996).

It has been shown that untreated thyrotoxicosis results in increased heart rate, raised systolic bl ood pr essure, a nd ve ntricular diastolic and s ystolic f unction c hanges. Hyperthyroidism in both humans and experimental animals leads to left ventricular hypertrophy. This car diac manifestation is pr imarily the r esult of i ncreased w ork imposed on t he he art t hrough i ncreases in ha emodynamic l oad. T hyroid hor mone exerts t heir ef fects on heart di rectly and via pe ripheral va scular s ystem (Mintz G, 1991; Klein I, 1990; Klein I and Danzi S, 2007; Ladenson PW, 1993). The thyroid gland primarily secretes T_4 (≈85%), w hich i s c onverted t o T_3 by 5' - monodeiodination in the liver, kidney, and skeletal muscle (Klein I and Danzi S et al., 200 7). The s mall u nbound (free) f raction of T 3 i s r esponsible f or bi ologic activity (Granner D K, 2005) . The he art r elies mainly on s erum T 3 because no significant myocyte intracellular deiodinase activity takes place in heart. T3, and not T4, is transported into the myocyte. T3 combines with its receptors and enters the nucleus, where it promotes the expression of some genes and inhibits the expression of ot hers. T hose t hat are s timulated i nclude genes f or • –myosin he avy chain, sarcoplasmic reticulum Ca^{2+} ATPase, •-adrenergic r eceptors, G pr oteins, Na+- K+

ATPase and certain k+ channels. Those that are inhibited include the genes for •-myosin heavy chain, phospholamban, two types of adenylyl cyclase, T3 nuclear receptors and the Na+- Ca2+ exchanger (Fig. 6.). The net result is increased heart rate and force of contraction. (Haider AW, 1998; Pachucki J et al., 1999; Ganong W, 2005; Klein I and Danzi S, 2007).

The heart contains two myosin heavy chain (MHC) isoforms, • –MHC and •-MHC. They are encoded by two highly homologous genes located in tandem in humans on the short arm of chromosome 17. Each myosin molecule consists of two heavy chains and two pairs of light chains. The myosin containing •-MHC has less ATPase activity than the myosin containing • –MHC. • –MHC predominates in the atria in adults and its levels are increased by treatment of thyroid hormone. This increases the speed of cardiac contraction.

Thyroid hormones cause extra heat production which in turn activates heat-dissipating mechanisms. Peripheral resistance decreases because of cutaneous vasodilation and this increases levels of renal Na+ and water absorption, expanding blood volume (Ganong W, 2005; Klein I and Danzi S, 2007).

Thyroid hormones stimulate renin synthesis independently of sympathetic nervous system. Infusion of supraphysiologic doses of thyroxine in rat results in thyroxine and triiodothyronine concentrations in the kidneys. Kidney to plasma ratio of T3 levels of 10.7 to 1 suggests trapping of circulating T3 or conversion of LT4 into T3 by type iodothyronine-deiodinase in renal parenchyma. This, in turn may explain the activation of the renin- angiotensin system during prolonged LT4 treatment at TSH suppressive dose and the consequent sodium reabsortion and increase in blood pressure. However, the activation of the renin-angiotensin-aldosterone system may also be secondary to the thyroid hormone induced decrease in systemic vascular resistance. Increased thyroid hormone level increases atrial natreuretic peptide levels and nitric oxide synthase activity, these factors may protect heart mainly against the increase in diastolic blood pressure, but not against the development of the systolic hypertension characteristic of hyperthyroidism (Botella-Carretero JI et al., 2004).

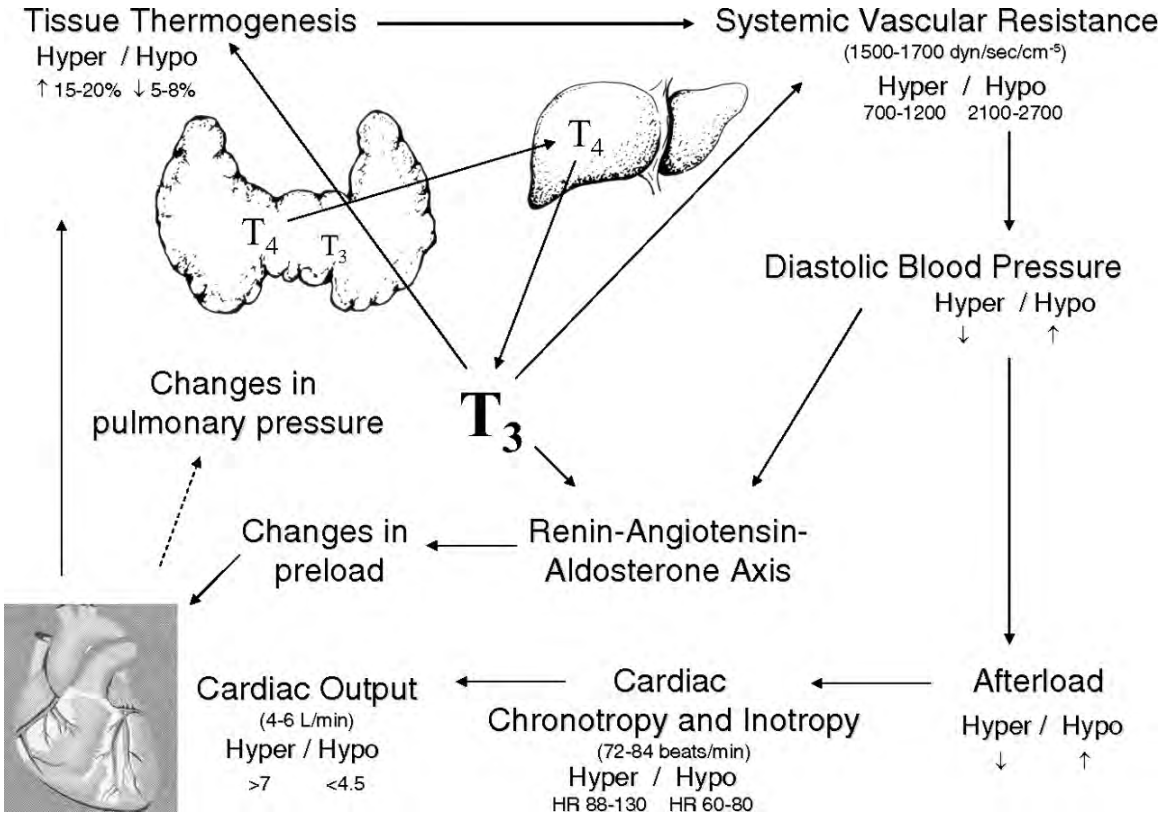

Fig. 5. Effects of thyroid hormone on cardiovascular hemodynamics (Klein I and Danzi S, 2007). Hyper - hyperthyroidism; hypo- hypothyroidism.

T3 affects tissue thermogenesis and increase tissue heat production increasing $\mathbf{O_2}$ consumption, which in turn decreased systemic vascular resistance. In this situation, diastolic blood pressure decreases and lowers afterload. As a result, chronotropic and ionotropic activity increase causing increased heart rate. Thus cardiac output is increased. On the other hand, decreased diastolic blood pressure stimulates renin-angiotensin mechanism increasing water and salt absorption and enhances preload. As a result, cardiac output increases- all these effects of thyroid hormones on hemodynamics are shown in Fig. 5.

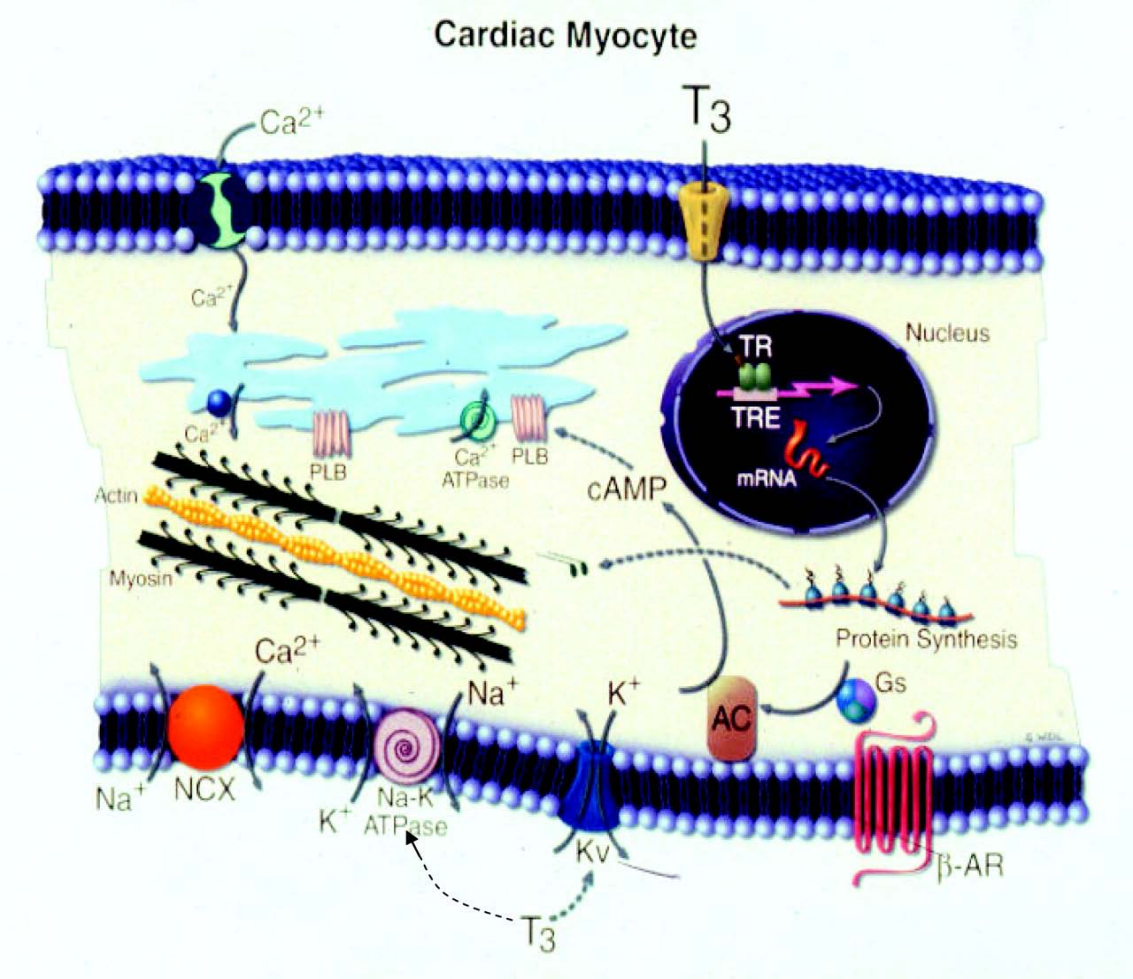

Fig. 6. Mechanism of action of T_3 on the cardiac myocyte. AC-adenylyl cyclase; ß-AR- ß adrenergic receptor; Gs-guanine nucleotide binding protein; Kv- voltage- gated potassium channels; NCX- sodium calcium exchanger and PLB- phospholamban (Klein I and Danzi S, 2007)

T_3 has both genomic and nongenomic effects on the cardiac myocyte. Genomic mechanisms involve T_3 binding to TRs (thyroid receptors), which regulate transcription of specific cardiac genes. Nongenomic mechanisms include direct modulation of membrane ion channels as indicated by the dashed arrows (Fig. 6).

2.5 An introduction of electrocardiogram and its clinical role

The parts of the heart normally beat in orderly sequence which include contraction of the atria (atrial systole) followed by ventricular contraction (ventricular systole) and during diastole all four chambers are relaxed. Electrical activity is a basic characteristic of the heart and is the stimulus for cardiac contraction. Fluctuations in potential that represent the algebric sum of the action potentials of myocardial fibers can be recorded extracellularly because the body fluids are good conductors. The record of these potential fluctuations during the cardiac cycle is the electrocardiogram (ECG). Heart diseases are commonly associated with disturbances of electrical function. The ECG has many uses: it can serve as an independent marker of myocardial disease; it can reflect anatomic, haemodynamic, molecular, ionic, and drug induced abnormalities of the heart. It can provide information that is essential for the proper diagnosis and therapy of many cardiac problems and most commonly used laboratory procedure for the diagnosis of heart disease and one of the most commonly employed tests in medicine (Julian DG, 2005; Castellanos A, 2008).

2.6 An introduction to Echocardiography

Echocardiography is the ultrasound imaging of he art. It is a frequently used dominant diagnostic imaging modality giving anatomical as well as functional information about he art. Use of echocardiography becomes versatile due to its portability in emergency room, operation theatre and intensive care unit (Lang MR et al, 2005).

Different measurements of chambers of heart including diameters of ventricles and atria, interventricular septal wall and walls thickness, left ventricular mass, wall motion and vulvular integrity can be potentially evaluated by 2D and M mode echocardiographic methods. Diastolic and systolic functions can be evaluated by measuring velocities through mitral and tricuspid valves by pulsed Doppler and color Doppler imaging and spectral analysis (Dodson JA, 2009).

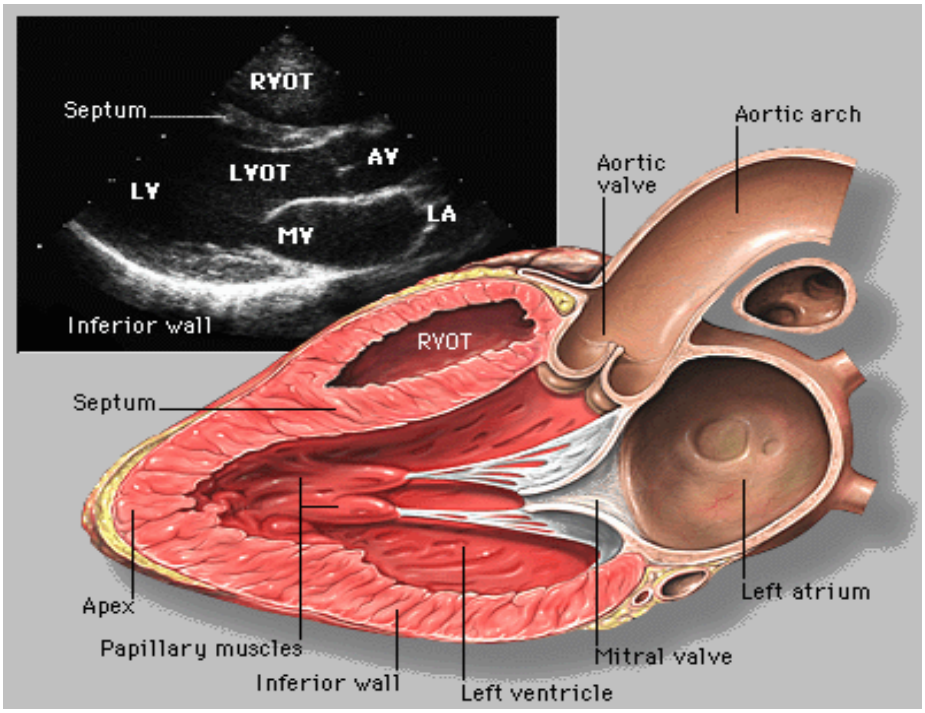

Fig. 7. Long sagittal section of heart and corresponding echocardiographic view in left parasternal approach (Wikipedia, 2009)

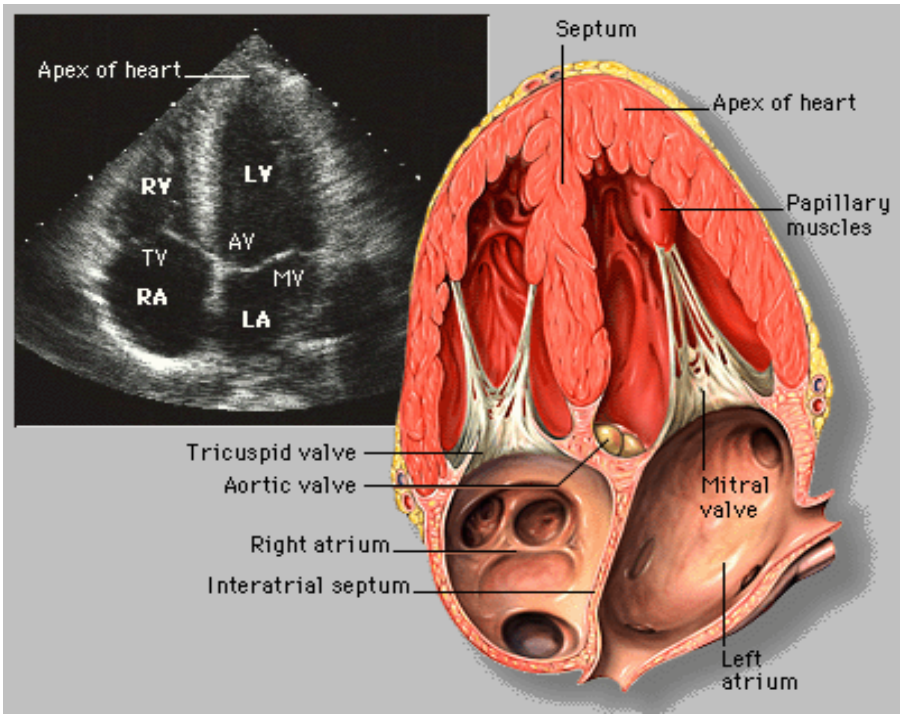

Fig. 8. Apical 4- chamber view of heart and corresponding Echocardiographic image (Wikipedia 2010).

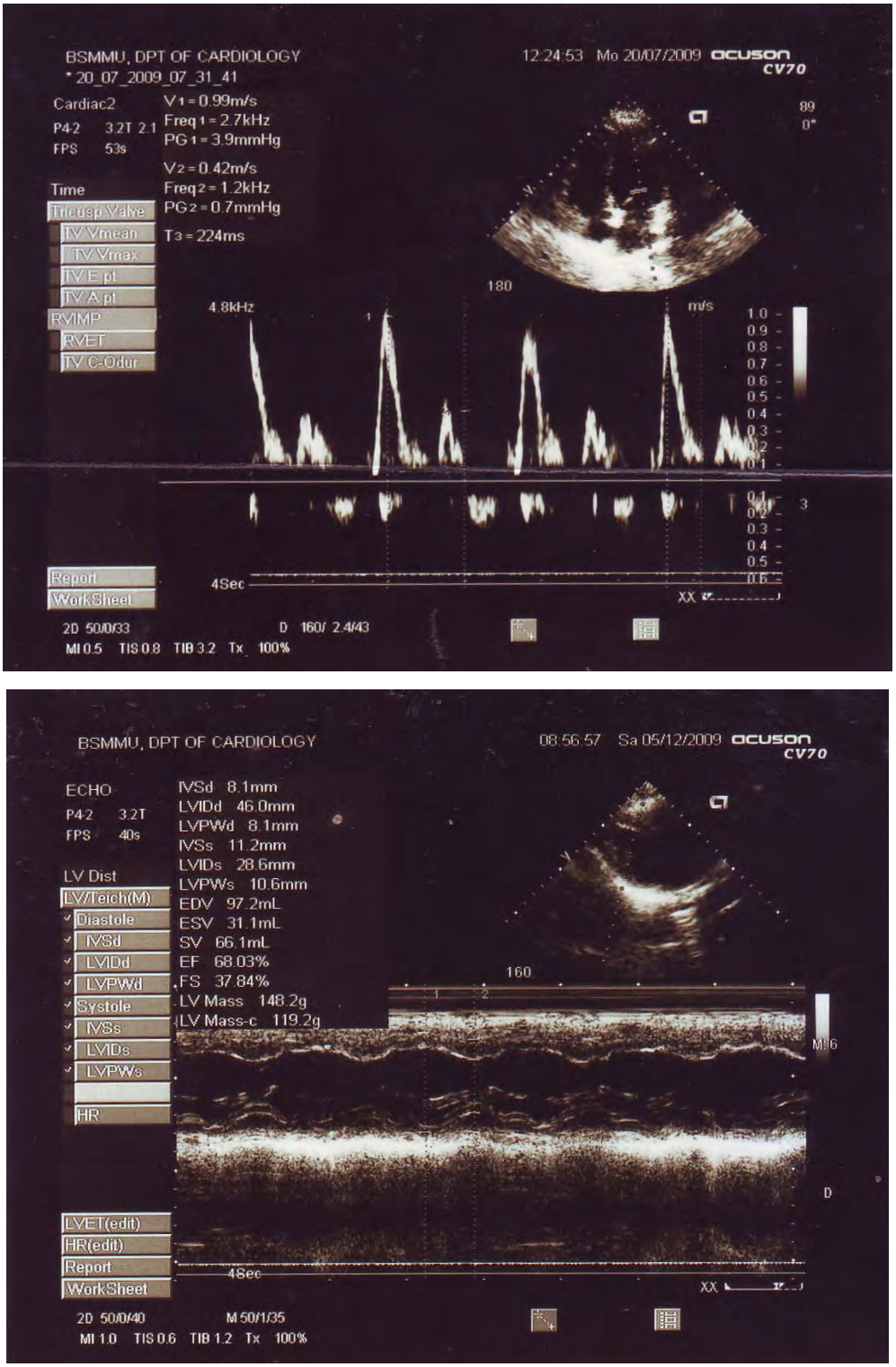

Fig. 9. Upper: Normal pattern of diastolic E and A wave through mitral valve in spectral analysis of Doppler e chocardiography. Lower: M mode an d l ong scan o f heart f or l eft ventricular wall measurements.

Echocardiographic methods and techniques have been improved tremendously over the last decades with the introduction of higher frequency transducers, tissue harmonic imaging, fully digital machine, left-sided contrast agents and other technical advancements (Lang MR et al., 2006; De Maria et al., 2008).

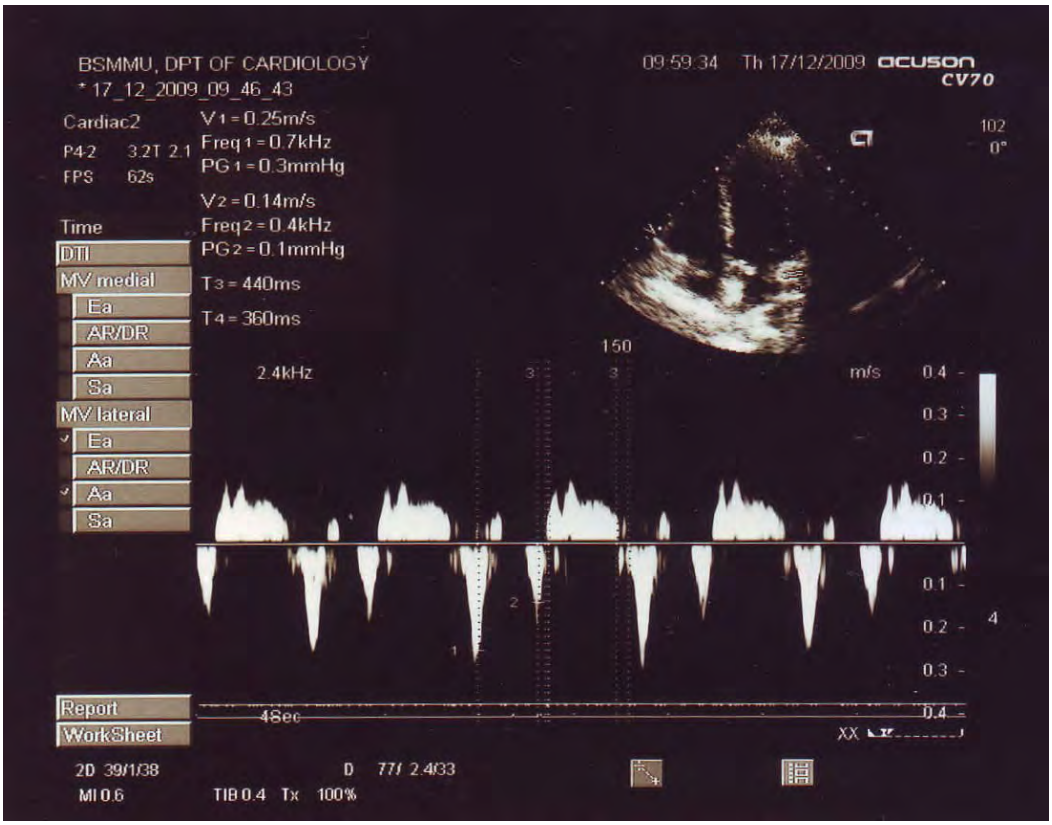

Fig. 10. Normal pattern of Tissue Doppler Imaging in lateral wall of mitral annulus showing Em (25 cm/sec) and Am (14 cm/sec) waves.

Recently, Tissue Doppler Imaging (TDI) has been developed through proper modification of the hardware and software of the ultrasound platform. It allows the analysis of velocity signals having high amplitude and low frequency originating from tissue, which are not usually detected by Doppler examination. TDI allows the non-invasive calculation of time intervals and velocities of myocardial contraction and relaxation during various phases of cardiac cycle by using post processing application software. Although it gives information of regional velocity of myocardium, still it is influenced by global heart movements. To overcome the

limitation strain imaging introduced the concept of myocardial deformation as a sensitive index of contractile capacity intrinsic to myocardium (Citro R et al., 2008)

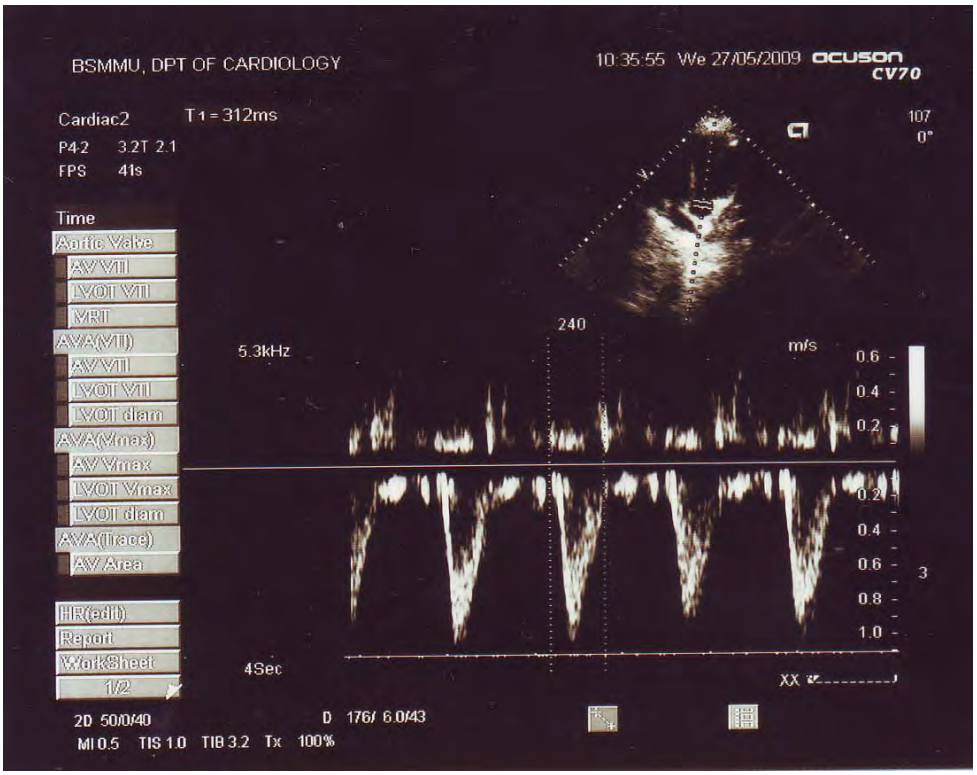

Fig. 11. Normal Peak aortic velocity in spectral analysis of Doppler Echocardiography.

2.7 Exercise Tolerance Test (ETT)

Exercise testing is a noninvasive tool to evaluate the cardiovascular system's response to exercise under carefully controlled conditions. Exercise is the body's most common physiologic stress and it places major demands on the cardiopulmonary system (Engel G and Froelicher VF, 2008; Vanhees L et al., 2005). Thus, exercise can be considered the most practical test of cardiac perfusion and function. It remains an important testing method of diagnostic, prognostic and functional information. The adaptation that occurs during an exercise test allow the body to increase its resting metabolic rate up to 20 times, during which time cardiac

output can increase as much as 6 times. The magnitude of these adjustments is dependent on age, gender, body size, type of exercise fitness and the presence or absence of heart disease.

Regarding physiology of exercise two basic principles are important to understand exercise testing. The first physiologic principle: total body oxygen uptake and second principle is myocardial oxygen uptake and both are distinct in their determinants. Total body or ventilatory oxygen uptake [volume oxygen consumption (VO)] is the amount of oxygen that is extracted from inspired air as the body performs work. The determinants of VO_2 are cardiac output and the peripheral arteriovenous oxygen difference. Maximal arteriovenous difference is physiologically limited to roughly 15-17 ml/dl. Thus maximal arteriovenous difference behaves more or less as a constant, making maximal oxygen uptake an indirect estimate of maximal cardiac output (Vanhees L et al., 2005)

Myocardial oxygen uptake is the uptake is the amount of oxygen consumed by the heart muscle. The determinants of myocardial oxygen uptake include intramyocardial wall tension (left ventricular pressure and end diastolic volume), contractility and heart rate. It has been shown that myocardial oxygen uptake can be reasonably estimated by the product of heart rate and systolic blood pressure (double product).

The second principle is one of pathophysiology: considerable interaction takes place between the exercise test manifestations of abnormalities in myocardial perfusion and function. The electrocardiographic response and angina are closely related to myocardial ischemia. Exercise capacity, systolic blood pressure, and heart rate responses to exercise can be determined by the presence of myocardial ischemia, myocardial dysfunction or responses in the periphery.

Exercise testing fundamentally involves the measurement of work, there are several concepts regarding work. The common biologic measure of total body work is the oxygen uptake, which is usually expressed as a rate in liters per minute. MET stands

for 'metabolic equivalent' or 'metabolic equivalent tasks', is a term commonly used clinically to express the oxygen requirement of the work rate during an exercise test on a treadmill or cycle ergo meter. MET is the amount of energy used by an average adult at rest. An average adult needs 1 calorie for every kg body weight per hour while sitting or sleeping (internet: Health drgily.com). One MET is equated with the resting metabolic rate (approximately 3.5 ml of O_2/kg/min).

Clinically significant Metabolic Equivalents for maximum exercise

1 MET	Resting
2 METs	Level walking at 2 mph
4 METs	Level walking at 4 mph
< 5 METs	Poor prognosis; peak cost of basic activities of daily living
10 METs	Prognosis with medical therapy as good as coronary artery bypass surgery
13 METs	Excellent prognosis regardless of other exercise responses
18 METs	Elite endurance athletes
20 METs	World-class athletes
(Engel G and Froelicher V, 2008)	

The protocol of exercise tolerance test include following:

1. Continuous ECG monitoring
2. A type of activity that can be performed by sedentary, poorly developed and under conditioned subject as well as by the trained athlete.
3. A workload can be varied according to the capacity of the individual. It should give reproducible results and allow comparison with other patients tested.
4. There must be facility of frequent blood pressure measurement before, during and after exercise.
5. Facility of aerobic requirement of individual tested.
6. Maximum safety and minimum discomfort for each individual

7. The highest possible sensitivity and specificity in the discrimination between health and disease.
8. First stage should be long enough for warm up to occur
9. Procedure should be short enough to be practical

2.8. Lean body mass and Dual energy X-ray Absorptiometry

In 1963, single photon absorptiometry (SPA) was described by Cameron and Sorenson. The first commercial dual energy X–ray absorptiometry (DXA) was introduced in 1987 for measurement of bone mineral densitometry (BMD) (Banks LM, 2001). Lean body mass is the weight of muscles, organs and bone without fat and bone mineral concentration. Total body mass was calculated as follows: total body mass=total bone mineral concentration (BMC) + total fat mass + total lean mass (Kim J et al., 2006; Stikkelbroeck NMML et al., 2003). DXA has been shown to be an accurate and precise technique associated with a low dose of radiation for measuring body composition. Unlike neutron activation analysis or underwater weighing, DXA is a simple and quick procedure and can be performed on readily available equipment. DXA is a method of estimating bone mineral utilizing a pencil beam x-ray beam filtered to provide the two distinct energy peaks necessary to distinguish bone from soft tissue. Dual Na-I (sodium iodide) scintillation crystals or are used to detect the X-ray energies separately. The technique for separating X-ray output into two distinct energy levels is known as K-edge filtration. One type of DXA scanner machine uses samarium as the filter material because it produces energy peaks at 46.8 Kev and 80 kev, which have proven to be the most effective at differentiating between soft tissue and bony tissue. Direct –Digital CZT (Cadmium Zinc Telluride) scintillation detector is used in GE healthcare Prodigy DXA machine. Na-I scintillation crystals of 7.0 mm thickness are used for high energy detection and that of 0.3 mm thickness is used for low energy detection. The DXA total body measurement provides a comparison with the normal age and sex matched range, together with information on BMD (Bone Mineral Density) (g cm^2), BMC (g), percentage fat, fat tissue mass (g), lean tissue mass (gm) and total tissue mass for the whole body composition (Andreoli A et al., 2009).

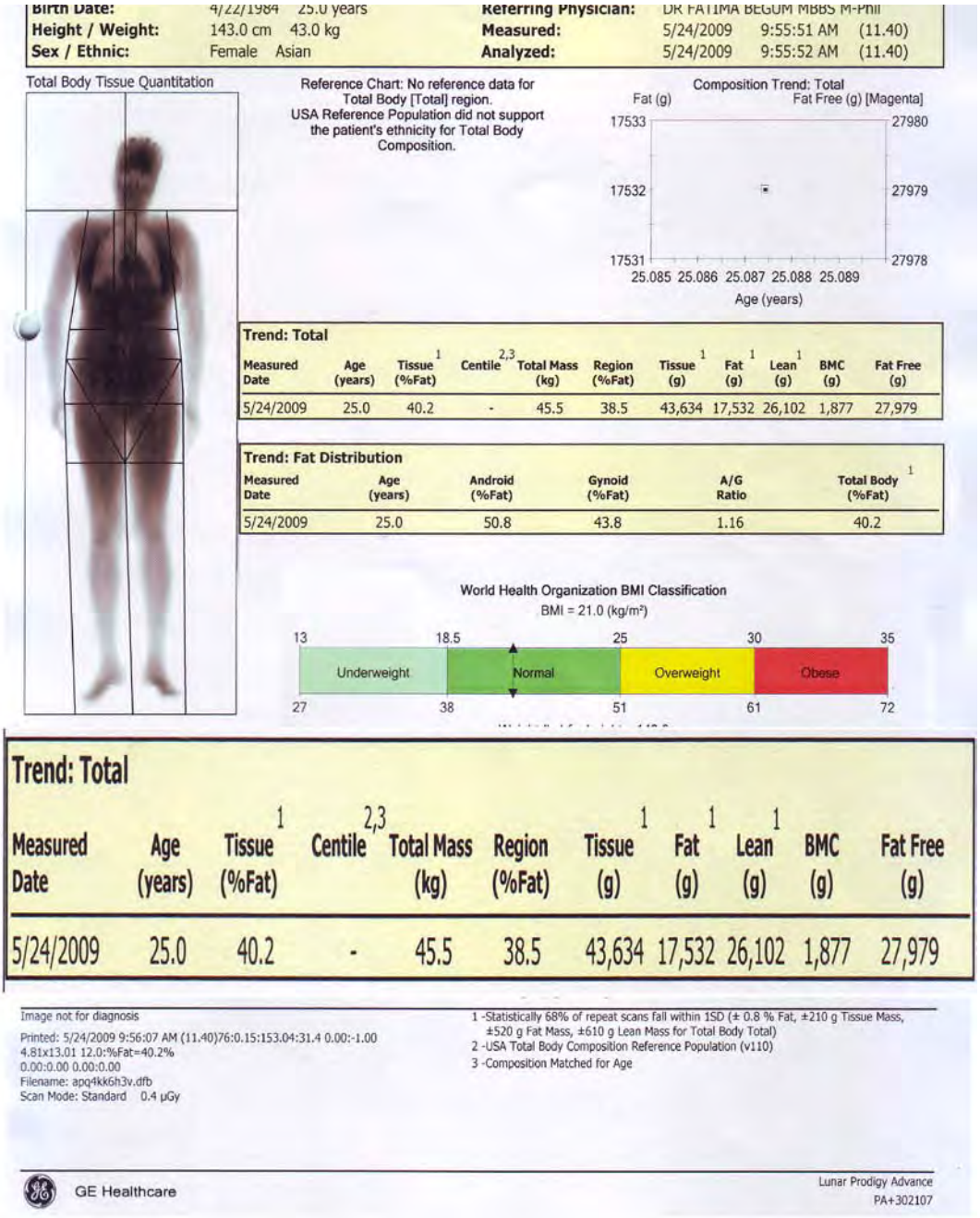

Fig. 12. Whole body DXA for lean body mass of a 29 years old female patient with DTC.

DXA body composition measurements have been used in a number of clinical settings, which include the alteration of body composition and tissue distribution with disease, gender differences and the effect of menopause and therapy (Linda, 2000, Deurenberg et al., 2002). Lean body mass is a potentially useful predictor of

the pharmacokinetics behavior of drugs that are highly water soluble (Green B and Dufful SB, 2004).

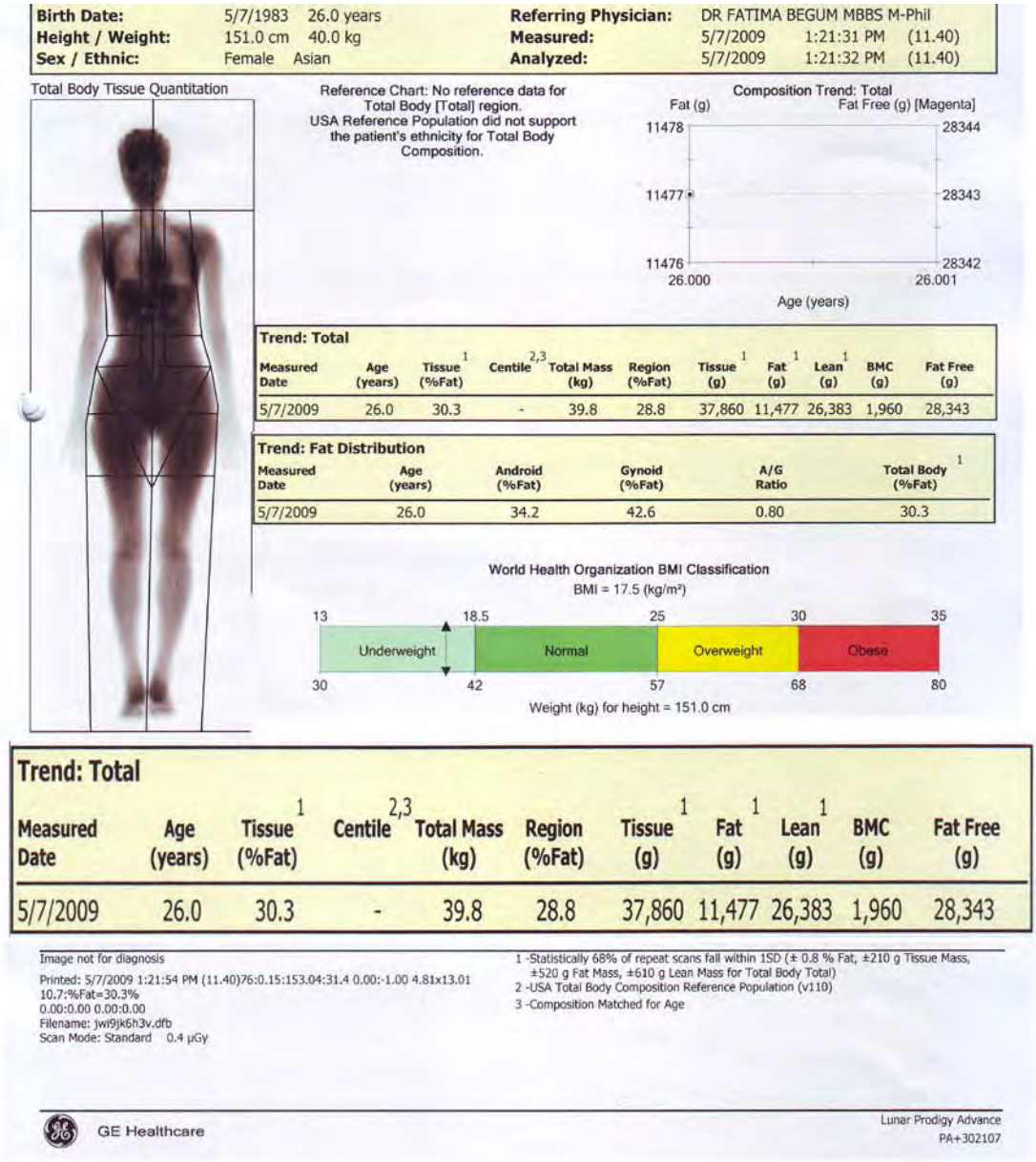

Fig. 13. Whole body DXA for estimation of lean body mass in 21 year old female patient with DTC**.**

Chapter III

Materials and Methods

Chapter III

Materials and Methods

3.1 Place of study

The current study was conducted at Institute of Nuclear Medicine and Ultrasound, Dhaka under Bangladesh Atomic Energy Commission at Bangabandhu Sheikh Mujib Medical University (BSMMU) campus and Department of Cardiology, BSMMU campus, Dhaka.

3.2 Study Subjects

Seventy two patients with differentiated thyroid carcinoma of low risk group (T1, N0, M0) treated with total thyroidectomy and ablated by radioiodine therapy were recruited randomly in this study for experimental group. They were referred to Institute of Nuclear Medicine and Ultrasound, Dhaka, for radioiodine ablative therapy after total thyroidectomy during the year 2007-2009. All patients were diagnosed as papillary thyroid carcinoma on histological examination. Ten patients refused to participate in subsequent visits. Two patients were excluded from the study as their serum thyroglobulin (Tg) levels were high, so they could have been suffered from micrometastases. Age, BSA and lifestyle matched 23 healthy adults were taken as control subjects. Informed consent had been taken from experimental subjects and all patients before participation in the present study. They were informed about the risk and benefit of the present study before participation. All control and patients were explained in Bangla and the consent form was prepared also in Bangla.

Inclusion criteria of patients in experimental group includes patients with differentiated thyroid carcinoma with low risk group, who had undergone total

thyroidectomy and subsequently received radioiodine ablative therapy, young age group age range 20-39 years and serum Tg level is below 2 ngm/L.

Exclusion criteria: Patients who have any sort of cardiac dysfunction, pulmonary disease and patients in high risk of recurrence and already presented with metastasis, with ECG abnormality, or uninterpretable ECG, patients who have any deformity, not fit for ETT, diabetes mellitus have been excluded. Healthy adults age range, 20-39 years, euthyroid state with no chronic cardiopulmonary disease, diabetes and deformity were included in volunteer group.

Initially baseline study of cardiac functions such as clinical symptoms and pulse rate, respiratory rate and blood pressure have been recorded and symptom rating scale score (Klein I, 1988) were evaluated in all subjects. Then patients of both control and experimental groups have been evaluated by electrocardiogram, echocardiography and exercise tolerance test (ETT). Then experimental groups have been requested to come after 2 months of radioiodine treatment. Then bone mineral density and whole body composition had been assessed and lean body mass are calculated in 30 patients of among all 60 patients and regarded as Group-I. Patients of Group-I received LT4 oral levothyroxine on the basis of lean body mass. Rest of the patients was regarded as group-II received conventional dose of LT4 (200 µ gm / day). Levothyroxine of same reputed brand was taken by each patient in the morning in empty stomach, half an hour before breakfast. It was advised to take drugs separately which hamper absorption of LT4 specially calcium tablet. Patients of both groups have been advised to come 3 monthly for clinical and biochemical follow up for routine checkup. Cardiac functions were assessment and ETT had been assessed at the beginning of treatment and after 6 -12 months at the Department of Cardiology, Bangabandhu Sheikh Mujib Medical University. The data generated from the study were computerized and appropriate statistical analysis had been done.

3.3 Hormone assay of FT3, FT4 and TSH

Serum TSH concentration was measured by an ultrasensitive immunoradiometric assay kit (IMK-432), Beijing Atom Hightech Co., LTD. with a detection limit of 0.04 mIU/L. The coefficient variation of TSH assay at 0.04 m IU/L and at 0.1mU/L. was 10 %. Serum FT3 was measured by radioimmunoassay methods (RIA kit, IMK-436, HTA Co). Euthyroid (normal) reference range of FT3 is 2.8 - 9.5 pmol/L. Serum FT4 was determined by two-step radioimmunoassay (IMK-435) Department of Isotope, China. The normal range of FT4 is 9.5 -25.5 pmol/L. The measurements were performed during FT4 suppressive therapy at 2 months and in every follow up visit and after 6-12 months in both groups of patients and healthy adults initially.

3.4 Procedures of Electrocardiogram (ECG)

A standard 9-leads electrocardiogram was performed by K D Yasen ECG-903 machine on each patient at first visit and last visit and in healthy volunteers. A conventional ECG consists of tracings from 12 leads. The term 'lead' refers to the ECG obtained as a result of recording the difference in potential between a pair of electrodes. Conventional unipolar chest leads are:

V1 is placed in the fourth intercostals space just right to sternum
V2 is placed in the fourth intercostals space just left to sternum
V3 is placed midway between V2 and V4
V4 is placed in 5 th intercostals space in left midclavicular line
V5 is placed in the left anterior axillary line at the same horizontal level as V4
V6 is placed in the left midaxillary line at the same horizontal level as V4.

The exploring electrode chest lead is connected to the positive pole of ECG and the negative to the central terminal of Wilson. Modified unipolar limb leads are augment (a) lead. They are designated as follows: aVR, right arm lead; aVL, left arm lead and aVF, left foot lead.

Normally, The ECGs are recorded at a rate of 25 mm/sec. The ECG is printed with thin vertical lines 1 mm apart and thick vertical lines 5 mm between two thick lines 0.02 sec. If the heart rate is regular, the rate can be counted by dividing the number of small squares between two consecutive R waves into 1500 or large squares into 300. There are also thin horizontal lines at 1-mm interval and thick horizontal lines at 5 mm intervals. An ECG recording is standardized so that I mV gives a deflection of 10 mm on the paper. The height of a deflection indicates its voltage. The spread of the cardiac impulse gives rise to the main deflections of the ECG: P, QRS and T waves.

The P wave represents the atrial depolarization.
The PR interval represents the time taken for the cardiac impulse to spread over the atrium and through the AV node and His-Purkinje system.
The QRS complex represents ventricular depolarization.
The T wave represents ventricular repolarization.

3.5 Methods of Exercise Tolerance Test

The exercise test protocol was performed in the morning, at least two hours after last meal. To determine the relative physical fitness of each subject, information was collected on the patient's level of physical activity. Exercise testing was then performed on Marquette Medical System, Series 2000 treadmill ergometer using Bruce protocol. At the first stage the treadmill speed and slope were (1.7 mph) and (0%) respectively to allow the patients to warm up. At the second stage the treadmill slope and speed were increased according to the Bruce protocol (Engel G and Froelicher VF, 2008)

Blood pressure was measured utilizing a mercury sphygmomanometer at rest and at the end of each stage of exercise and until return to baseline into recovery. Heart rate was measured in every stage of exercise and at recovery. ECG was continuously monitored during the stage. Codel Master ECG and BP monitor has been utilized.

The test was stopped upon the onset of severe fatigue or achievement of maximum predicted heart rate. Heart rate, systolic blood pressure and diastolic blood pressure were measured during exercise and peak exercise. MET (metabolic equivalent) was measured, which indicated the amount of energy utilized by a person during exercise. A double product, used as an index of cardiac workload, was calculated as the product of heart rate and systolic blood pressure.

3.6 Procedures of Echocardiography

A complete M (motion) mode and 2D (two dimensional), color Doppler, spectral and tissue Doppler Echocardiographic evaluation were performed by using an ultrasound imaging system Siemens Acuson CV70 equipped with a 2.8 -3.5 megahertz transducer. Echocardiographic studies were performed by a single blinded experienced cardiologist, unaware of study protocol. Echocardiographic recordings were made with subjects in left lateral decubitus position, with the head elevated 20-30 degrees using conventional para sternal and apical views, according to the standardization of the American Society of Echocardiography (ACC/ AHA guidelines 1997, Lang R., 2006; De Maria, 2008;). The following parameters were assessed using 2D images from the para sternal long-axis acoustic window: left ventricular internal diameter at end diastole (LVIDD; millimeters), left ventricular internal diameter during systole (LVIDS; millimeters), interventricular septum thickness (IVST; millimeters) and posterior wall thickness (PWT; millimeters) at end diastole.

Left ventricular systolic function was investigated by determining ejection phase indices, such as the percentages of fraction shortening [FS%=LVIDD-LVIDS/LVIDD (percentage)] and rate adjusted mean velocity of fiber shortening (mVCFc; circumferences/sec) was calculated by dividing the fraction shortening by ejection time.

Left ventricular mass (LVM) was calculated by using Penn convention, with the following regression corrected cube formula: LVM=0.832 [1.04 {(IVST+ LVIDD+PWT)^3 − (LVIDD)^3] + 0.6 g. LVM was indexed by body surface area [LVMi=LVM/body surface area (grams/m^2)] (Biondi B et al., 2000)

Doppler tracings were acquired during quiet respiration with the transducer positioned at, or slightly left of the apical impulse, according to the previously reported method at averaging five consecutive cycles at a paper speed of 50 mm/100 mm/sec. Care was taken to place the sample volume at the mitral valve annulus and moving it toward the tips of the mitral valve at the point where maximal velocity was measured. The wave forms chosen were those with more defined morphology showing a narrow range of frequency shift and consequently minimal spectral broadening. The following parameters were measured and calculated on mitral flow velocimetry: maximal early diastolic flow (E, cm/sec), maximal late diastolic flow (A, cm/sec), E/A ratio and early flow deceleration time (Dct). Dct is the time interval from the point of peak early filling of the ventricle until the point of diastasis in middiastole, determined and measured by an extrapolation of the rate of decline of the flow velocity from the E point to the baseline. Isovolumic relaxation time (*i. e.* the time interval from aortic valve closure to the onset of early diastolic flow) was obtained by simultaneous recording of aortic and mitral flow by continuous –wave Doppler tracings. Aortic peak velocity and mean aortic acceleration were obtained by aortic flow velocimetry. In particular, mean aortic acceleration was obtained by dividing the peak flow velocity by the acceleration time.

Tissue Doppler imaging (TDI) of the mitral annular motion was recorded from the apical 4-chamber view. A 2 mm sample was placed sequentially at the lateral mitral annulus. Early (Em) and late (Am) diastolic annular velocities were measured from TDI images. The ratio of mitral E to TDI Em was calculated using lateral (E/Em lat).

The LV Tei index (myocardial performance index), a combined index of systolic and diastolic function, was also calculated using mitral inflow velocity and LV outflow velocity as previously reported. Tei index, defined as the sum of isovolumic contraction (at the start of the ventricular systole, mitral and atrioventricular (AV) valve closed before opening of aortic and pulmonary valves, muscles of ventricles shorten and intraventricular pressure rises; IVRT- at early diastole- time period between aortic and pulmonary valves closure, ventricular pressure drops and before opening mitral and AV valves) and relaxation times divided by ejection time, has been proposed to express global left ventricular function. Tei index= (IVCT+IVRT)/ET is a conceptually new, simple and reproducible Doppler index of combined systolic and diastolic myocardial performance in patients with primary myocardial systolic dysfunction. (Keser N et al., 2005; Karatzis EN et al., 2009; Citro R et al., 2008)

Left ventricular systolic function was expressed as fractional shortening (FS %), which was considered normal if $\geq$ 29%. LV hypertrophy was defined as LVMi greater than 134 gm/m^2 in men and greater than 110 gm / m^2 in women (Biondi B et al., 1993).

Body surface area was measured by

BSA =TBW (kg) $^{0.425}$ × Ht (m) $^{0.725}$ × 0.007184 (Green B and Duffull SB, 2004)

3.7 Measurement of Lean body mass by Dual Energy X-ray absorptiometry

The subject's body weight and height were measured. Body mass index (BMI) was calculated by weight/ (height)^2 (kg/m^2). Total body mass is calculated by Dual Energy X-ray Absoptiometry (DXA) as follows: Total body mass (TBW) = total bone mineral concentration (BMC) + total fat mass (FM) + total lean mass. Thereby, lean body mass (LBM) = the total body mass − (total fat mass + total BMC) (Stikkelbroeck NMML et al., 2003).

Lean body mass of 30 patients of group-I was estimated by Dual energy X –ray Absorpsiometry (DXA) by GE Health care, Lunar Prodigy Advance PA+301470 at

whole body version at first follow up visit. According to operator's manual, scanning method: its narrow angle fan beam made multiple passes across the patient to acquire multiple images, with each image overlapping the previous one. Then, Multi-view Image Reconstruction was done.

Technical specifications:

enCORE™ Software Platform

Advanced intuitive graphical interface

Multiple Patient directories with Microsoft Access R database

SmartFan™ for scan window optimization and dose reduction

Automated scan mode selection

Autoanalysis™ for a better precision Exam copmparison process**.**

Typical Scan Time and Radiation Dose at best precision

Whole body composition was 4 min 30 seconds: 0.0003 m Gy (<1% CV).

Calibration and Quality Assurance

Automated test program with complete mechanical and electronics tests and global measurement calibration.

Scanning Method

Narrow Fan Beam (4, 5^{o} angle) with Smart Fan and Truview algorithms

X-ray characteristics

Constant potential source at 76 KV

Dose efficient K-edge filter

Detector technology

Direct-Digital CZT (Cadmium Zinc Telluride) detector

Energy sensitive solid state array

Magnification

None-Object-plane measured

Dimensions (L × H × W) and weight

263 ×111 × 128 cm-272 kg (full)

202 × 111 × 128 cm-254 kg (compact)

External shielding

Not required

3.8 Score of signs and symptoms of hyperthyroidism

Hyperthyroid Symptom Rating Scale (SRS) is potentially useful to assess the severity of hyperthyroidism and to assess quality of life (Klein I et al., 1988).

Every patient was evaluated by according to SRS at first and subsequent visits and healthy volunteers were also evaluated by same scale. SRS format is given below.

Hyperthyroid Symptom Rating Scale

	Characteristic	**Score**
	Nervousness	
0	Absent	
1	Anxious only with stress	
2	Occasionally anxious at rest	
3	Often anxious, difficulty working or concentrating	
4	States freely that feels very nervous most	----
	Sweating	
0	Only with activity	
1	At rest but only in warm temperature	
2	At rest in temperate climates, mainly involving the hands and intriginous zones	
3	At rest involving many body areas.	
4	Profusely diaphoretic almost constantly.	------
	Heat intolerane	
0	Normal temperature tolerance.	
1	Periods of feeling warmer than those in the same room	
2	Significant difficulty with heat, requiring air conditioner constantly in the summer time	
3	Excessive difficulty with heat even in temperature climate.	
4	Extreme difficulty with heat, does not feel comfortable even in cold weather as evidenced by lack of need for warm clothing or bed covers.	-------
	Hyperactivity	
0	Normal activity	
1	Increased activity level, increased productivity	
2	Increased productivity; decreased sleep time.	
3	Performs some purposeless activity	
4	Frequent episodes of purposeless activity; unable to sit still	

	during examination	------
	Tremor: Examination of outstretched hands	
0	Absent	
1	Barely perceptible	
2	Tremor demonstrated readily on examination	
3	Marked tremor but able to perform fine motor skills	
4	Hands shake excessively, difficulty performing motor skills.	

	Weakness	
0	Normal strength	
1	Subjective weakness but with normal tolerance	
2	Decreased exercise tolerance to near maximal activity	
3	Decreased tolerance to stair climbing or arising from chair	
4	Extreme weakness such that patient can barely lift objects or walk up stairs	------
	Hyperdynamic precordium	
0	Normal precordium activity apical impulse	
1	Tachycardia, 90 beats per minute with normal apical impulse.	
2	Tachycardia, 90 beats per minute with increased apical impulse	
3	Tachycardia, 110 beats per minute with increased apical impulse	
4	Tachycardia, 110 beats per minute and carotid upstroke both increased, systolic outflow murmur.	------
	Diarrhoea	
0	1 bowel movement (BM) per day; formed stool	
1	2-4 formed BMs per day	
2	1-4 loose stools per day	
3	4 formed BMs per day	
4	4 loose stools per day	------
	Appetite	
0	Appetite normal, no weight loss	
1	Appetite normal, no weight loss	
2	Appetite increased, no weight loss	
3	Appetite increased, weight loss	
4	Appetite decreased, weight loss	------
	Assessment of daily function (degree of incapacitation)	
0	Normal (none)	
1	Minimal impairment (10%)	
2	Mild impairment (30%)	
3	Moderate impairment (60%)	
4	Severe impairment (90%)	

3.9 Statistical analysis

The study was designed to compare patients with differentiated thyroid carcinoma with age and BMI, BSA matched normal healthy controls at the time of enrollment. Sample size was verified at the beginning of study by using online calculator by Lenth 2000, Iowa University, USA (Lenth RV, 2001). Then two groups of patients receiving two protocol of LT4 supplement were included. Cardiac morphology and function by echocardiography and ETT at different time points were evaluated. Values were expressed as mean ± SD with 95% confidence intervals. Statistical analysis was performed by using SPSS, version 13 software packages for windows [Apache Software foundation, USA]. The two tailed unpaired Student's t test was used to compare basal data between control subjects and patients group.

One way ANOVA was used to compare all the clinical, hormone, Echocardiographic and ETT data between patients of Group-I and Group-II at first visit and second visit and between two visits. The post hoc covariates were analyzed at Tukey's HSD (honestly significant difference) test.

A probability (*P)* value less than 0.05 was considered statistically significant.

Chapter IV

Results and discussion

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Results and discussion

4.1 Comparison between baseline data of control subjects and patients with DTC at first follow-up

Patients with differentiated carcinoma of thyroid receive life long LT4 therapy after total thyroidectomy and radioiodine ablative therapy. LT4 is given at TSH suppressive dose to keep the patients in subclinical hyperthyroid state. Low level TSH prevents metastases lowering the stimulus for follicular growth by this hormone (Mazzaferri EL and Kloos RT, 2001). Subsequent follow up strategies vary according to the patient's individual risk. In patients with differentiated thyroid carcinoma, adequate TSH suppression may assure a survival rate of more than 98% at 20 years (De Groot et al., 1990). Treatment schedule or protocol of LT4 supplement slightly differs from institute to institute and from country to country. Some institutes have been practicing LT4 dose at 200 µgm/day/patient irrespective of age, sex, body weight and type of carcinoma for initial 3 months of RIT starting from 3rd day of RIT therapy. Thereafter, LT4 is adjusted with the hormone levels (FT3, FT4 and TSH) to keep the levels in TSH suppressive condition. Recent recommendations by American Thyroid Association (Cooper DS et al., 2006) advocated that patients with high risk thyroid carcinoma are to be maintained in suppressed TSH level condition but patients with low risk of metastases are to be kept in euthyroid state with low normal TSH level. This recommendation is not followed uniformly in different institutes throughout the world. Patients are usually kept in subclinical hyperthyroid state in which they suffer from some symptoms and signs of thyrotoxicosis (Biondi B et al., 2000; Hoftijzer HC et al., 2008). Long term administration of LT4 in TSH suppressive dose has some ill effects on heart such as increased heart rate, atrial fibrillation, left ventricular hypertrophy, systolic and diastolic dysfunction which in turn increases morbidity and mortality of the patients (Biondi B et al., 1993; Klein I and Danzi S et al., 2007; Ladensen PW., 1990; Ladenson PW, 1993). In several studies, it has been shown that chronic replacement

therapy with suppressive doses of levothyroxine impairs quality of life and psychometric functionality in patients DTC (Botella-Carretero JI et al., 2003). The purpose of the present study was to optimize the dose of LT4 on the basis of lean body mass measured by Dual Energy X-ray absorptiometry. Moreover, pharmacokinetics of LT4 depends mostly on lean body mass compartment as levothyroxine is water soluble. The fat mass of body does not contribute in LT4 metabolism. The objective of the present study was to optimize the dose of LT4 depending on lean body mass and prevention of cardiac effects due to chronic overdose of LT4 in carcinoma of thyroid of low risk group.

Initially, 60 consecutive patients with differentiated thyroid carcinoma of low risk group between the age group of 20-39 years were enrolled in the present study. The control group consisted of 23 age, BMI and BSA matched clinically healthy euthyroid volunteers (Table I). All patients were given LT4 at dose of 200 µ gm/day, commencing on 3rd day of the radioiodine ablative therapy. This therapy is practiced in our country and also in some institutes of neighboring country India (Samuel A M, 1999) . The dose pattern of LT4 followed in patients Group-I and Group-II did not differ the conventional dose at the very beginning of the study keeping in mind the risk of development of metastases. Another purpose of this initial LT4 dosage was to alleviate postoperative hypothyroid state shortly. Though this initial dose of LT4 keep the patient in TSH suppression less than 0.1 mIU/ml. Moreover, the aim behind the following of conventional dose initially was to observe the clinical and cardiac parameters with same dose of LT4.

Table I. Biophysical characteristics of control subjects and patients

Parameters	Control (n=23 (F/M-13/10) mean ± SD	Patients (n=60) (F/M-55/5) mean ± SD
Age (yrs)	30 ± 5	28 ± 6
Weight (kg)	55 ± 6	53 ± 10
Height (cm)	156 ± 6	153 ± 6
BSA (m^2)	1.53 ±0.10	1.48 ±0.14
BMI (kg/m^2)	23 ± 2	23 ± 4
***P* > 0.05** Control versus patients (no significant difference) ***P* <0.05** is considered significant difference BSA- Body surface area, BMI- Body mass index		

Thereafter, patients were divided into two groups (Group-I and Group-II). In Group-I, 30 patients received optimized LT4 dose depending on lean body mass and patients of Group-II continued the same conventional LT4 dose. After 6-12 months the study parameters were reported and compared to see the differences in two groups receiving different protocol of LT4 dosage and also with baseline data of first visit.

There were no significant differences between patients and control subjects in terms of age, height, weight, BSA and BMI ($p>0.05$) as shown in (Fig. 14,15 and 16; Table I). Among 60 patients with differentiated thyroid carcinoma, 55 were female and 5 were male. On the other hand, among 23 healthy adults 13 were female and 10 were male. Biophysical characteristics regarding female to male ratio in patients of present study population has reflected the incidence of sex pattern of the disease and female to male ratio is 9:1 (Maitra A and Abbas AK, 2004). In previous studies, similar sex patterns in their study population have been observed (Biondi B et al., 1993; Fazio S et al., 1995; Biondi B et al., 1996; Mercuro G et al., 2000; Botella – Carretero JI et al., 2004).

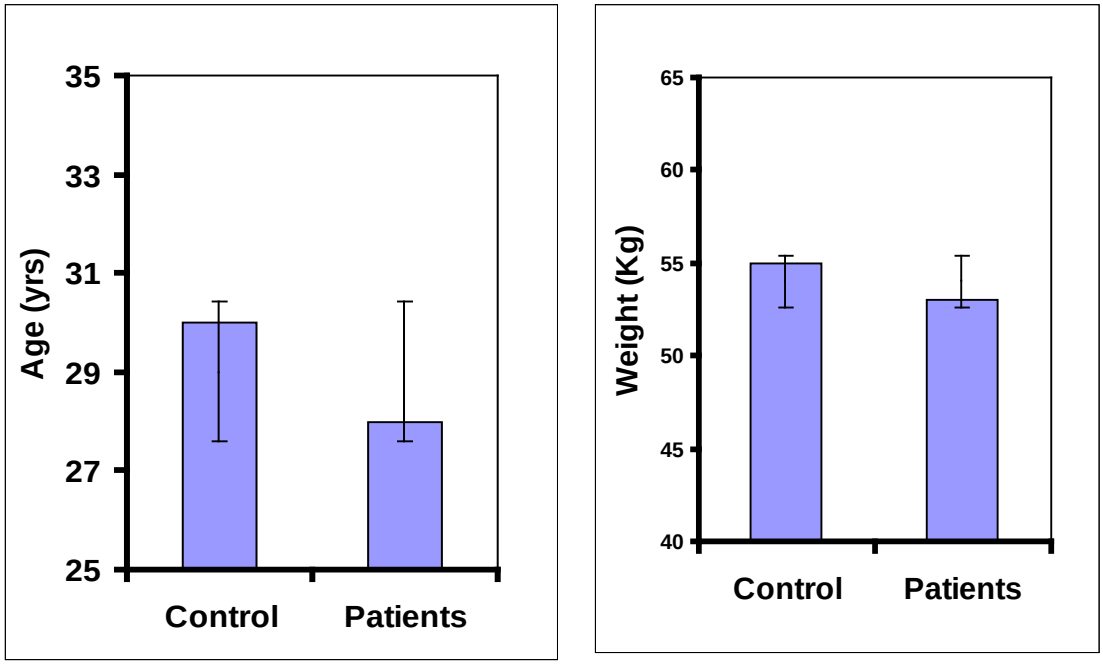

Fig. 14. Left: Mean age in year (yr) and Right: Mean weight (kg) in control subjects and patients. Data are expressed in mean ± SD.

Age: The baseline clinical characteristics and hormone data of the study subjects (healthy volunteers and patients) are shown in Table II. Mean age of control subject was 30±5 yrs (range 20-39 yr), which did not differ significantly with patient group of 28±6 yrs (range-20-39 yrs) (*p>0.05*) (Fig. 14 and Table I). The patients and healthy controls were well matched for age, height, and weight and body surface area. Biondi B et al., (1993) included also the patients of young age group having mean age 36 ±11 years. In contrast, the author of another study estimated LT4 requirement in population of higher age group, mean age 45±17 years, range, 22-85 years (Burmeister L et al., 1992).

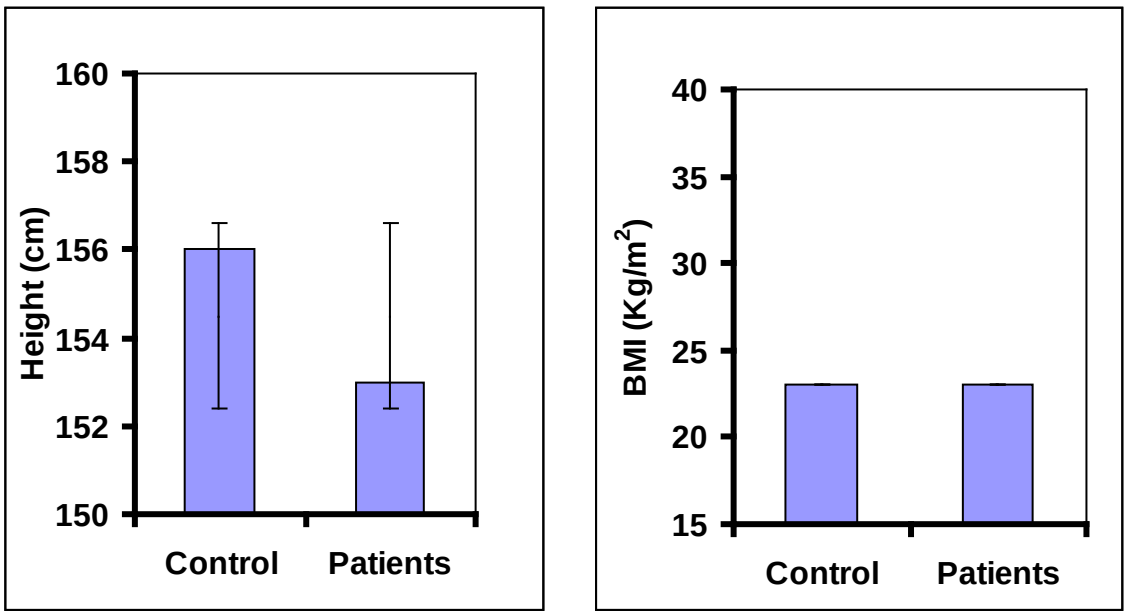

Fig. 15. Left: Mean height (cm) and Right: Mean BMI in control subjects and patients. Data are expressed in mean ± SD.

Height: Subjects of control group showed mean height of 156 ± 6 cm (range, 145-168 cm) and in patient group it was 153 ± 5 cm (range, 139-170 cm) (Fig.15 and Table I). Range of weight and height of the population of the present study was lower than other studies because the previous studies were performed in white people of Italy, their people are taller and have more weight compared to people of Bangladesh (Biondi B et al., 1993; Biondi B et al., 1996; Biondi B et al., 2000 and Fazio S et al., 1995).

Weight: Control subjects and patients with carcinoma of thyroid showed comparable mean weight in the present study. The mean weight of control group was 55±6 kg (range, 40-63 kg) and in patient group was 53±10 kg (range, 33-70 kg) (Fig. 14).

Subjects of control group and patients have similar sedentary lifestyle. In the present study, during selection of age, BMI and BSA matched control subjects, persons with significant physical activity have been deliberately avoided because they could have differed in exercise capacity and cardiac parameters (Daimon S et al., 2008).

In the present study, patients with differentiated carcinoma of thyroid were consecutively selected from younger age group and age and BMI matched control were recruited. These patients are supposed to receive LT4 for prolonged period of time throughout their life, so optimization of dose of LT4 is necessary to maintain the quality of life preserving normal cardiac function avoiding chronic exposure of slightly higher dose of LT4 (Biondi B et al., 1996; Biondi B et al., 2000, Biondi B., et al., 2002; Caro DE et al., 2006). Other reasons to select the younger age groups were to avoid any existing cardiac problems and also to avoid chronic diseases such as diabetes mellitus; asthma and any kind of disability affecting the different parameters of the present study.

BMI: Calculation of BMI (wt/ Ht m^2), (Green B & Duffull S B, 2004) between control subjects (mean, 23±3 kg/m^2, range, 17-26 kg/m^2) and patients group (mean, 23±4 kg/m^2; range, 15-31 kg/m^2) showed similar BMI (23 kg/m^2). This calculated value of BMI is within normal range (Green B and Dufful SB, 2004). However, seventeen patients of the present study population were over weight (BMI ranged from 25-29 kg/m^2). Prevalence of obesity is 20% in USA, UK and Australia (Green B and Duffull SB., 2004). Lower prevalence of obesity was noted among young by Santini F et al., (2005) when they compared young versus middle aged adults in their study. Similarly, only four obese patients were noted among 60 (6.6%) patients in the present study which is lower than developed countries but in agreement with the observation that young age group has low percentage of obesity.

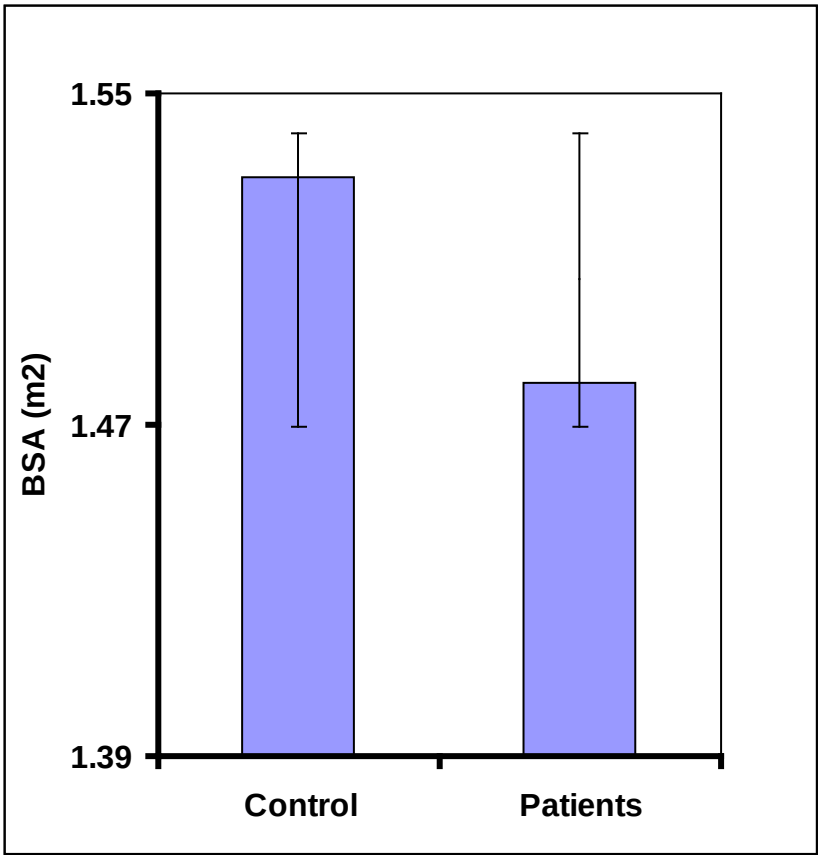

Fig. 16. Body surface area (BSA) in control subjects and patients at first visit.

BSA: Calculation of body surface area (BSA) =Total body weight (kg) $^{0.425}$ × Ht (m) $^{0.725}$ × 0.007184 derives from height and weight measurement of study subjects. Comparable weight and height in control subjects and patients groups in the present study showed similar BSA as they are derived from study subjects of similar height and weight (control, BSA, mean 1.53 ± 0.10 m^2; range, 1.32-1.72 m^2), (patient, BSA, mean 1.48 ± 0.13 m^2; range, 1.18-1.8 m^2) (Fig. 16). Mean BSA of Japanese men between age group 20-39 years was 1.8 ±0.1 m^2 and that of women was 1.5±0.1 m^2 (Daimon S et al., 2008). The BSA of female control subjects of the present study was comparable to Japanese healthy adult female. They have evaluated Echocardiographic parameters in stratified age groups in healthy Japanese adults (Daimon S et al., 2008). In this way, Echocardiographic parameters of the present study could be standardized with abovementioned study conducted on Japanese population as having similar BSA.

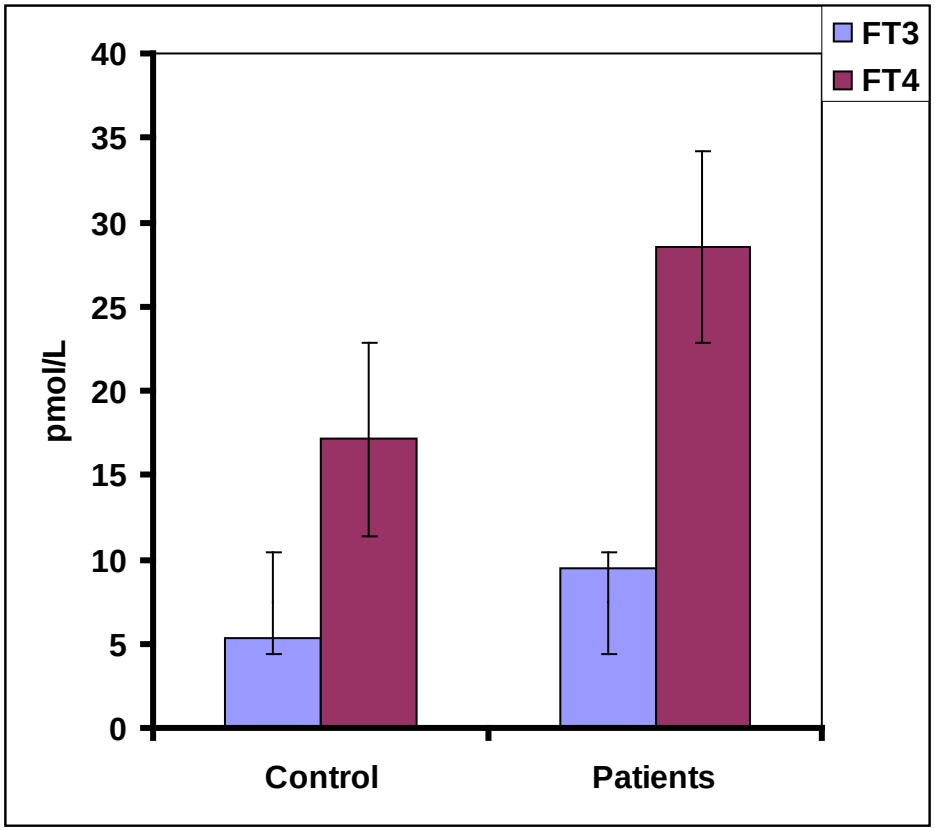

Fig. 17. Mean FT3 and FT4 levels in control subjects and patients at first visit.

4.2 Hormone data and Symptom Rating Scale score in control subjects and patients at baseline

Control subjects showed serum FT3, FT4 and TSH within normal reference ranges. All patients who received LT4 on conventional dose (200 µgm /day for initial 2 months) showed high FT3, FT4 and suppressed TSH. Significant differences ($p<0.001$) were noted in hormone status between control subjects and patient group (Fig. 17 and Table II).

Table II. Clinical characteristics and hormonal status of control subjects and patients at first visit.

Parameters	Control (n=23) m ±SD	Patients (n=60) m ±SD
Pulse (bpm)	76 ±5	94±12*
SBP (mmHg)	117 ±6	115 ±8
DBP (mmHg)	72 ±3	76 ±10
SRS	1 ± 1	8 ± 1*
FT3 pmol/L	5.3 ±1.04	9.5 ±0.66*
FT4 pmol/L	17.13 ±3.12	28.55±2.56*
TSH (mIU/L)	1.95 ±0.42	0.08 ± 0.017*
* p<0.05 Control versus patients		

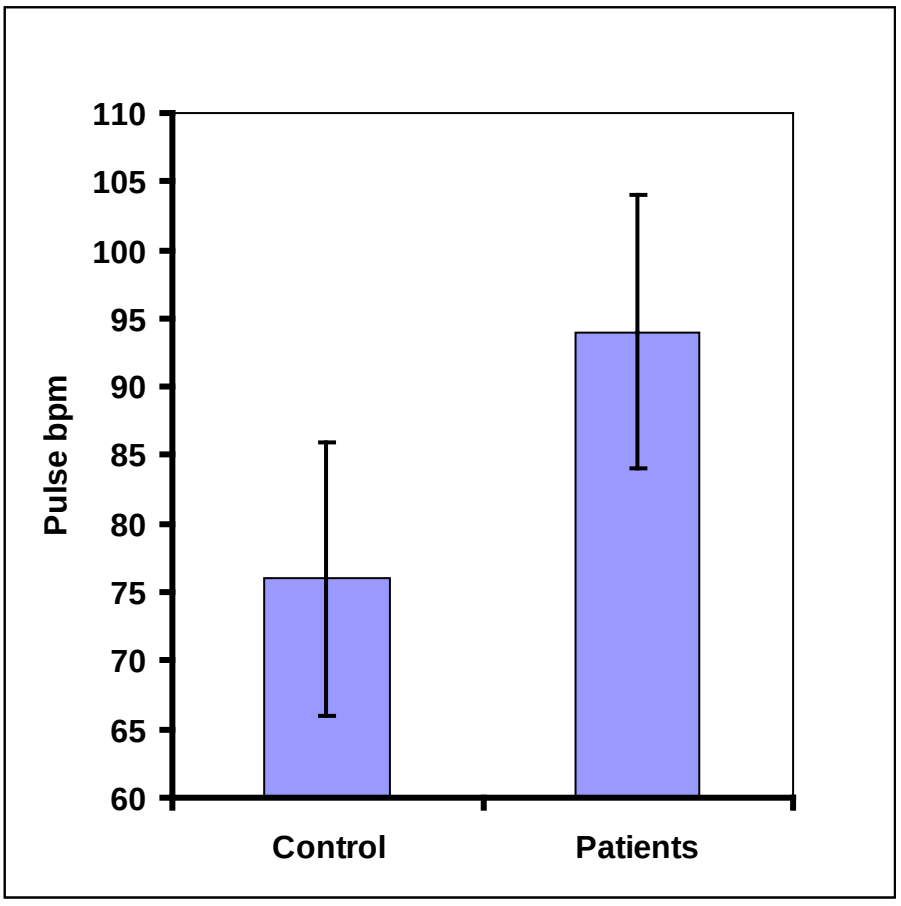

Fig. 18. Mean pulse rate in control subjects and patients at first visit.

HR (heart rate): The above mentioned Table II shows patient group had higher mean resting heart rate 94 ±12 bpm compared to heart rate of control subjects (HR, mean 76±5 bpm) (*P<0.05) (Fig. 18).

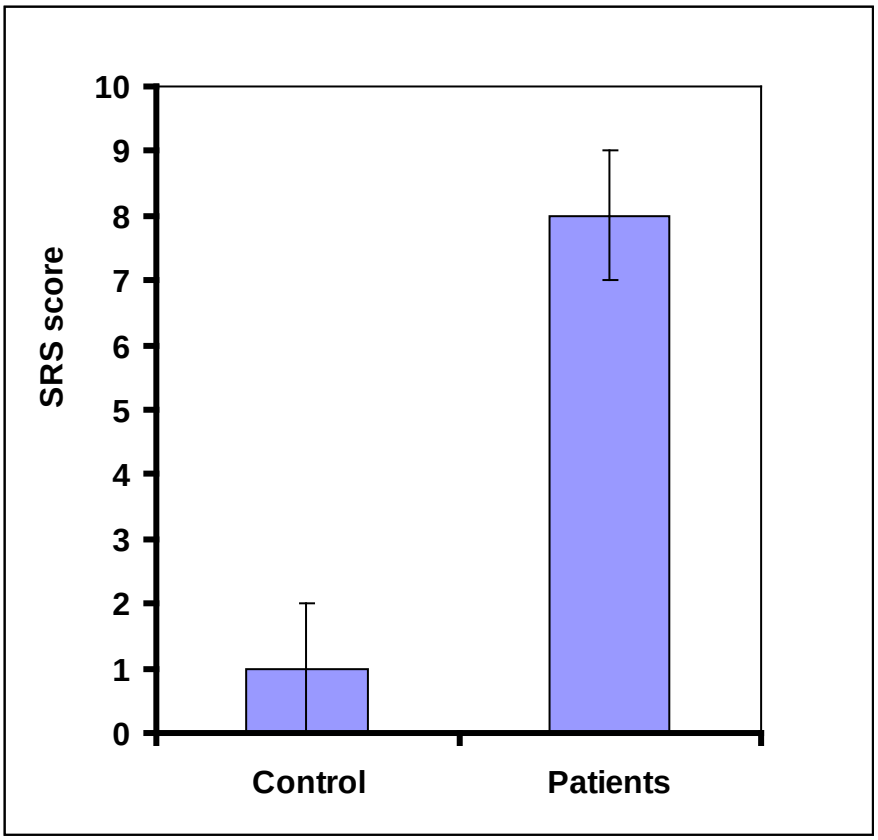

Fig. 19. Mean Symptom Rating Scale score in control subjects and patients at first visit.

SRS (Symptom Rating Scale)**:** SRS score was significantly higher in patients compared to healthy controls. In control group, SRS was 1± 1 and in the patient group SRS 8± 1 who received LT4 at T SH suppressive therapy (200 µgm/day) (Fig.19). Increased heart rate, palpitations, heat intolerance, anxiety tremor and nervousness were more evident features among patients and these symptoms are similar to those present in hyperthyroid state. These findings of current study were comparable to Biondi B et al., (2000), in their study, the study population was kept on to endogenous subclinical hyperthyroid hormone for atleast 6 months and in agreement of findings of another study by same author and his associates (Biondi B et al., 1993).

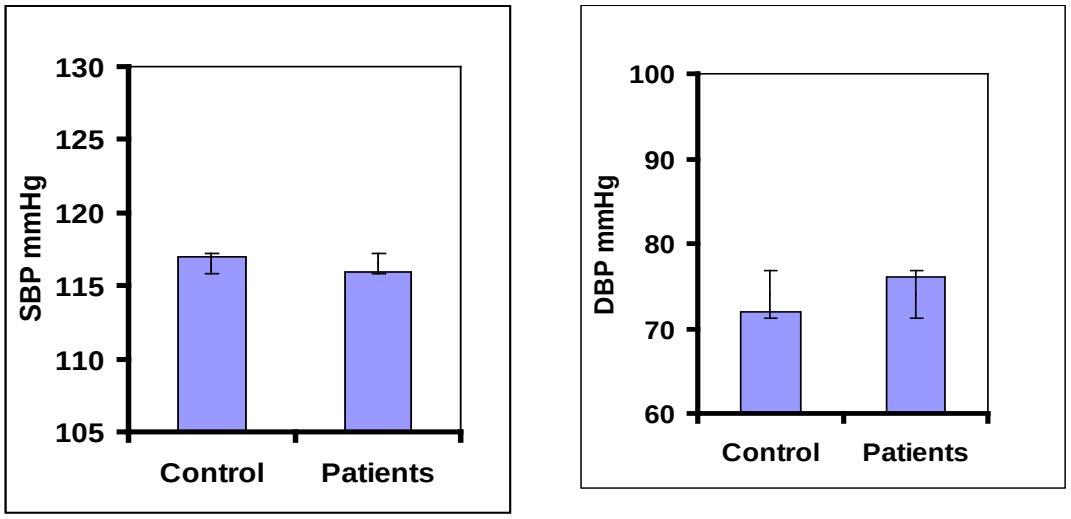

Fig. 20. Left: Mean SBP and Right: Mean DBP in control subjects and patients at first visit.

SBP and DBP: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) did not differ in patients group and the control subjects at first visit (Fig. 20.). These findings were in agreement with the study where patients with carcinoma of thyroid showed significantly higher heart rate (HR, patients ; 80 ± 10 bpm, control, 70±9 bpm), they received LT4 dose at mean, 163 ± 34 µgm/day (2.5 ±0.5 µgm/kg/day) (Boindi B et al., 1993).

4.3 Levothyroxine dosage

To reach the goal of attaining low TSH level (0.04-0.1 mIU/L) and FT3 and FT4 within normal range, the dose of LT4 was optimized on the basis of lean body mass of each patient of Group-I at first visit. After 3 months repeat hormone assay of Group-I patient showed that LT4 dosing at 3.5 to 4 µgm/kg / lean body mass (mean dose of LT4 per day was 131 ± 23 µgm/day, range 120-220 µgm/day), was optimal to obtain normal thyroid hormone levels (FT3~5.5 pmol/L; FT4~17.9 pmol/L and expected TSH level (0.1 ± 0.01 mIU/L). This dose was comparable as dose of LT4 based on lean body mass by DXA in a previous study (Satini F et al., 2005). There are several recommendations about requirement of daily dose of LT4 based on total body weight. It ranged from 2.2-3.0 µgm/kg in different previous literatures (Fig.

21) (Biondi B et al., 1993; Biondi B et al., 2000; Burmeiester LA et al., 1992 and Fazio S et al., 1995).

If arbitrarily 3 µgm/kg total body weight/day was considered in patients of Group-I of the present study, then the daily dose would have varied in the range of 111-210 µgm/day (mean 156 ± 27 µgm/day). This mean dose of LT4 is quite high compared to daily dose depending on LBM in the present study and also in a previous study by Santini F et al., (2005) in which daily dose of LT4 was calculated on the basis of LBM.

It is a matter of great concern; the physicians of our country have been practicing 200 µgm/day dose in post radioiodine ablated patients with DTC. This dose pattern is of irrespective of age, sex, body weight of patients and classification of DTC. This dose (200 µgm/day) appears higher in low risk group of DTC, young patients having relatively low body weight. In our neighboring country India, physicians have been practicing 300 µ gm/day dose of LT4 as initial dose, though 100 µ gm reductions (200 µ gm/day) is advised for older patients with cardiac problems (Samuel AM, 1999).

The dose of LT4 is based on total body weight (TBW) increase linearly with the increment of (TBW) (Burmeister LA et al., 1992) as shown arbitrarily in Fig. 17 in patients of Group-I. BMI always depends on fat accumulation (Andreoli A et al., 2009; Green B and Duffull SB, 2004). Fat mass has no role in deiodination of T4 to T3, rather depends on lean body mass. It is known that T4 is deiodinated to active hormone T3 in liver, muscle and kidneys and to reverse T3 in skin (liver, muscle, kidneys and skin are included in lean compartments of body composition). On the other hand, lean body mass does not increase linearly with the increase of body weight, which depends mainly on muscular activity and individual body build (Santini F et al., 2005; Andreoli A et al., 2009). As shown in Fig. 21, remarkable nonlinearity/fluctuations of doses of LT4 were noted in LBM based dosing with small difference of total body weight. If one could lessen minimum 25 µ gm/day by

giving dose of LT4 on LBM, several adverse effects would have been avoided (Biondi B et al., 2000; Botella-Carretero JI et al., 2004; Jonklaas J et al., 2008).

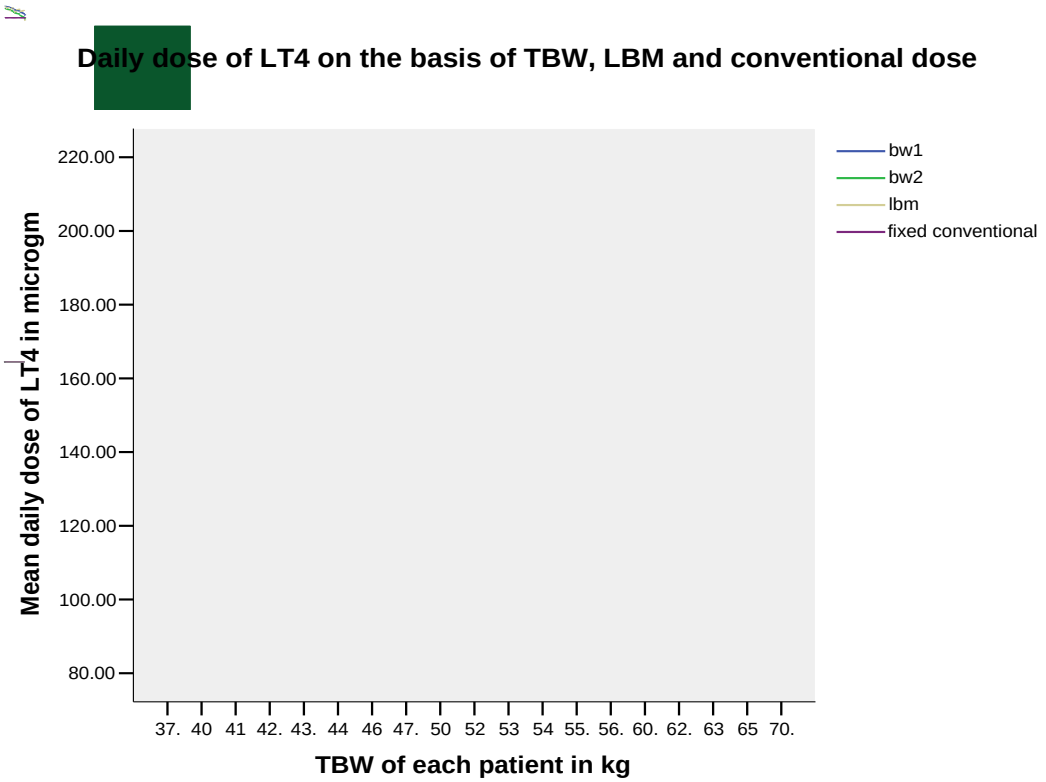

Fig. 21. Different lines in graph are showing the daily dose requirement of LT4 in each patient with differentiated thyroid carcinoma of low risk (Group-I) to attain TSH level range 0.04-0.1 mIU/L. Yellow line is depicting the daily dose based on lean body mass (4 µgm/kg/LBM), blue line indicates if same patients are given arbitrarily LT4 at 2.5 µgm/kg/ TBW and green line indicates daily dose based arbitrarily on total body weight (arbitrary, 3 µgm/kg/TBW). Purple line shows fixed dose of LT4 at 200 µgm/day (conventional).

If instead, 2.5 µgm/kg /TBW of LT4 was considered in patients of Group-I, then it would have been 130± 22 µgm/ day (range 93-175 µgm/day), which also increased linearly with body weight. The authors (Santini F et al., 2005) recommended in his study that patients with higher body weight comparatively are to be prescribed low dose (1.8 µgm/kg /TBW) compared to patients with low body weight (2.56 ±5

µgm/kg /T BW) considering high fat accumulation in obese patients (analysed by DXA whole body composition).

Mild increment of LT4 dose may cause fall of TSH level mildly to subnormal level, conversely a decrease in dose by 25 µ gm caused the rise of the TSH level in almost in all subjects to above normal range. A physician should not be overzealous to prescribe any drug strictly following the single dose method for dosing. Because, he should also consider other influencing factors on the pharmacokinetics of drugs. There are several known factors that may affect the dose of LT4. Absorption of LT4 may be interfered by certain drugs such as chlestipol, cholestyramine, ferrous sulfate, aluminum hydroxide antacids and calcium salts. Administration of LT4 and the above mentioned drugs at different time and readjustment of their dosage may solve the problem (Sawka AM et al., 2009). Soya protein and high fiber diet may inhibit LT4 absorption. Other drugs, such as phenobarbital, phenytoin and carbamazepine and rifampicin may accelerate the metabolism of LT4. In case of celiac sprue and malabsorption dose of LT4 are to be increased (Sawka AM et al., 2009).

Table III. Echocardiographic data of left ventricle in control subjects and patient group

Parameters	Control (n=23) mean ±SD	Patients (n=60) mean ±SD
IVST (mm)	8 ± 1	7 ± 1
PWT (mm)	8 ± 1	8 ± 1
LVIDD (mm)	43 ± 3	44 ± 3
LVIDS (mm)	28 ± 2	28 ± 2
EF (%)	66 ± 4	65 ± 4
LVM (gm)	103 ± 21	98 ± 17
LVMi (gm/m^2)	68 ± 12	66 ± 10
FS (%)	34 ±3	35 ± 3
mVCFc (cir/sec)	1.12 ± 0.12	1.22 ±0.18*
Peak Aortic Velocity (cm/sec)	89 ± 9	101 ±17*
ET (ms)	300±18	288±19*
*p<0.05 control subjects versus patients		

In case of pregnancy, common recommendation is to increase dose of LT4 upto 30% and then adjust sequentially depending on TSH level. Finally, dose requirement may slowly decline with age in turn which is due to decreased lean body mass in older people (Green B and Duffull SB, 2004). There are some evidences that suppressing the TSH level below 0.1 mIU/L has no additional benefit in treatment of patients with DTC of low risk group (Lameloise N et al., 2001; Hoftijzer HC et al., 2008).

4.4 Echocardiographic data in control subjects and patients at first follow-up

On M mode echocardiography, IVST, PWT, LVIDD, LVIDS of left ventricle were measured in patient groups and control subjects at first visit as shown in Fig. 22 and Table III. Interventricular septal thickness (IVST, control, 8±1 and patients 7±1, ***P > 0.05***), left ventricular posterior wall thickness (PWT, control, 8±1 mm and patients 8±1 mm, ***P>0.05)***, internal diameter of left ventricle during diastole (LVIDD, control subjects, 43 ± 3 mm and patients 44±3 mm, ***P>0.05***) and internal diameter of left ventricle during systole (LVIDS, control subjects, 28 ± 2 mm and patients group 28±2 mm, ***P>0.05***), left ventricular mass (LVM, control subjects, 103±21 gm and in patients group, 98 ± 17 gm, ***P>0.05***) and left ventricular mass index (LVMi, control subjects, 68 ±12 g m/ m^2 and in patients group 66 ± 1 gm/m^2; ***p> 0.05***) were comparable in control subjects and patients group.

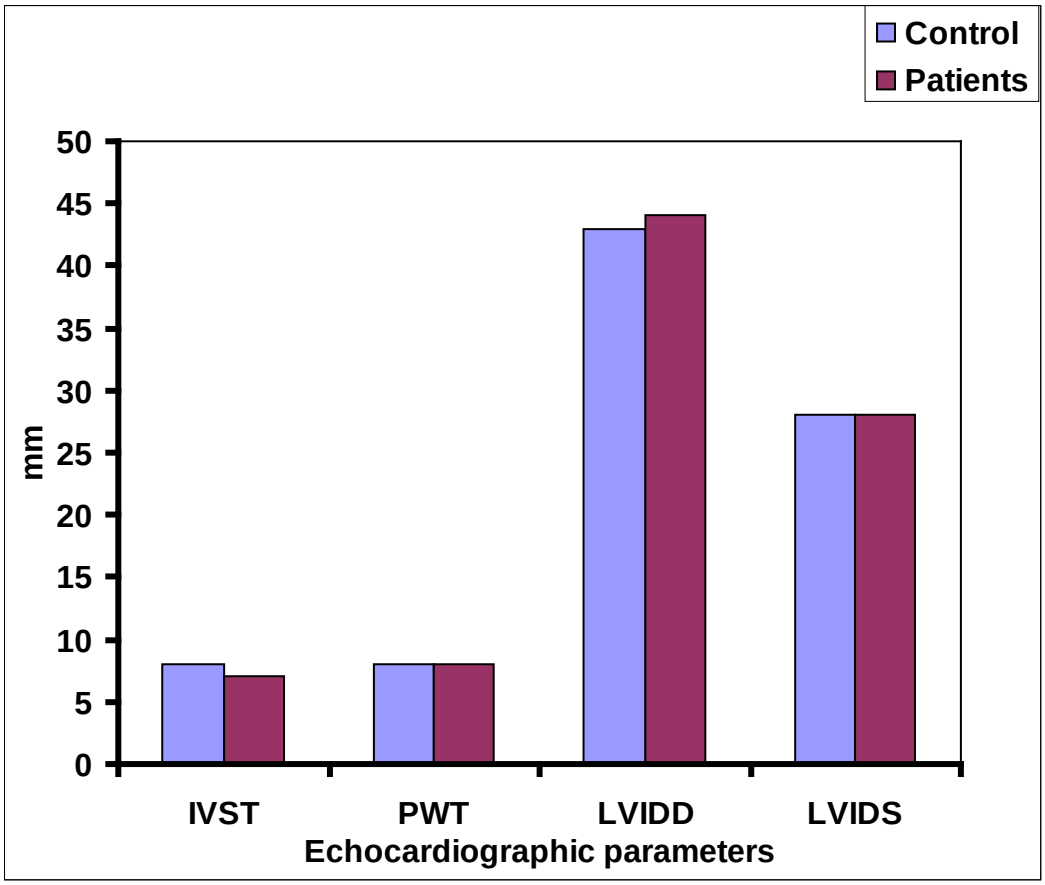

Fig. 22. Comparison basic Echocardiographic data in control subjects and patients at first visit

Measurements of IVST, PWT, LVIDD, LVIDS, LVM and LVMi (Figs. 22 and 23) in control subjects of the present study were comparable with the same parameters in Japanese female healthy adults of same ages (Daimon S et al., 2008).

Ejection fraction was comparable in both control subjects and patients group (EF%, control subjects, 66±4%, patients group 65±4%; ***p>0.05***) (Fig. 25), ejection fraction rather increased initially in hyperthyroid state, so this similarity of data of patients with healthy adults were understandable (Klein I and Danzi S, 2007).

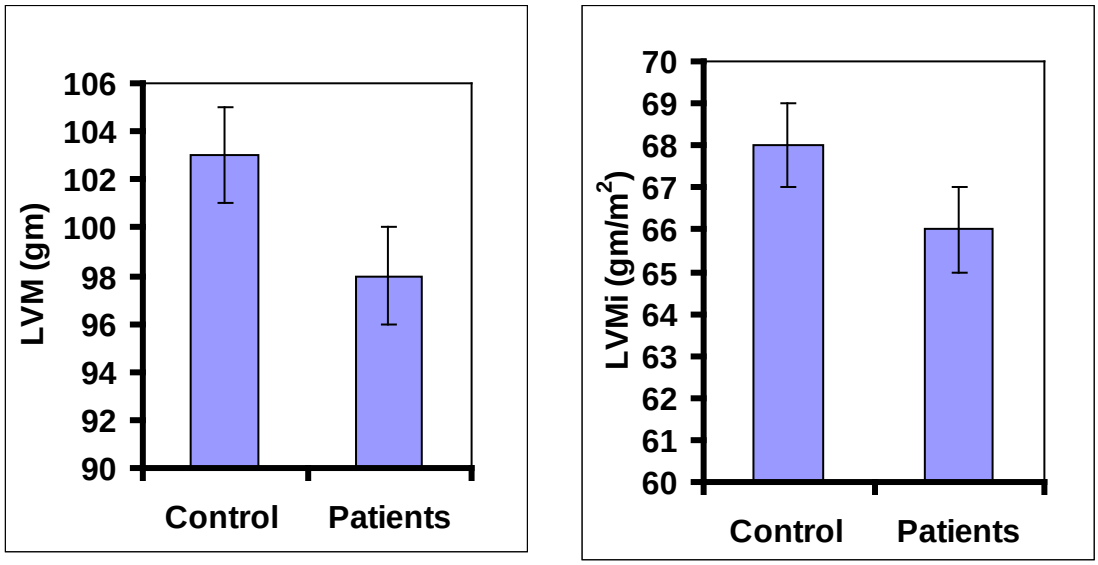

Fig. 23. Left: Mean ventricular mass and Right: Left ventricular mass index in control subjects and patients at first visit

No significant differences were found between control subjects and patients group in fraction shortening (FS, control subjects, 34±3%; patients group, 35±3%; *P>0.05*) (Fig. 24) . Significant differences were observed between control subjects and patients group in peak aortic velocity (PAV, control subjects, 89±9 cm/sec; patients group- 101±17 cm /sec, ***P<0.05***) (Fig. 26), heart rate adjusted circumferential fiber shortening (mVCFc, control subjects, 1.12±0.12 circumferences/sec; patients group 1.22±0.18 circumferences /sec, ***P<0.05***) (Fig. 24) and ejection time (ET, control subjects, 300±18 m sec; patients group, 288±19 m sec, ***P<0.05***) (Fig. 26 and Table III). There were no morphological changes in heart in the patients group at first visit, which may be due to short duration of LT4 exposure though slightly higher (statistically significant ***P<0.05***), peak aortic velocity and mVCFc were noted. Decreased ejection time of patients at this time point can be explained by hyper contractile state of the heart muscle on LT4 therapy (Haider AW et al., 1998; Klein I and Danzi S, 2007; Ladenson PW, 1993)

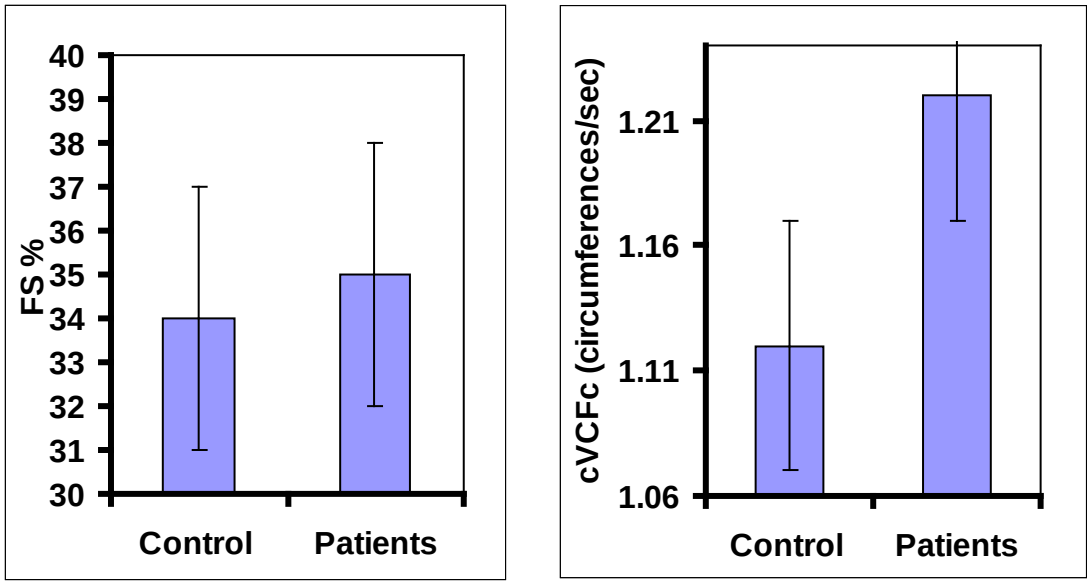

Fig. 24. Left: Mean fraction shortening (FS %) and Right: mean velocity of circumferential fiber shortening (mVCFc) in control subjects and patients.

All diastolic parameters measured by Doppler Echocardiography are shown in Table IV. Early diastolic flow velocity (E) through mitral valve in both groups (control subjects, 75±10 cm/sec, patients group, 80±16 cm /sec, ***p>0.05)*** were observed and found similar (Fig. 27). They were matched with the normal range (E, 77±15 cm /sec) of Japanese population shown in the study by Daimon S et al., 2008.

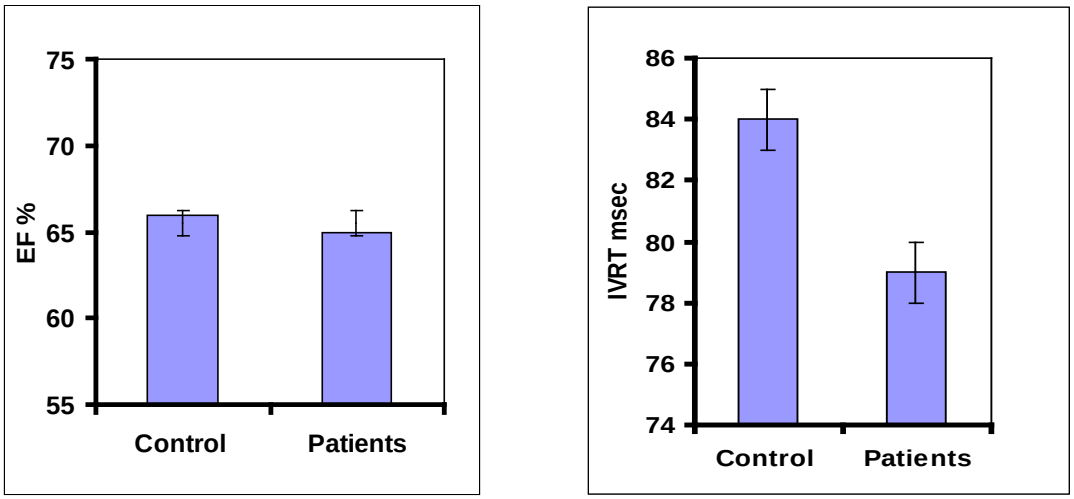

Fig. 25. Left: Mean ejection fraction (EF %). Right: Isovolumic relaxation time (IVRT) in control subjects and patients at first visit

Late diastolic flow velocity (A) through mitral valve was increased in patient groups and it was statistically significant higher than control subjects (A, control subjects, 44±5 cm/ sec; patients group, 56±10 cm /sec, **** p<0.05***) (Fig. 27 and Table IV) (Fazio S et al., 1995; Mintz G et al., 1991). Late diastolic flow velocity, A wave of control subjects was observed similar with the normal range (A, 45±10 cm /sec) of Japanese population found in the study by Daimon S et al 2008.

Table IV. Diastolic function parameters evaluated by Doppler Echocardiography and tissue Doppler imaging in control subjects and patients at first visit

Parameters	Control (n=23) mean ±sd	Patients (n=60) mean ±sd
E (cm/s)	75 ±8	80 ±16
A (cm/s)	44 ±5	56±10*
E/A	1.7±0.3	1.5±0.3*
IVRT (ms)	84 ± 6	79 ± 10*
Dct (ms)	173±19	151±18*
Tei index	0.32±0.05	0.33±0.08
Lateral mitral annular		
Em (cm/s)	19±3	22±5*
Am (cm/s)	9 ± 1.6	15±5*
E/Em	4±0.8	4±1*
Mod Tei	0.33±0.04	0.31±0.05*
*$P<0.05$ significant difference between control subjects versus patient group		

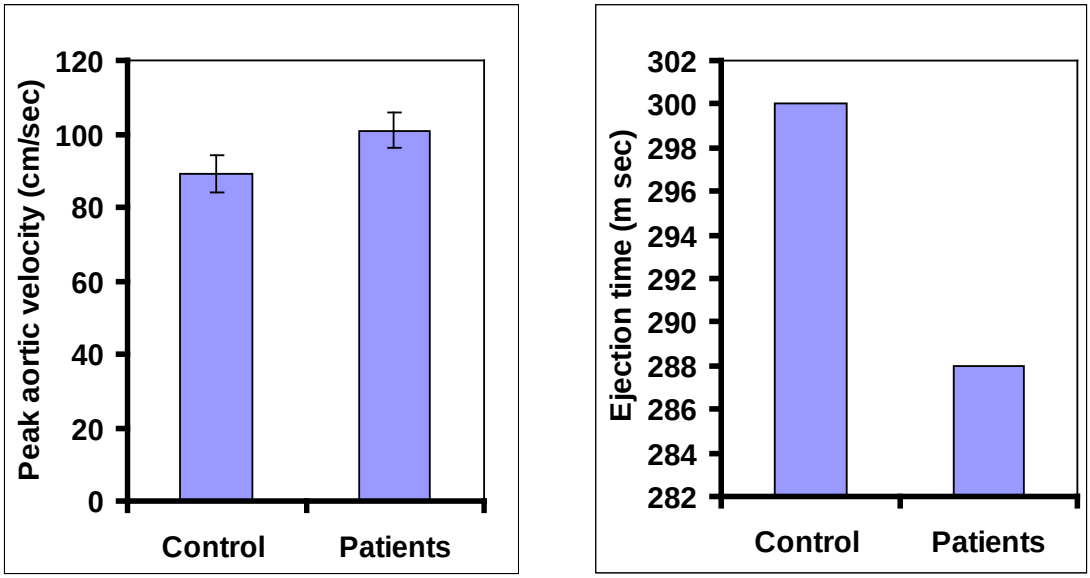

Fig. 26. Left: Mean peak aortic velocity. Right: Ejection time in control subjects and patients.

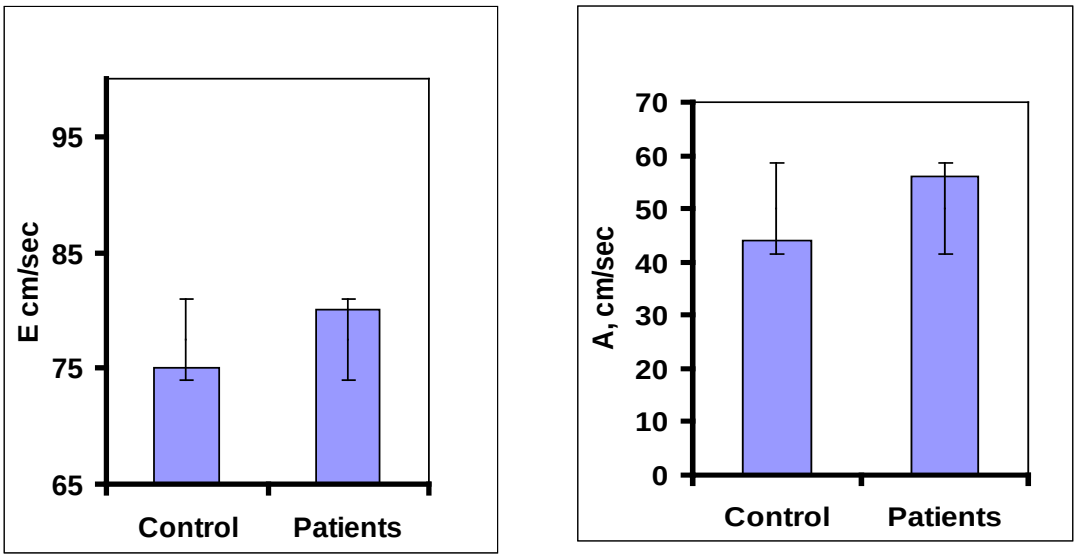

Fig. 27. Left: Mean early diastolic velocity (E cm /sec). Right: Mean late diastolic velocity (A cm/sec) In control subjects and patients at first visit

E/A ratio was significantly ***(*p<0.05)*** decreased in patients group at first visit compared to control subjects (Fig. 28 and Table IV) may be due to comparatively high A value in patients of the current study. Decreased deceleration time is noted in patients compared to control subjects (Dct, control, 173±19 msec, patients, 151±18 msec, ****p<0.05***) (Fig. 28 and Table IV). This decreased deceleration time is due to hyperthyroid state in patients on LT4 replacement causing hypercontractilility of heart. It has been mentioned in previous literatures that thyroid hormone cause decrement of E wave due to rapid heart rate and decreased ventricular filling due to low distensibility (Fazio S et al., 1995; Haider AW et al., 1998).

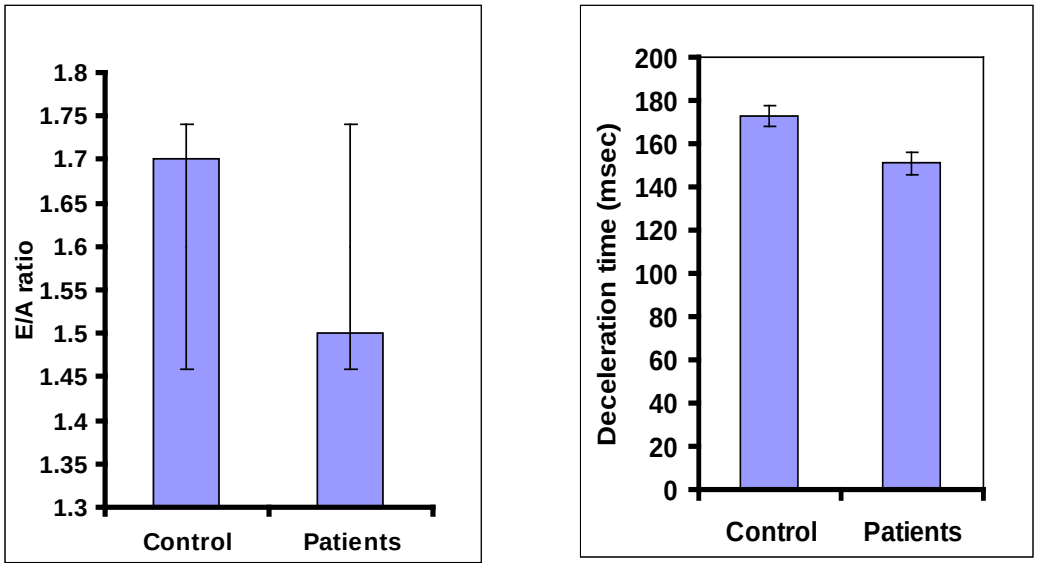

Fig. 28. Left: E/A ratio and Right: Deceleration time (Dct m sec) in control and patients at first visit.

There was increment of A wave leading to decreased E/A ratio (Fig. 28 and Table IV). It was notable that these features were appearing in the present study even within this short period (6-12 months) of LT4 replacement therapy. By observing similar findings (diastolic dysfunction), Biondi B et al., (2000) advised to take caution when prescribing LT4 therapy. Tei index which is considered recently the parameter to measure the systolic and diastolic performances of heart (Karatzis EN et al., 2009). It was measured in control subjects and patients group showing no significant difference (Tei index; control subjects, 0.32± 0.05; patients group, 0.33± 0.08, ***P>0.05***) (Fig. 29 and Table IV). This parameter depends on isovolumic relaxation time (IVRT) (Fig. 25 and Table IV) (Karatzis EN et al., 2009) and this relaxation time is decreased due to hypercontractility of heart influenced by LT4 therapy (Haider AW et al., 1998; Klein I and Danzi S, 2007)

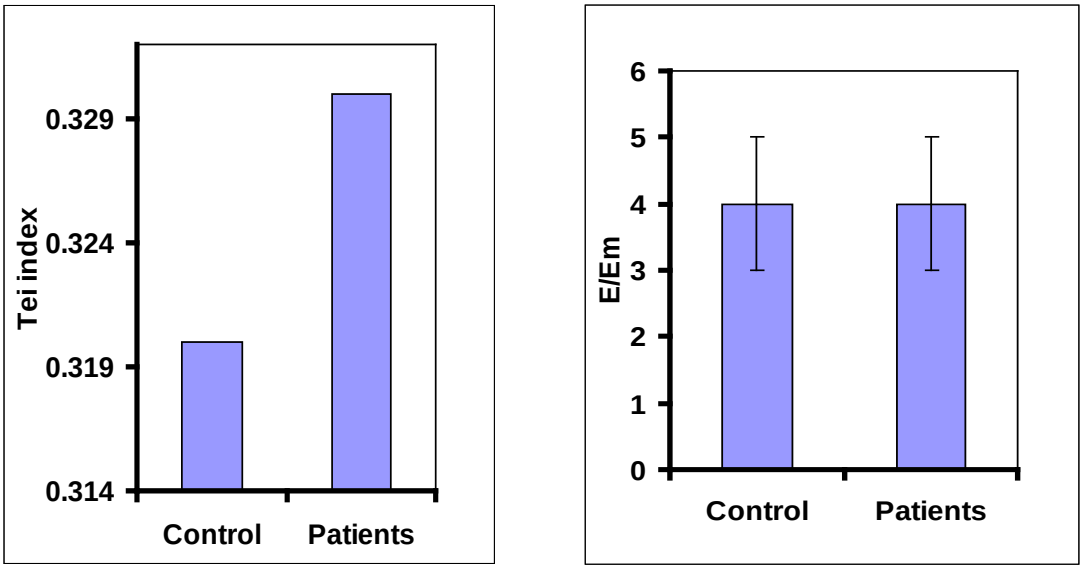

Fig. 29. Left: Mean Tei index and Right: Mean E/Em in control subjects and patients at first visit

Previous studies have shown that chronic exposure of TSH suppressive dose of LT4 therapy can induce cardiac structural abnormalities, such as increased IVST, PWT and cardiac hypertrophy (Biondi B et al., 1993, Ching CW et al., 1996). The absence of significant cardiac morphological changes in patients of the present study might be due to short period of TSH suppressive LT4 therapy (maximum one year) in contrast to others (6 months upto 9 years) (Biondi B et al., 1993)

Table V. Exercise Tolerance Test in control subjects and patients groups at first visit.

Parameters	Control (n=23) mean ±SD	Patients (n=60) mean ±SD
Exercise		
HR (beats/min)	171 ±15	175±12
SBP (mmHg)	155 ±18	145 ±14
DBP (mmHg)	95±5	92±7
METS	12 ± 1	10 ± 1*
Double product ($X10^3$)	27 ± 4	25 ± 4
Duration of exercise (min)	10 ± 1	9 ± 1*
*P<0.05 control subjects versus patients group		

4.5 Exercise Tolerance Test in control subjects and patients at first follow-up

Exercise Tolerance Test (ETT) was done at first visit in control subjects and patients group, ETT was terminated when complaints of severe fatigue or attainment of maximum predicted heart rate. The data of ETT have shown comparatively less metabolic equivalent (MET) in patients group compared to control subjects (control subjects, 12±1 vs patients group, 10± 1; * ***p<0.05***) (Table V). Although this range of MET in patients group was within normal performance of exercise capacity, still it was considered as decrement of capacity in young adults. Duration of exercise was 9 ± 1 minute in patients group compared to control subjects 10 ± 1 minute (Table V).

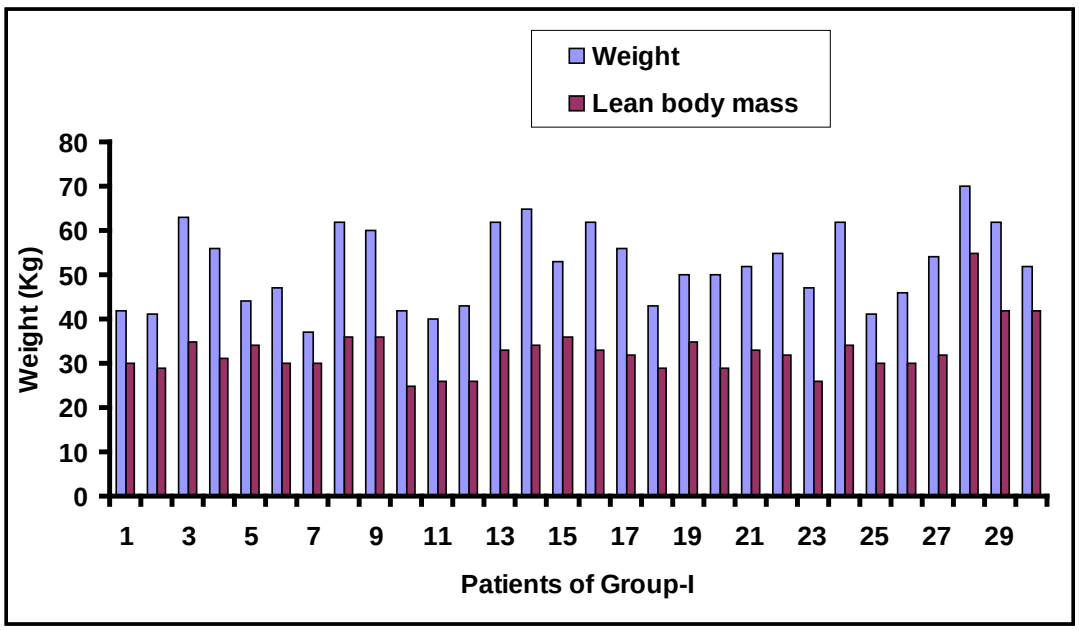

Fig. 30. Total body weight and lean body mass as measured by dual energy absorptiometry (DXA) in patients of Group-I.

4.6 Lean body mass in patients of Group-I

Total body weight and lean body mass of patients of Group-I are shown in Fig. 30. Excessive fat accumulation increase BMI value and so increment of LT4 dose would

be required as TBW based dosing system. However, they may need the same dose to attain the same TSH value as in lean subjects. In this context, lean body mass as assessed by body composition analysis of DXA appears as the best correlate of LT4 daily requirements, whereas fat mass has little or no effect (Santini F et al., 2005). Lean body mass measurement is superior to other measures of body size as predictor of dosage for many drugs. It is well known that most of the metabolic processes occur within this body compartment (Green B and Duffull SB, 2006; Fazio et al., 1995). Comparative TBW and LBM were shown in patients of Group-I (Figs. 30 and 31.)

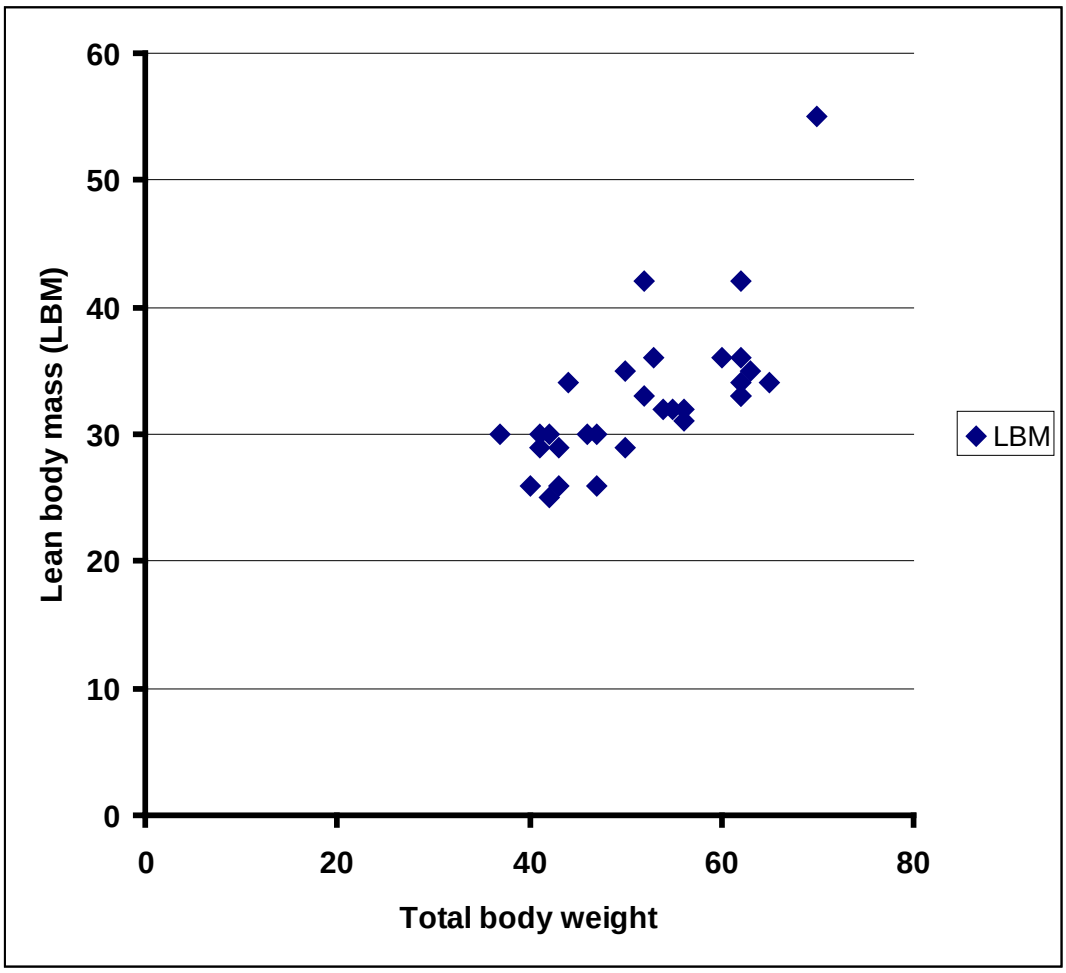

Fig. 31. Lean body mass and total body weight in patients of Group-I

Table VI. Clinical characteristics and hormonal status of patients of Group-I & Group-II at first and second visits.

Parameters	Group-I (n=30) mean ± SD		*Group*-II (n=30) mean ± SD	
	At first visit	At second visit	At first visit	At second visit
Pulse (bpm)	95 ± 11	87 ± 14*	93 ± 12	100 ± 20 † ‡
SBP (mmHg)	116 ± 7	114 ± 7	114 ± 9	119 ± 8
DBP (mmHg)	77 ± 5	75 ±7	76 ± 5	78 ± 4
SRS	8 ± 1	2 ± 1 *	8 ± 1	8 ± 1 ‡
FT3 pmol/L	9.4 ±0.7	5.5 ± 1.3 *	9.6 ± 0.6	10.1 ± 0.7 ‡
FT4 pmol/L	29.5 ± 2.9	17.9 ± 1.9 *	27.56 ± 1.6	27.4 ± 0.94 ‡
TSH (mIU/L)	0.08 ± 0.04	0.1 ± 0.01 *	0.0 8 ±0.05	0.09 ±0.05 ‡

- $p<0.05$ Group-I vs Group-I between first and second visits
- † $p<0.05$ Group-II vs Group-II between first and second visits
- ‡ $p<0.05$ Group-I vs Group-II at second visit

4.7 Comparison of different hormone and clinical parameters of patients of Group-I and Group-II, at first and second visits

Dose of LT4 and hormone data: After 3 months of first visit repeat hormone assay of Group-I patient showed that LT4 dosing at 3.5 to 4 µgm/kg / lean body mass (mean dose of LT4 per day was 131 ± 23 µgm/day, range 120-220 µgm/day), was optimal to obtain normal thyroid hormone levels (FT3~5.5 pmol/L; FT4~17.9 pmol/L and expected TSH level (`0.1±0.01 mIU/L). Patients of Group-I showed high serum FT3, FT4 and low TSH when they were on conventional dose of LT4 at first visit and after optimization hormone levels were within normal reference ranges (Fig. 27 and Table VI). All patients of Group-II who received LT4 on conventional dose (200 µgm/day) for initial 2 months and continued subsequently showed high FT3, FT4 (Fig. 31) and suppressed TSH levels (Fig.32 and Table VI). Significant differences ***(*p<0.05***) were noted in hormone levels of Group-I and Group-II at second visit. Optimization of LT4 dose increased the TSH level at second visit of Group-I patients. Thyroid hormones data were at first visit versus second visit, FT3,

9.4 ± 0.7 pmol/L Vs 5.5 ± 1.3 pmol/L, ***p<0.05***; FT4, 29.5 ± 2.9 pmol/L Vs 17.9 ± 1.9 pmol/L, ***p<0.05*** and TSH, 0.08 ± 0.04 mIU/L Vs 0.1 ± 0.1 mIU/L , ***p<0.05***) (Figs. 31and 32; Table VI).

HR, SBP and DBP in patients of Group-I and Group-II at first and second visits: Table VI shows mean resting heart rate of patients of Group-I was 95±11 bpm at first visit and it decreased to 87 ±14 bpm (***P<0.05***) at second visit after optimization of dose. Subsequent increment of pulse rate was noted in patients of Group-II at second visit (first visit, 93±12 bpm, at second visit 100±20 bpm) (Fig. 33). SBP and DBP did not differ in patients of Group-I in between visits (Fig. 34). Slight increment of SBP of DBP were observed, but it was within normal range in patients of Group-II at second visit (SBP, at first visit 114±9 mmHg; at second visit, 119±8 mmHg) (Fig. 33). These findings were similar to findings of other study where patients with carcinoma of thyroid received LT4 dose 176 ± 20 µgm/day (2.8 ± 0.28 µgm/kg/TBW) and mean body weight of patients was 63±7 kg (Boindi B et al., 1993)

SRS: Score of Symptom Rating Scale (SRS) showed a significant clinical improvement (SRS, Group-I, at second visit 2± 1, at first visit 8± 1, **P<0.05*) of patients who received optimized dose (132±23 µ gm/day) of LT4 at second visit as shown in Table VI compared to the patients who received in conventional dose of LT4 at first and second visits (SRS, Group-II, at first and second visit, 8± 1). Optimization of LT4 dose showed expected influence on blood levels of FT3, FT4 and TSH showing normal levels of FT3 and FT4 and low level of TSH. After optimization of LT4, signs and symptoms of hyperthyroid state were alleviated in patients of Group-I. On the other hand, patients on conventional dose showed levels of FT3, FT4 in thyrotoxicosis levels and TSH was in suppressed level. Biochemical findings of increased FT3, FT4 were also evidenced by their clinical signs and symptoms of thyrotoxicosis in patients of Group-II (Fig. 32 and Table VI)

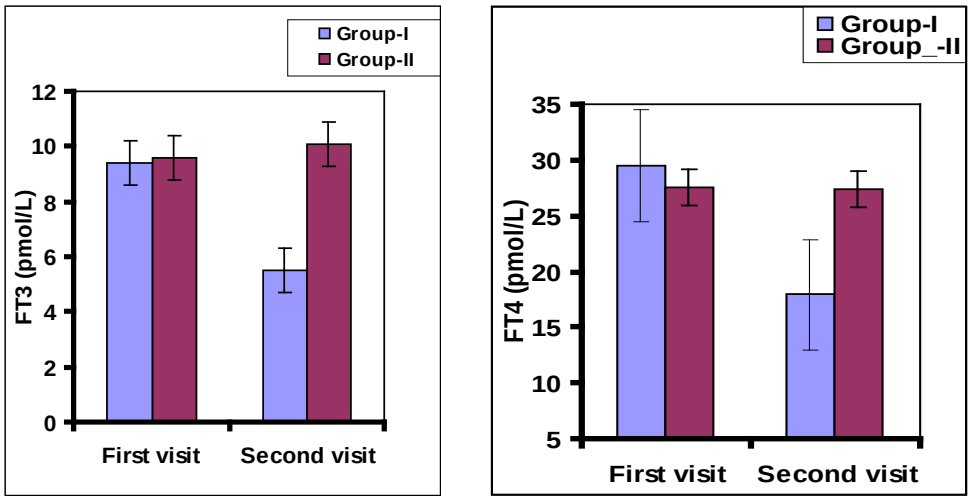

Fig. 32. Left: Mean FT3 and Right: FT4 in patients of Group-I and Group-II in first visit and second visits

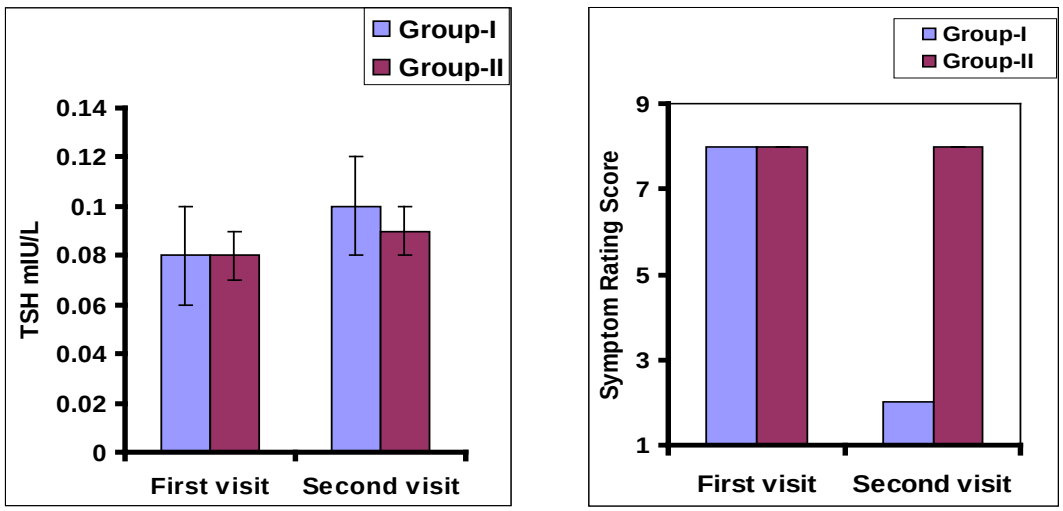

Fig. 33. Left: Mean TSH and Right: Mean Symptom Rating Score in patients of Group-I and Group-II at different visits.

Symptom Rating Scale score significantly improved (SRS, 2±1) after optimization of LT4 dose in patients of Group-I compared to Score of Group II at second visit (Fig. 32 and Table VI). Excessive LT4 replacement produce signs and symptoms of hyperthyroidism and patients continually suffer from impairment of emotional and physical health (Hoftijzer HC et al., 2008). It is now clear from previous published data and from this study that TSH suppressive dose of LT4 inevitably produces

alterations in cardiac morphology and function that may worsen quality of life (Fazio S et al., 1995; Hoftijzer HC et al., 2008).

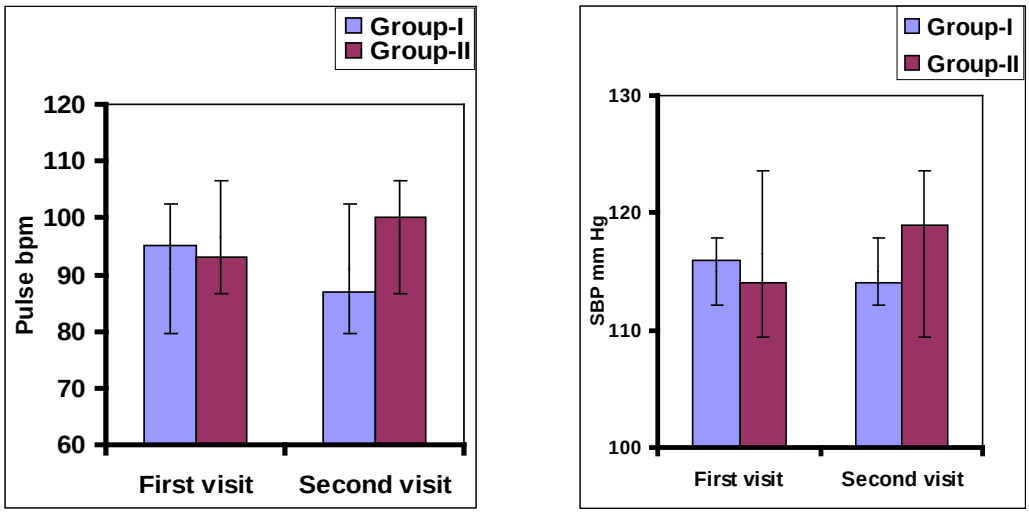

Fig. 34. Left: Mean pulse rate and Right: Mean systolic blood pressure in patients of Group-I and Group-II

Increased heart rate, palpitations, heat intolerance, anxiety, tremor and nervousness were more evident features among them and symptoms similar to those present in hyperthyroid state (Klein I et al, 1984; Klein I et al, 1988; Ladenson P W, 1990; Geffner DK et al., 1992 and Cacciatori V et al., 1996). This finding of current study was comparable to the study performed by Biondi B et al., (2000), in their study patients were exposed to excessive endogenous thyroid hormone for short time and effects on heart were observed subsequently.

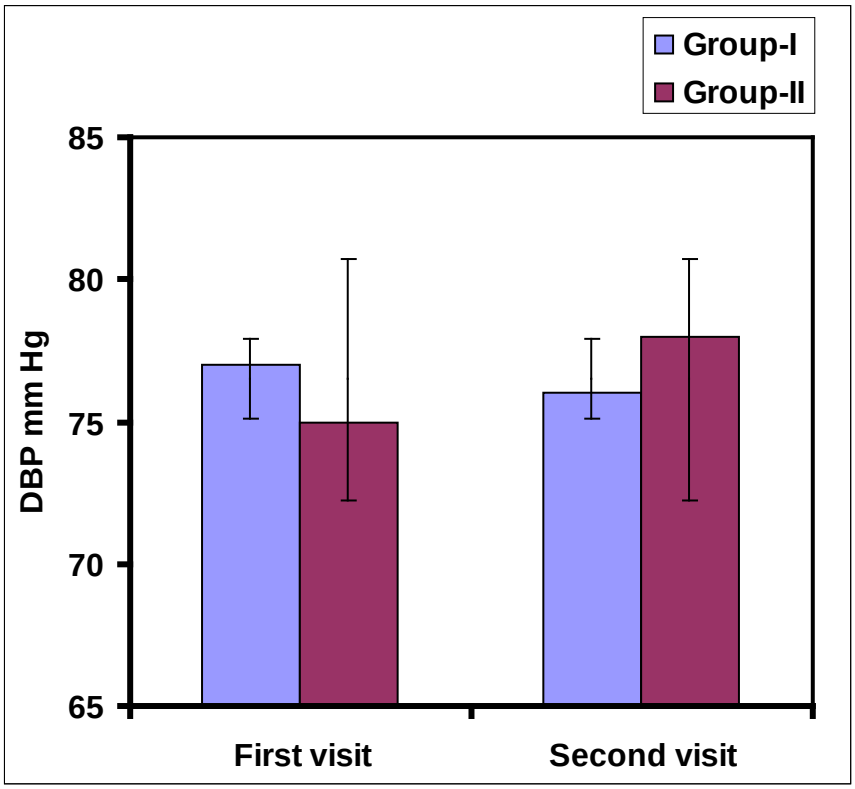

Fig. 35. Mean diastolic blood pressure in patients of Group-I and Group-II at different visits

4.7 Comparison of Echocardiographic and ETT parameters of patients of Group-I and Group-II, at first and second visits

Echocardiographic data: In patients of Group- I, Echocardiographic data obtained from left ventricular M mode measurements such as IVST, PWT, LVIDD and LVIDS were comparable between first and second visit (Fig. 35 and Table VII). This may be due to short period of observation. Cardiac anatomical changes such as increment of wall thicknesses were found after prolonged exposure of LT4 at suppressive dose in other studies (Biondi et al., 1993; Biondi et al., 2000).

Table VII. Echocardiographic data of left ventricle in patients of Group-I and Group-II at first and second visits.

Parameters	Group-I (n=30) mean ±SD		Group-II (n=30) mean ±SD	
	At first visit	At second visit	At first visit	At second visit
IVST (mm)	7 ± 1	7±1	7 ± 1	7 ± 1
PWT (mm)	8 ± 1	8 ± 1	7 ± 1	8 ± 1 †
LVIDD (mm)	43 ± 3	42 ± 4	44 ± 3	45 ±3 †
LVIDS (mm)	28 ± 2	28 ±2	28 ± 2	28 ± 2
EF (%)	65 ± 4	65 ± 5	66 ± 4	66 ±3
LVM (gm)	98 ± 17	96 ± 18	99 ± 17	110 ±15 †‡
LVMi (gm/m^2)	66 ± 10	65 ± 10	66 ± 10	74 ±10 †‡
FS (%)	34 ± 3	34 ±4	35 ± 3	39 ± 3 †‡
mVCFc (cir/sec)	1.21 ±0.2	1.16 ± 0.22	1.23 ± 0.14	1.42 ± 0.18†‡
Peak Aortic Velocity (cm/sec)	102 ± 16	94 ± 12	99 ± 16	102 ±13
ET (msec)	291 ± 19	284 ± 24	286 ± 19	274 ± 26 •

* p <0.05 Group-I between first and second visits
† p <0.05 Group-II between first and second visits.
‡ p <0.05 Group-I versus Group-II at second visits
• p <0.05 Group- I at first visit versus Group-II at second visit

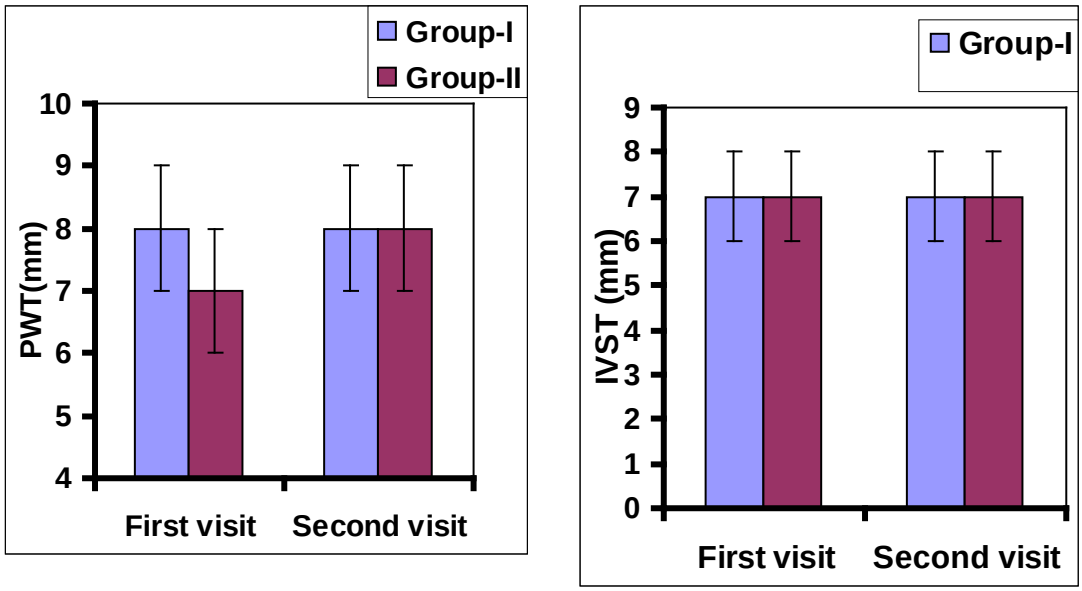

Fig. 36. Left: Mean posterior wall thickness (PWT). Right: Mean interventricular septal thickness (IVST) of two patients groups at two visits

Observing these data it can be assessed that deterioration of cardiac morphology can be minimized by optimization of dose of LT4 which are keeping with findings of previous studies (Fazio et al., 1995; Mercuro G et al., 2000). IVST at first and second visits of Group-II patients was comparable. PWT and LVIDD were significantly higher in patients of Group-II at second visit compared to first visit (*$p<0.05$) (Fig. 36).

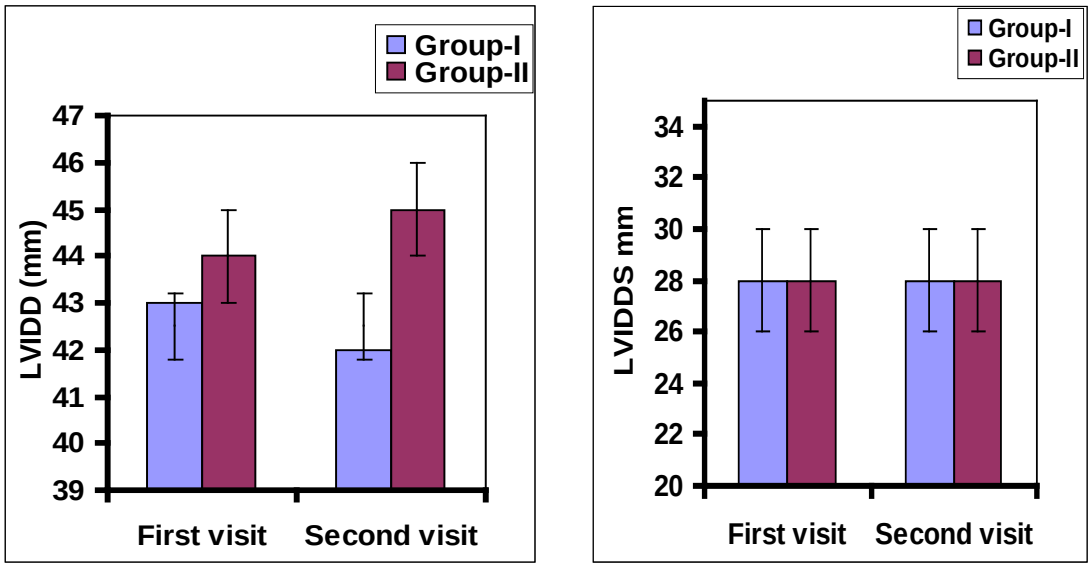

Fig. 37. Left: Mean left ventricular internal diameter during diastole (LVIDD)
Right: Mean left ventricular internal diameter during systole (LVIDS) in patients of Group-I and Group-II at first and second visits

No change was found in LVIDS, ejection fraction between patients of Group-I and Group-II between first and second visits (Fig. 36 and Table VII). It can be explained by the basic pathology causing cardiac alteration by thyroid hormone mentioned by other authors that ejection fraction remains unaffected for a period of time as contractility of myocardium is increased and systemic vascular resistance is decreased in hyperthyroid condition (Haider AW et al., 1999, Klein I and Danzi S, 2007). It was found that left ventricular mass (Group-II, second visit, 110 ± 15 gm (range, 83- 148 gm); first visit, 98 ± 17 gm (range, 70- 143 gm), ***$p<0.05$***) and left ventricular mass index (Group –II, at second visit, mean, 74 ± 10 gm/m^2, range, 59-

97 gm/m^2; at first visit, mean 66 ± 10 gm/m^2, range, 51-97 gm/m^2, (***p<0.05***) as shown in Fig. 37 and Table VII were significantly different at first and second visits. It has been interpreted that left ventricular mass increment reflects the integrated adverse effects on the heart of increased hemodynamic load and vascular damage and predicts subsequent mortality. There is increase the risk of sudden death due to increment of left ventricular mass even not exceeding hypertrophy threshold (Devereux RB, 2004; Haider AW et al., 1998).

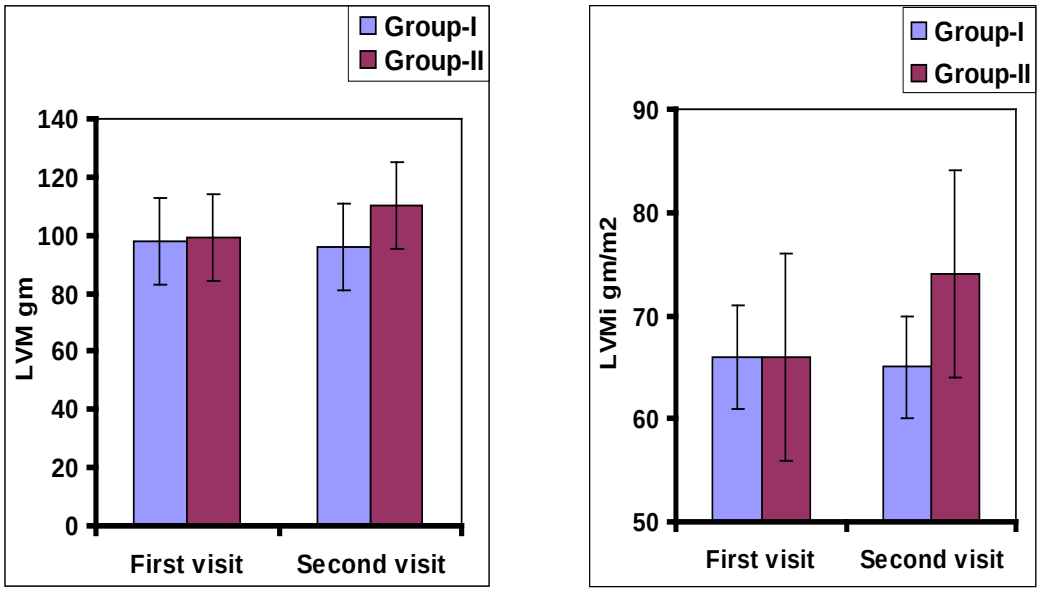

Fig. 38. Left: Left ventricular mass (LVM) and Right: Left ventricular mass index (LVMi) in two groups at two visits

In the present study, significant changes were observed in patients of Group-II at second visit regarding their cardiac morphology and functions. Increased LVM, LVMi, FS% and mVCFc were also observed in patients with DTC receiving LT4 reported by Biondi B et al., (1993) in their study. It is remarkable that the period of exposure of LT4 was shorter in present study (6-12 months), whereas similar undesirable cardiac effects were also observed where period of exposure of LT4 to patients varied from 1-9 yrs (Biondi B et al., 1993). Cardiac hypertrophy induced by thyroid hormone excess may be due to increment in total myocardial protein which is indirectly mediated by increase in cardiac workload (Biondi B et al.1993)

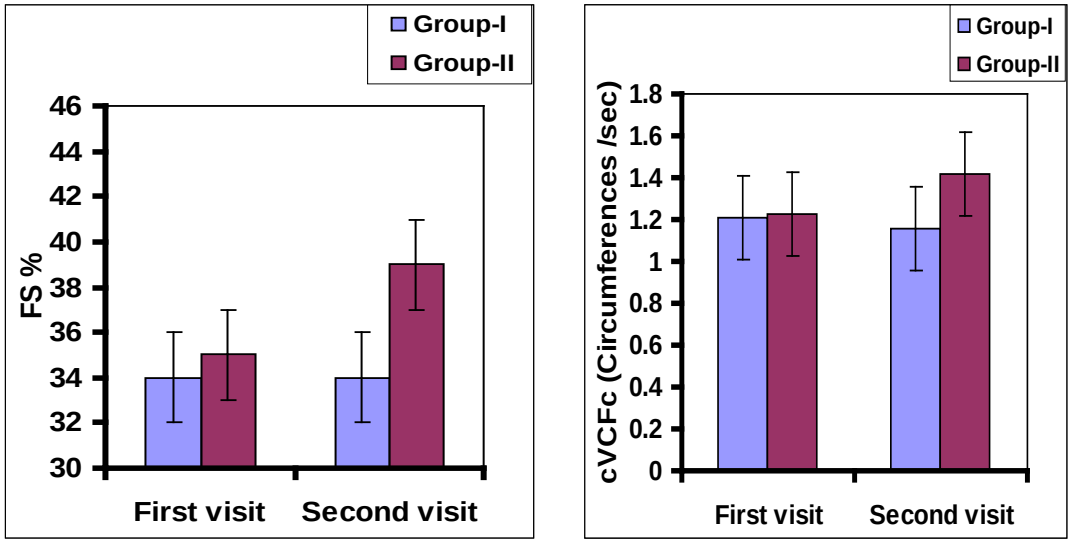

Fig. 39. Left: Mean fraction shortening and Right: Mean heart rate adjusted circumferential fiber shortening in patients of Group-I and Group-II at first and second visits.

Fraction shortening was increased at second visit of patients on conventional dose (Group-II) compared to their first visit and also differed from data of second visit of Group-I patients (FS%, Group-II, second visit, mean, 39 ± 3%; range, 32-44%; at first visit, mean, 35 ± 3%; range, 30-41% ***p<0.05***; Group –I, at second visit, mean, 34 ± 4%; range, 26-46%; at first visit, mean, 35 ± 5%; range, 29-40%, p>0.05) as shown in Fig. 38 and Table VII. Heart rate adjusted mean velocity of circumferential fiber shortening (mVCFc) was also slightly higher in patients of Group-II at their second visit compared to their first visit parameters and Group-I patients data (mVCFc, Group-II, second visit, 1.42 ±0.18 circumferences/sec versus first visit, 1.23±0.14 circumferences/sec, (***p<0.05***) and with second visit of group-I, 1.16±0.22, ***p<0.05***) (Fig. 38 and Table VII). These findings were also comparable with the data of another study done by the same author on patients of endogenous subclinical hyperthyroidism where patients were kept to slightly high thyroid hormone for at least 6 months and cardiac parameters were observed. The authors observed that even short time thyroid hormone exposure might have adverse effects on heart (Biondi B et al., 2000). Although, findings of a previous study done by Shapiro LE et al., (1997) differed from their results.

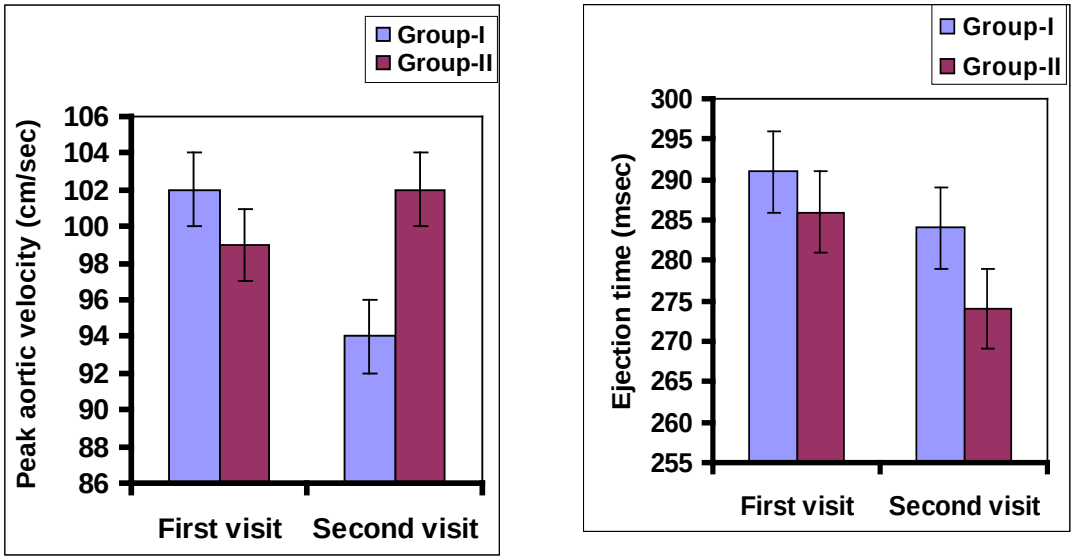

Fig. 40. Left: Mean peak aortic velocity and Right: Mean ejection time and in patients of Group-I and Group-II at first and second visits.

PAV and ET: Low peak aortic velocity was observed after dose optimization but it was consistently increased in patients who were getting higher doses of LT4. These observed differences were not statistically significant in peak aortic velocity in patients of Group II at second visit. Statistically significant shorter ejection time was noted in Group-II patients at second visit compared to first visit of Group-I (ET, Group-I, at first visit, 291 ± 19 msec, Group-II, 274 ± 26) (***p<0.01***) (Fig. 39 and Table VII).

Table VIII. Doppler and tissue Doppler Echocardiographic diastolic function parameters in patients of Group-I and Group-II at first and second visits.

Parameters	Group-I (n=30) mean ±SD		Group II (n=30) mean ± SD	
	At first visit	At second visit	At first visit	At second visit
E (cm/s)	83 ± 12	77 ±10	79 ± 12	73 ± 9 •
A (cm/s)	55 ± 11	51 ± 8	56 ±9	58 ± 8 ‡
E/A	1.54 ± 0.3	1.54 ± 0.3	1.4 ± 0.2	1.29 ± 0.2 †
IVRT (msec)	82 ± 10	85 ± 8	76 ± 9	71 ± 8 ‡
Dct (ms)	154 ± 16	155 ± 16	150 ± 20	127 ± 18 ‡
Tei index	0.33 ± 0.04	0.33 ± 0.09	0.33 ± 0.1	0.31 ± 0.17
Lateral septal mitral annular				
Em (cm/s)	19 ± 6	23 ± 3	22 ±3	23 ±4 •
Am (cm/s)	13 ± 4	15 ± 3	15 ± 5	19 ± 6 • †‡
E/Em	4.2 ± 1	3.5 ± 1	3.5 ± 1	3 ±1 •
Mod Tei	0.32 ± 0.05	0.34 ± 0.08	0.31 ±0.05	0.48 ± 0.06• †‡

* $p<0.05$ Group-I versus Group-I between first and second visits
† $p<0.05$ Group-II versus Group-II between first and second visits.
‡ $p<0.05$ Group-I versus Group-II at second visit
• $p<0.05$ Group-I at first visit versus Group-II at second visit

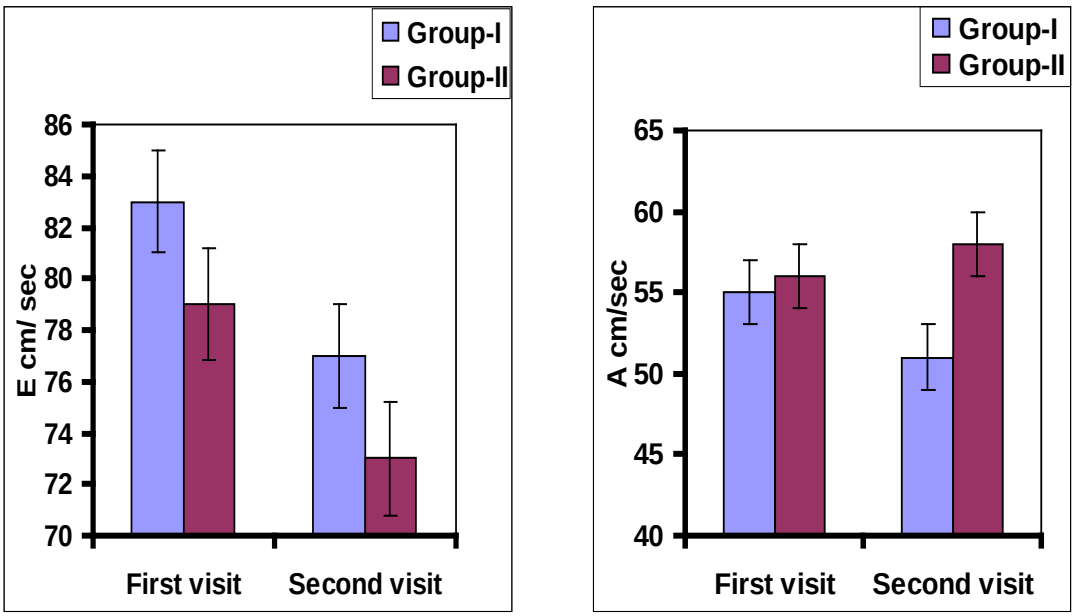

Fig. 41. Left : Mean early diastolic velocity (E). Right: Mean late diastolic velocity (A) in patients of Group-I & Group-II at first and second visits

E and A velocity: Significantly low early diastolic flow velocity (E) through mitral valve in Group-II was observed at second visit compared to first visit of Group-I. (Group –I, 83±12 cm/sec and Group-II, 73±12 cm/sec) (Fig. 40 and Table VIII).

Increased late diastolic flow velocity (A) through mitral valve in Group-II was observed in second visit mean 58± 8 cm/sec compared to second visit finding of patients of Group-I (Group-I, mean, 51±8 cm/sec, Group-II mean, 58±8 cm /sec at second visit (***p<0.01***) (Fig. 40 and Table VIII). By the influence of thyroid hormone, hypercontractility causes low left ventricular filling and low distensibility of myocardium cause low E wave and it also causes decreased afterload and systemic vascular resistance, thereby increased late (A) diastolic flow is seen. These findings are comparable with findings of the study by Minz G et al., 1991.

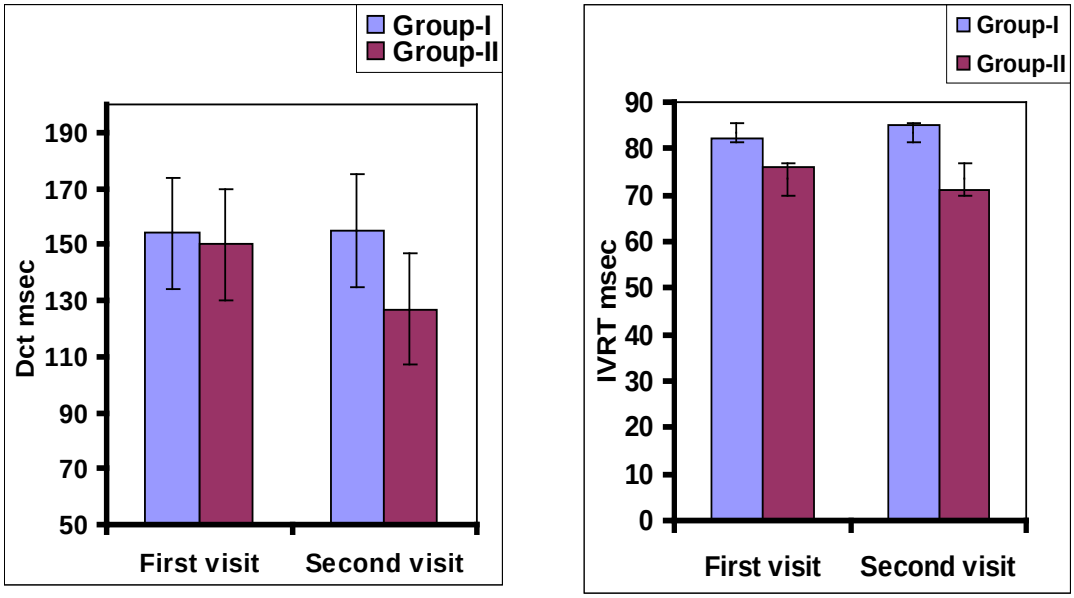

Fig. 42. Left : Mean deceleration time (Dct) and Right: Mean isovolumic relaxation time (IVRT) in patients of Group-I & Group-II at first and second visits

Isovolumic Relaxation Time and Deceleration Time: IVRT, (Group-I, mean 85 ± 8 m sec, Group-II, 71±8 m sec at second visit, **** p<0.001***), deceleration time (Group-I, mean, 155±16 m sec, Group-II, 127 ± 18 m sec at second visit, ****p< 0.001***) of E wave of Group-II were significantly low compared to values of Group-I patients at second visit. Tei index was comparable in all groups at different visits (Fig. 41 and Table VIII). Decreased deceleration time and IVRT in the patients of Group–II

could be explained by the hypercontractile state of myocardium due to LT4 exposure in higher dose (Haider AW et al., 1998; Klein I and Danzi S, 2007; Minz G et al., 1991). The increased levels of mRNA encoding hyperpolarization- activated cyclic nucleotide –gated channel (HCN2) may be due to the hyperthyroid state. This acts on myocyte causing each myocyte to act as latent pace making unit. Thus hypercontractile state is consistent with thyroid hormone effect on heart rate. Small increment of LT4 increases the contractility of heart by increasing HCN2 mRNA (Pachucki J et al., 1999).

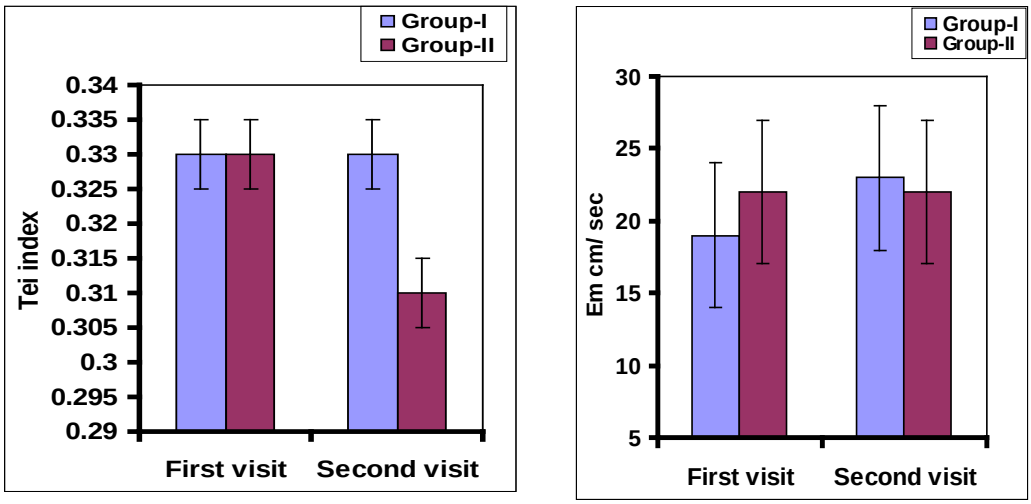

Fig. 43. Left: Mean Tei index and Right: Mean early diastolic myocardial velocity (Em cm /sec) in lateral mitral annulus in tissue Doppler imaging in patients of two groups at two visits.

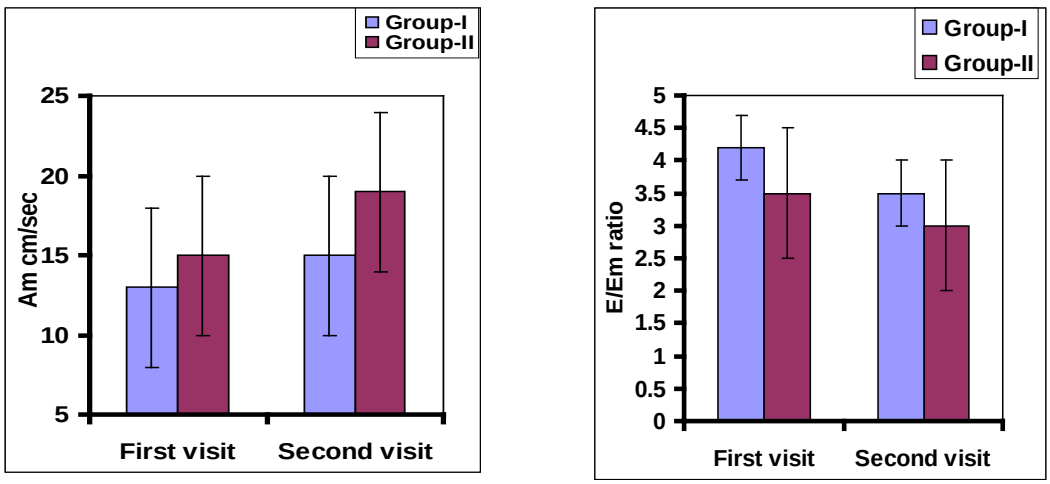

Fig. 44. Left: Mean late myocardial diastolic velocity (Am) in tissue Doppler imaging and Right: E/Em in patients of Group-I and Group-II at first and second visits.

Tissue Doppler imaging at lateral wall of mitral annulus showed that early diastolic peak (Em) was comparable in patients of Group-I at two visits but patients of Group–II showed slightly higher Em level at second visit compared to Em of Group –I at first visit (Em, Group-I, 19±6 cm /sec at first visit, Group-II, 23 ± 4 cm /sec at secondt visit ***p<0.03***) (Fig. 42 and Table VIII). Late diastolic flow (Am) (mean 19±6 cm/sec) of Group-II patients was higher (***p<0.004***) at second visit compared to other values of patients of Group-I at different visits and Group-II **(*p< 0.003**) at first visit (Figs. 43 and Fig. 45). In few patients of Group-II, late tissue diastolic flow (Am) were higher or equal to early tissue diastolic flow (Em), showing diastolic abnormality may be due to hyperthyroid state (Fig. 46). As a result mean Am velocity was increased. In some of the above mentioned cases Doppler E and A waves were normal but reverse pattern is seen in Em and Am which indicating 'pseudonormalization' of diastolic abnormality (Paulus W J, 1998). In these cases tissue Doppler imaging provides information about early changes of diastolic dysfunction.

E/Em was low at second visit of Group-II compared to value of E/Em in patients of Group-I at first (Fig. 43 and Table VIII).

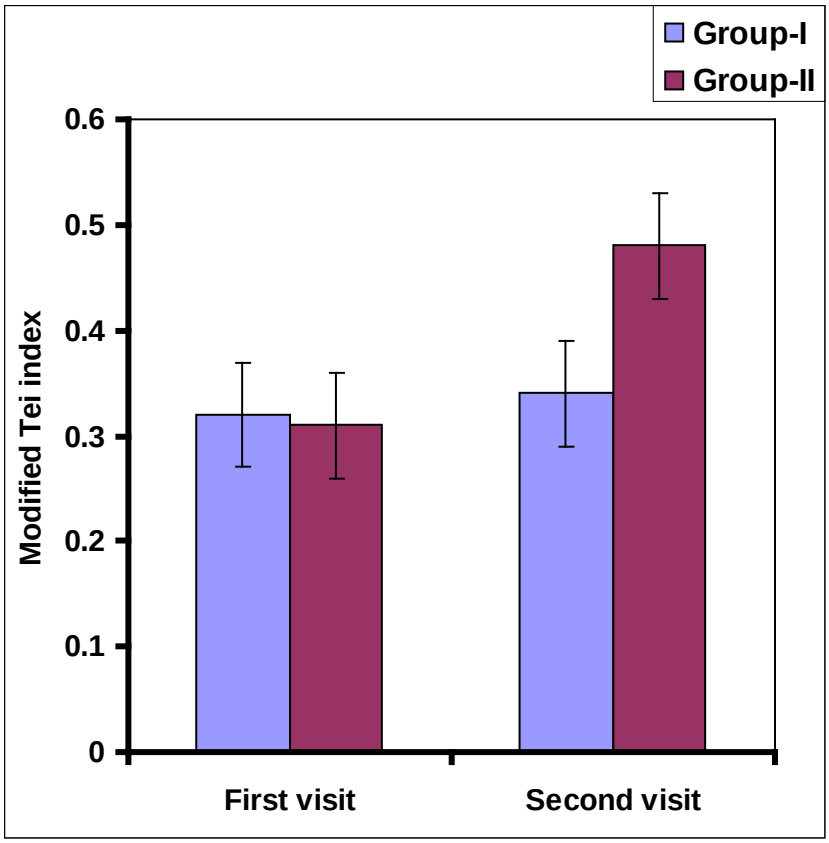

Fig. 45. Mean modified Tei index in patients of Group-I and Group-II at first and second visits.

Significantly increased modified Tei index was observed (mean 0.48 ± 0.06) in last follow up of patients of Group-II compared to value of Mod Tei index of Group-I patients at two visits and that of Group-II patients at first visit (***p<0.001***) (Fig. 44 and Table VIII). Although similar Tei Index was observed in the patients at all time points (Fig. 42). Tei index is dependent on he art rate, preload and after load, but Modified Tei index is not dependent on those. Another advantage of modified Tei index is, it is measured by the parameters (IVRT, ET) in same cardiac cycle (Keser N et al., 2005; Karatzis EN et al., 2009; Citro R et al., 2008)

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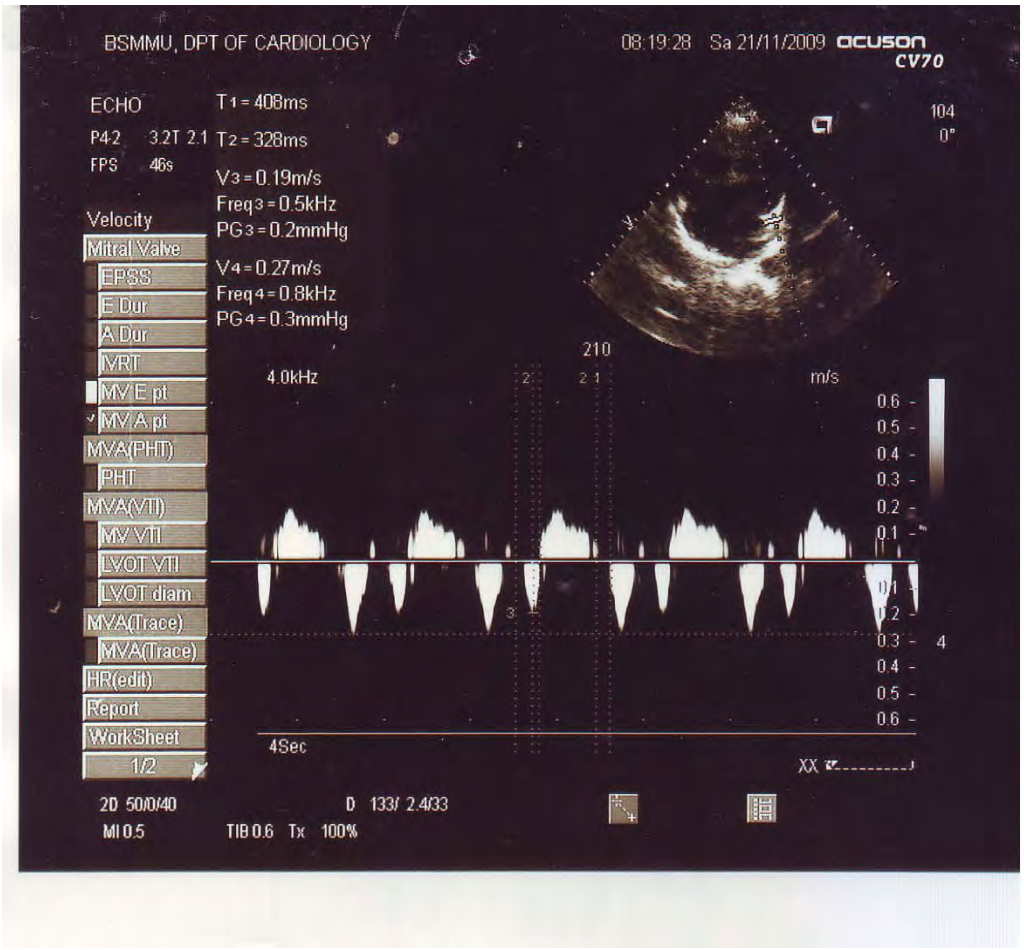

Fig. 46. Normal pattern of Em (27cm/sec) and Am (21 cm /sec) waves of tissue Doppler imaging of a patient with differentiated thyroid carcinoma on LT4 therapy showing slightly high velocities.

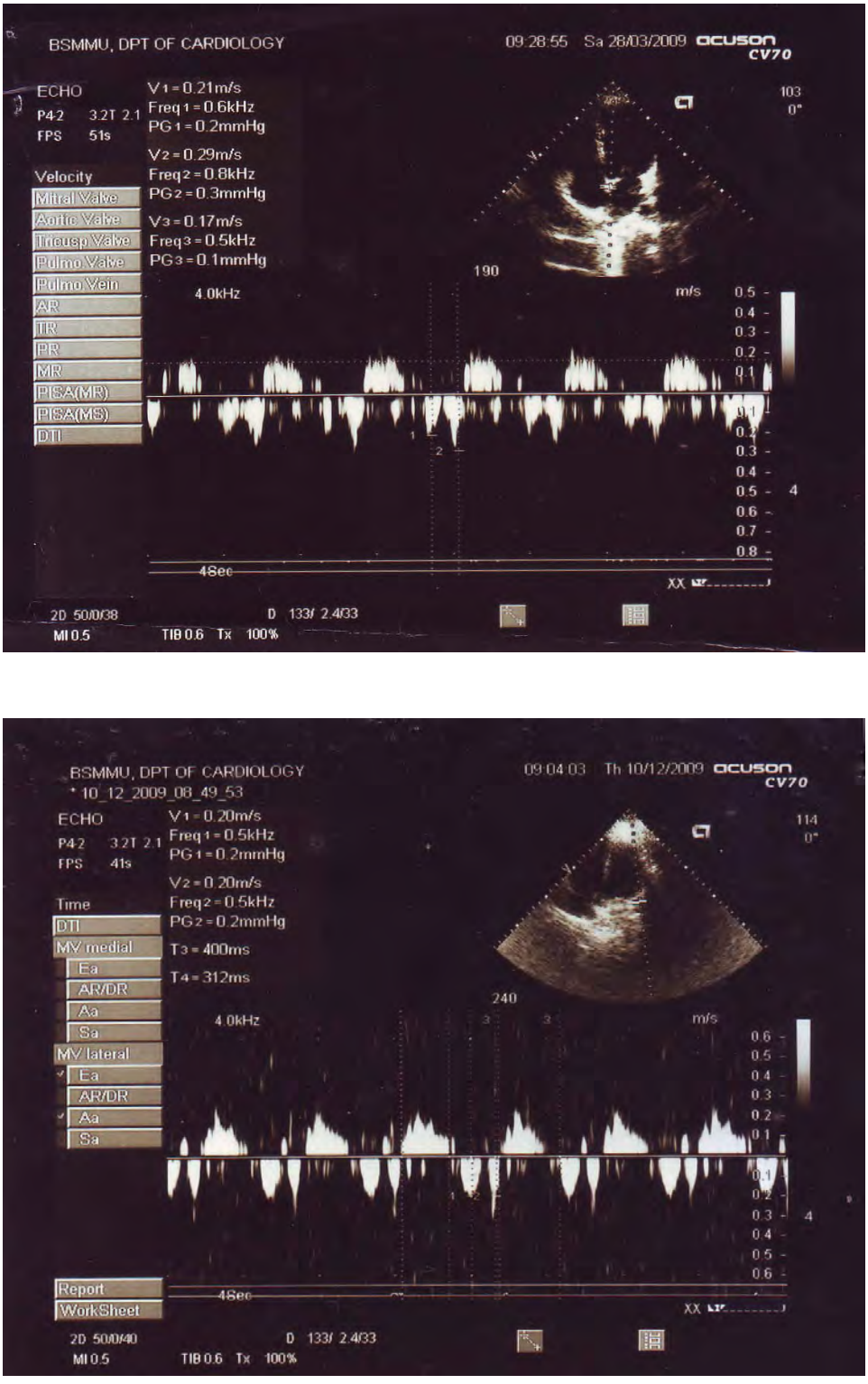

Fig. 47. Abnormal pattern (reverse) of Em and Am waves observed in two different patients of Group- II at second visit indicating diastolic abnormality

Table IX. Exercise Tolerance Test of patients of Group-I and Group-II at first and second visit.

ETT parameters	Group-I (n=30) mean ±SD		Group II (n=30) mean ±SD	
	At first visit	At second visit	At first visit	At second visit
Exercise				
HR (beats/min)	173 ± 13	169 ± 14	179 ± 11	175 ±13
SBP (mmHg)	147 ± 15	149 ± 18	142 ± 14	148 ± 13
DBP (mmHg)	91 ± 6	93 ± 5	92 ± 7	92 ±6
METS	10 ± 1	11 ± 1*	10 ± 1	10 ± 1
Double product ($X10^3$)	25 ± 4	25 ± 4	25 ± 4	26 ± 4
Duration of exercise (min)	9 ± 1	9 ± 1	9 ± 1	9 ± 1
**p<0.05 significant difference between data of Group-I between visits*				

At the first visit, it was observed that METS of patients of Group-I and Group-II were lower compared to control subjects (Table V). It could be explained by the fact that most of the patients with DTC feel some sort of fear and uncertainty and some short and long-term emotion related physical negative effects attributed by surgical procedure and radioiodine therapy (Hoftijzer HC et al., 2008; Sawka et al., 2009), which in turn lowered their exercise capacity. It was observed that patients of Group-I at second visit showed improved METS compared to similar METS of Group-I at first visit and Group-II patients at different visits (***P<0.05***). Patients of all groups at different visits showed similar duration of exercise capacity. Patients exercise capacity was less compared to age matched healthy adults of control groups (***p <0.05***) (Tables V and IX). Maximum predicted heart rate during ETT was achieved by almost every patient quickly. It may be explained that muscle contractility is slightly increased in excess exposure of thyroid hormone. Exercise intolerance in hyperthyroid patients may result from an inability to further increase heart rate and ejection fraction or lower systemic vascular resistance as would normally occur with exercise (Klein I and Danzi S, 2007).

The present study shows that TSH suppressive therapy with LT4 can cause hyperthyroid symptoms and changes in myocardial structure and function and deterioration of exercise capacity. However, LT4 dose adjustment on the basis of lean body mass can reverse and almost completely normalize cardiac parameters and significantly reduce thyrotoxic symptoms.

ECG: There was no ECG abnormality in either control subjects or patients of Group-I and Group-II. Patients of Group-I and Group-II, were in sinus rhythm but patients had shown increased heart rate. None showed ECG criteria of LV hypertrophy and atrial fibrillation in the present study may be due to shorter period of LT4 therapy.

4.8 Strength and limitation of the study

Strength of this study includes selection of young, low risk group of patients with differentiated thyroid carcinoma who have comparable BMI with healthy volunteers and without any associated cardiac problems. DXA is a precise and reproducible method to measure body composition including measurement of lean body mass. Echocardiographic parameters using Doppler and tissue Doppler imaging technique were evaluated by a single blinded cardiologist. Unlike other studies, cardiac effects of increased LT4 were compared prospectively with the same patients at different time points and also with healthy volunteers at baseline. Other studies evaluated cardiac effects of LT4 in patients after exposure of LT4 for a certain period of time (ranged 6 months to 9 yrs) and compared with healthy volunteers only (Biondi B., et al 1993, Mercuro G et al., 2000). They did not compare the cardiac effects of conventional dose of LT4 with optimized dose of LT4 based on lean body mass. Fixed dose of 200 µgm/day of LT4 was found to be overdose for the comparatively lean and thin patients of our country in the present study. This optimization of dose of LT4 would keep the patients free from undesirable cardiac effects for the rest of

their life (Smit J W et al., 2005). So far known, present study is the first study where cardiac effects of LT4 were compared between conventionally advocated dose and optimized dose depending on lean body mass. Moreover, this is the first study to measure myocardial systolic and diastolic performance by using Tissue Doppler imaging in LT4 supplemented patients with DTC prospectively. Tei index was measured and modified Tei index was also measured to see the total myocardial performance, which was not observed, before on patients with DTC in the settings of present study.

Limitation of the present study was comparatively short follow up time after administration of high LT4 and optimized dose of LT4 in two groups of patients with differentiated thyroid carcinoma. Still some significant cardiac changes have been observed within this period.

Chapter V

Conclusions

Chapter V

Conclusions

Differentiated thyroid carcinomas are most curable cancers. Properly treated patients with differentiated thyroid carcinomas have almost normal life expectancy. In case of papillary thyroid carcinomas 10 years survival were found in 95% cases. Conventional mode of treatment of patients with differentiated thyroid carcinomas is total thyroidectomy followed by radioiodine ablative therapy. These treatment procedures totally destroy the thyroid tissue in the view of prevention of regrowth and recurrences of carcinoma. As a result patients become hypothyroid and patients have to be supplemented by levothyroxine life long. This LT4 supplement is given not only to alleviate hypothyroid state but also in TSH suppressive dose to retard growth and spread of cancer.

This LT4 supplement in TSH suppressive dose keeps the patient in subclinical hyperthyroid state. This LT4 dose has some cardiac side effects such as increased heart rate, increased incidence of atrial arrythmias, enhanced left ventricular systolic function, diastolic dysfunction and increased left ventricular mass.

American Thyroid Association recommended initial thyrotropin (TSH) suppression to below 0.1 mIU/ml in high risk patients and maintenance of the TSH at or slightly below the lower limit of normal (0.1-0.5 mIU/L) is appropriate for low risk patients with DTC.

Lean body mass is the precise predictor in dosing of the drugs which are hydrophilic. In a recent study, it has been shown that individual requirement of LT4 supplement is mostly dependent on lean body mass rather than total body weight. LBM is a potentially useful predictor of the pharmacokinetic behavior of drugs which are highly water soluble. LT4 is water soluble and its pharmacokinetics is dependent on lean portion of body. LT4 is deiodinated to T3 (active form of hormone) in muscle, kidney and liver.

T4 is deiodinated to rT3 (reverse T3, inactive form) in skin. Fatty tissue has no role in metabolism of LT4. Dual Energy X-ray Absoptiometry is the recent and precise method to measure the lean body mass.

Sixty patients with differentiated (papillary) thyroid carcinoma (young age group) without any signs of metastases, previous cardiac problems and chronic disease were consecutively enrolled in the study. All patients had undergone total thyroidectomy and then received about 100 mci radioiodine ablative therapy and subsequently 200 µgm LT4 daily for initial 2 months. Age, weight, height, body surface area, body mass index and life style matched 23 healthy euthyroid volunteers were also selected. All clinical, biochemical, echocardiographic and Exercise Tolerance Test (ETT) data of healthy adults control were obtained for comparison with patients at baseline study after two months of radioiodine ablative therapy and on LT4 replacement on conventional 200 µgm/day at first follow up visit. Then 60 patients were grouped as Group-I and Group-II, each group consisted of 30 patients. Thirty patients of Group-I had undergone dual energy X-ray absortiometry (DXA) investigation to estimate lean body mass and received optimized LT4 dose depending on lean body mass (about 131± 23 µgm/day, 3.5-4.0 µgm/kg/ LBM/day). In Group-II, 30 patients continued the conventional fixed dose of LT4 (200 µgm/day). Patients of both groups were followed up clinically and hormone assay were done at 3 months interval. At 6-12 months of LT4 supplement (conventional and LBM based) all study parameters (Symptom Rating Score, hormone data, echocardiographic data and ETT) were reevaluated.

Serum FT3, FT4 were higher and TSH was suppressed in patients with DTC at conventional LT4 dose (200 µgm/day) compared to healthy control and patients with optimized dose of LT4 (mean±SD, 131± 23 µgm/day) of Group-I at second visit. Symptom Rating Scale score and heart rate were significantly higher in Group-II than healthy adults. SBP, DBP were slightly higher in patients (Group-II) after receiving conventional LT4 suppressive dose but were not statistically significant. Left ventricular mass, left ventricular mass index, fraction shortening and heart rate adjusted

mean velocity of circumferential fiber shortening were increased in patients of Group-II after exposure of conventional LT4 dose compared to patients received optimized dose (Group-I) at second visit. Ejection time was also decreased in patients of Group-II at second visit compared to patients of Group-I at first visit. Mild degree of diastolic function abnormalities were also noted in Group-II patients at second visit compared to Group-I patients. Early (E) diastolic velocity of Group-II was significantly low at second visit compared to that of Group-I at first visit and late (A) was comparatively high in group II compared to Group-I at second visit. Deceleration time (Dct) was significantly low in Group-II compared to patients in Group-I at two visits and patients of Group-II at first visit. Similarly in tissue Doppler imaging technique, late diastolic mitral annular velocity (Am) was higher in Group-II compared to Group-I at second visit. Significantly high modified Tei index was also noted in patients of Group-II at second visit compared to their first visit value and patients of Group-I at different visits. Exercise capacity as evaluated by exercise tolerance test, showed significant difference in metabolic equivalent between healthy volunteers and patients groups at first visit but no difference was found between two patient groups at different time points.

From the observations of the present study, it may be concluded that therapeutic suppression of thyroid stimulating hormones requires optimization of LT4 dose. Lean body mass based LT4 therapy (3.5-4 µgm/kg/LBM/day; 131±23 µgm/day) keeps the TSH level in expected level. This levothyroxine supplement dose inevitably prevents deterioration of cardiac morphology and function and thus improves quality of life for the patients with differentiated thyroid carcinoma of low risk group.

Further studies are recommended at extended time points for evaluation of good exercise tolerance and other cardiac parameters in patients with differentiated thyroid carcinoma with low risk group on lean body mass based LT4 replacement therapy.

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Appendix

Data sheet of patients with thyroid carcinoma

Name: Optimized Group-I	Age: 35 yrs	Sex: F	**Reg no: Sl no-*1**
Ht- 147 cm	Wt: 42 Kg	BMI- 19 Kg/m^2	BSA- 1.32 m^2
LBM- 30 kg			
Address: **		Phone:**	
Diagnosis: Differentiated thyroid carcinoma	**Histopathology:** Papillary thyroid carcinoma		
Surgery:			
1. Partial thyroidectomy—right/left hemithyroidectomy -X		Date:	
2. **Total thyroidectomy-done**		Date:25/11/2008	
Postsurgical Investigations: After 15 days of operation	**1.TSH- >90** mIU/L	2. Tg- 2.39 n gm/dL	
3. Usg: No thyroid tissue	**4. Thyroid scan:** No radiotracer concentration in thyroid bed		
5.^{131}I Uptake: 1%	**6. Serum calcium level:** 8.9 mg/dl (Normal, 8.5-10.5 mg/dl)		
Radioiodine therapy: Dose: 100 mci			**Date: 07/01/09**
Post therapy scan: faint activity			Date:14/01/09

Hormone Assay:	First visit- Date: 11/03/09	Second visit- Date: 10/11/09
FT3 (Normal, 2.8-9.5 pmol/L)	9.45	7
FT4 (Normal, 9.5 25.5 pmol/L)	28	22
TSH (Normal, 0.3-5 mIU/L)	0.08	0.1
Thyroglobulin (Normal, 4-14 ng/dL)	3	2.8

Hyperthyroid Symptom Rating Scale (Reg no: Op Gr *1)

	Characteristics	Score: 1st visit	2nd
	Nervousness	11/03/09	10/11/09
0	Absent		
1	Anxious only with stress		
2	Occasionally anxious at rest		
3	Often anxious, difficulty working or concentrating	**1**	0
4	States freely that feels very nervous most	----	
	Sweating		
0	Only with activity		
1	At rest but only in warm temperature		
2	At rest in temperate climates, mainly involving the hands and intriginous zones		
3	At rest involving many body areas.		
4	Profusely diaphoretic almost constantly.	2 ----	1
	Heat intolerane		
0	Normal temperature tolerance.		
1	Periods of feeling warmer than those in the same room		
2	Significant difficulty with heat, requiring air conditioner constantly in the summer time		
3	Excessive difficulty with heat even in temperature climate.		
4	Extreme difficulty with heat, does not feel comfortable even in cold weather as evidenced by lack of need for warm clothing or bed covers.	2 ------	1
	Hyperactivity		
0	Normal activity		
1	Increased activity level, increased productivity		
2	Increased productivity; decreased sleep time.		
3	Performs some purposeless activity		
4	Frequent episodes of purposeless activity; unable to sit still during examination	0 ------	0
	Tremor: Examination of outstretched hands		
0	Absent		
1	Barely perceptible		
2	Tremor demonstrated readily on examination		
3	Marked tremor but able to perform fine motor skills		
4	Hands shake excessively, difficulty performing motor skills.	0 ------	
	Weakness		
0	Normal strength		
1	Subjective weakness but with normal tolerance		
2	Decreased exercise tolerance to near maximal activity		
3	Decreased tolerance to stair climbing or arising from chair		

4	Extreme w eakness su ch that p atient c an barely l ift o bjects or walk up stairs	**2** ----	0
0 1 2 3 4	Hyperdynamic precordium Normal precordium activity apical impulse Tachycardia, 90 beats per minute with normal apical impulse. Tachycardia, 90 beats per minute with increased apical impulse Tachycardia, 110 beats per minute with increased apical impulse Tachycardia, 110 beats per minute and carotid upstroke both increased, systolic outflow murmur.	 1 ------	 0
0 1 2 3 4	Diarrhoea 1 bowel movement (BM) per day; formed stool 2-4 formed BMs per day 1-4 loose stools per day 4 formed BMs per day 4 loose stools per day	 0 ------	 0
0 1 2 3 4	Appetite Appetite normal, no weight loss Appetite normal, no weight loss Appetite increased, no weight loss Appetite increased, weight loss Appetite decreased, weight loss	 0 ------	 0
0 1 2 3 4	Assessment of daily function (degree of incapacitation) Normal (none) Minimal impairment (10%) Mild impairment (30%) Moderate impairment (60%) Severe impairment (90%)	 1 ------	 0
	Total score	9	2

Echocardiographic data:

Patient's name: Optimized Group Age: 35 yrs Reg no: Sl no: *1

		Ist visit Dt:11/03/09	2 nd visit Dt: 11/11/09	Normal range
Echocardiographic data				
1	PWT (mm)	7	7	9 ± 1(M); 8 ± 1 (F), Japan (JP)
2	IVST (mm)	6	6	9 ± 1(M); 8± 1 (F), JP
3	LVIDD (mm)	40	39	48± 4(M); 44 ± 3 (F), JP
4	LVIDS (mm)	27	26	30± 4(M); 28 ± 3 (F), JP
5	LVmass (g)	78	75	133± 28(M); 105 ± 22 (F), JP
6	LVMi (g/m^2)	60	57	76± 16(M); 70± 14 (F, JP
7	EF%	66	63	64 ± 5 (M), 66 ± 5 (F), JP
8	FS%	32	33	35 ± 4
9	E (cm/s)	70	66	74 ± 14 (M); 88±13 (F), JP
10	A (cm/s)	50	48	43 ± 10 (M); 45 ±11 (F), JP
11	E/A	1.4	1.37	1.8 ± 0.5 (M); 2.0 ± 0.6 (F), JP
12	IVRT (msec)	77	80	83 ± 9
13	mVCF(circ/sec)	1.1	1.13	1.21± 0.14
14	a ms (IVRT+ET+ICRT)	398	400	400 ± 35
15	Ejection time (ms) (b)	290	298	306 ± 36
16	Tei Index (a-b/b)	0.37	0.34	0.35± 0.10 (M), 0.32 ± 0.09 (F), JP
17	Deceleration time (msec)	160	170	186± 34 (M), 175 ± 33 (F), JP
18	Peak aortic velocity (cm/s)	109	106	90 ± 10
19	E_m cm/sec (lateral)	25	22	16± 3.10 (M), 16.7 ± 3.1 (F), JP
20	A_m cm/sec	21	20	8.2 ± 2.8 (M), 7.2 ± 2.3 (F), JP
21	E/ Em	2.8	3	4.8 ± 2.8 (M), 5.5± 1.3 (F), JP
22	$a^{/}$ ms	398	415	426 ± 25; Turkey
23	$b^{/}$ ms	290	278	316 ± 36; Turkey
24	Modified Tei index ($a^{/}$- $b^{/}$ / $b^{/}$)	0.37	0.49	0.33 ± 0.05; Turkey

Patients name: Op Gr *1 **Reg no: Op Gr *1**

Exercise Tolerance Test:		
	First visit Date: 11/03/09	**Second visit Date:11/11/09**
Rest		
Pulse	**94**	**80**
SBP/DBP (mm Hg)	**120/70**	**115/75**
Exercise		
Pulse (bpm)	**189**	**192**
SBP/DBP (mmHg)	**160/90**	**170/100**
METS	**7.4**	**10**
Duration of exercise time	**6.18**	**9.1**
Double product	**30.24×10^3**	**32.62×10^3**
ECG change	**No change**	**No change**

Data sheet of patients with thyroid carcinoma

Name: Coventional Group--II	Age: 26 yrs	Sex: F	**Reg no: Con Gr-*9** 15/01/09
Ht- 147 cm	Wt: 58 Kg	BMI- 24 Kg/m^2	BSA- 1.56 m^2
LBM- X kg			
Address: **		Phone:**	
Diagnosis: Differentiated thyroid carcinoma	**Histopathology: Papillary thyroid carcinoma**		
Surgery:			
1. Partial thyroidectomy—right/left hemithyroidectomy		Date:	
2. Total thyroidectomy- done		Date: 13/11/08	
Postsurgical Investigations:	1.TSH- 71 mIU/L	2. Tg- 3 ngm/dL	
3. Usg: No visualized tissue	4. Thyroid scan: Focal Area of radiotracer activity		
5. ^{131}I Uptake: 3%	6. Serum calcium level: 9.9 mg/ml (normal 8.5-10.5 mg/dl)		
Radioiodine therapy: Dose: 100 mci		Date:15/01/09	
Post therapy scan: Focal Area of radiotracer activity		Date: 22/01/09	

Hormone Assay:	First visit-Date: 15/03/09	Second visit- Date:11/11/09
FT3 (pmol/L)	9.5	10.4
FT4 (pmol/L)	29.2	28.6
TSH (mIU/L)	0.08	0.07
Thyroglobulin (ng/L)	3	2.8

Hyperthyroid Symptom Rating Scale (Reg no: Con Gr-*9)

	Characteristics	Score: 1st	2nd
	Nervousness	15/03/09	11/11/09
0	Absent		
1	Anxious only with stress		
2	Occasionally anxious at rest		
3	Often anxious, difficulty working or concentrating		
4	States freely that feels very nervous most	2 ----	1
	Sweating		
0	Only with activity		
1	At rest but only in warm temperature		
2	At rest in temperate climates, mainly involving the hands and intriginous zones		
3	At rest involving many body areas.	2	2
4	Profusely diaphoretic almost constantly.	-----	
	Heat intolerane		
0	Normal temperature tolerance.		
1	Periods of feeling warmer than those in the same room		
2	Significant difficulty with heat, requiring air conditioner constantly in the summer time		
3	Excessive difficulty with heat even in temperature climate.		
4	Extreme difficulty with heat, does not feel comfortable even in cold weather as evidenced by lack of need for warm clothing or bed covers.	1 ------	1
	Hyperactivity		
0	Normal activity		
1	Increased activity level, increased productivity		
2	Increased productivity; decreased sleep time.		
3	Performs some purposeless activity		
4	Frequent episodes of purposeless activity; unable to sit still during examination	0 ------	0
	Tremor: Examination of outstretched hands		
0	Absent		
1	Barely perceptible		
2	Tremor demonstrated readily on examination		
3	Marked tremor but able to perform fine motor skills		
4	Hands shake excessively, difficulty performing motor skills.	1 ------	1
	Weakness		
0	Normal strength		
1	Subjective weakness but with normal tolerance		

2 3 4	Decreased exercise tolerance to near maximal activity Decreased tolerance to stair climbing or arising from chair Extreme weakness such that patient can barely lift objects or walk up stairs	 **2** ----	 2
 0 1 2 3 4	Hyperdynamic precordium Normal precordium activity apical impulse Tachycardia, 90 beats per minute with normal apical impulse. Tachycardia, 90 beats per minute with increased apical impulse Tachycardia, 110 beats per minute with increased apical impulse Tachycardia, 110 beats per minute and carotid upstroke both increased, systolic outflow murmur.	 0 ------	 0
 0 1 2 3 4	Diarrhoea 1 bowel movement (BM) per day; formed stool 2-4 formed BMs per day 1-4 loose stools per day 4 formed BMs per day 4 loose stools per day	 0 ------	 0
 0 1 2 3 4	Appetite Appetite normal, no weight loss Appetite normal, no weight loss Appetite increased, no weight loss Appetite increased, weight loss Appetite decreased, weight loss	 0 ------	 0
 0 1 2 3 4	Assessment of daily function (degree of incapacitation) Normal (none) Minimal impairment (10%) Mild impairment (30%) Moderate impairment (60%) Severe impairment (90%)	 2 ------	 1
	Total score	10	8

Echocardiographic data:

Patient's name: ** Age:26 yrs Reg no: Con Gr-*9

		Ist visit Dt:15/03/09	2 nd visit Dt: 11/11/09	Normal range
Echocardiographic data				
1	PWT (mm)	7	8	9 ± 1(M); 8 ± 1 (F), Japan (JP)
2	IVST (mm)	7	7	9 ± 1(M); 8± 1 (F), JP
3	LVIDD (mm)	42	46	48± 4(M); 44 ± 3 (F), JP
4	LVIDS (mm)	27	30	30± 4(M); 28 ± 3 (F), JP
5	LVmass (g)	85	116	133± 28(M); 105 ± 22 (F), JP
6	LVMi (g/m^2)	54	74	76± 16(M); 70± 14 (F, JP
7	EF%	70	69	64 ± 5 (M), 66 ± 5 (F), JP
8	FS%	35	38	35 ± 4
9	E (cm/s)	75	78	74 ± 14 (M); 88±13 (F), JP
10	A (cm/s)	50	52	43 ± 10 (M); 45 ±11 (F), JP
11	E/A	1.5	1.5	1.8 ± 0.5 (M); 2.0 ± 0.6 (F), JP
12	IVRT (msec)	88	74	83 ± 9
13	mVCFc (circ/sec)	1.2	1.5	1.21± 0.14
14	a ms (IVRT+ET+ICRT)	388	368	400 ± 35
15	Ejection time (ms) (b)	284	254	306 ± 36
16	Tei Index (a-b/b)	0.36	0.44	0.35± 0.10 (M), 0.32 ± 0.09 (F), JP
17	Deceleration time (msec)	120	120	186± 34 (M), 175 ± 33 (F), JP
18	Peak aortic velocity (cm/s)	126	124	90 ± 10
19	E_m cm/sec (lateral)	20	28	16± 3.10 (M), 16.7 ± 3.1 (F), JP
20	A_m cm/sec	28	15	8.2 ± 2.8 (M), 7.2 ± 2.3 (F), JP
21	E/ Em	2.2	2.7	4.8 ± 2.8 (M), 5.5± 1.3 (F), JP
22	$a^/$ ms	390	420	426 ± 25; Turkey
23	$b^/$ ms	298	290	316 ± 36; Turkey
24	Modified Tei index ($a^/$- $b^/$ / $b^/$)	0.30	0.44	0.33 ± 0.05; Turkey

Patients name: ** **Reg no: Con gr-*9**

Exercise Tolerance Test:		
	First visit Date:15/03/09	Second visit Date:11/11/09
Rest		
Pulse (bpm)	130	100
SBP/DBP mmHg	110/70	120/75
Exercise		
Pulse (bpm)	196	179
SBP/DBP mmHg	150/90	145/85
METS	10	10
Duration of exercise time	9 min 30 sec	9 min 20 sec
Double products	28.2×10^3	22.2×10^3
ECG change	No abnormality	No change

Data sheet of healthy volunteer

Name: **	Age: 28 yrs	Sex: F	**Reg no: Volun*2** 17/02/08
Ht- 148 cm	Wt: 52 Kg	BMI- 25 Kg/m^2	BSA-1.44 m^2
LBM- X kg			
Address: **		Phone:**	

Hormone Assay:	First visit-Date:17/02/08	Second visit- Date:
FT3 (pmol/L)	6.5	
FT4 (pmol/L)	16.2	
TSH (mIU/L)	1.82	

Hyperthyroid Symptom Rating Scale (Reg no: Volun*2)

	Characteristics	Score:1st Date:	2nd
	Nervousness	17/02/08	
0	Absent		
1	Anxious only with stress		
2	Occasionally anxious at rest		
3	Often anxious, difficulty working or concentrating		
4	States freely that feels very nervous most	----	
	Sweating		
0	Only with activity		
1	At rest but only in warm temperature		
2	At rest in temperate climates, mainly involving the hands and intriginous zones		
3	At rest involving many body areas.		
4	Profusely diaphoretic almost constantly.	------	
	Heat intolerane		
0	Normal temperature tolerance.		
1	Periods of feeling warmer than those in the same room		
2	Significant difficulty with heat, requiring air conditioner constantly in the summer time		
3	Excessive difficulty with heat even in temperature climate.		
4	Extreme difficulty with heat, does not feel comfortable even in cold weather as evidenced by lack of need for warm clothing or bed covers.	------	
	Hyperactivity		
0	Normal activity		
1	Increased activity level, increased productivity		
2	Increased productivity; decreased sleep time.		
3	Performs some purposeless activity		
4	Frequent episodes of purposeless activity; unable to sit still during examination	------	
	Tremor: Examination of outstretched hands		
0	Absent		
1	Barely perceptible		
2	Tremor demonstrated readily on examination		
3	Marked tremor but able to perform fine motor skills		
4	Hands shake excessively, difficulty performing motor skills.	------	
	Weakness		
0	Normal strength		
1	Subjective weakness but with normal tolerance		
2	Decreased exercise tolerance to near maximal activity		

3 4	Decreased tolerance to stair climbing or arising from chair Extreme weakness su ch that p atient c an barely l ift o bjects or walk up stairs	 **1** ----	
 0 1 2 3 4	Hyperdynamic precordium Normal precordium activity apical impulse Tachycardia, 90 beats per minute with normal apical impulse. Tachycardia, 90 beats per minute with increased apical impulse Tachycardia, 110 beats per minute with increased apical impulse Tachycardia, 110 beats per minute and carotid upstroke both increased, systolic outflow murmur.	 ------	
 0 1 2 3 4	Diarrhoea 1 bowel movement (BM) per day; formed stool 2-4 formed BMs per day 1-4 loose stools per day 4 formed BMs per day 4 loose stools per day	 ------	
 0 1 2 3 4	Appetite Appetite normal, no weight loss Appetite normal, no weight loss Appetite increased, no weight loss Appetite increased, weight loss Appetite decreased, weight loss	 ------	
 0 1 2 3 4	Assessment of daily function (degree of incapacitation) Normal (none) Minimal impairment (10%) Mild impairment (30%) Moderate impairment (60%) Severe impairment (90%)	 ------	
	Total score	1	

Echocardiographic data:

Patient's name: ** Age: 28 yrs Reg no: Volun *2 Date: 17/02/08

		Ist visit Dt:17/02/08	2 nd visit Dt:	Normal range
Echocardiographic data				
1	PWT (mm)	8		9 ± 1(M); 8 ± 1 (F), Japan (JP)
2	IVST (mm)	8		9 ± 1(M); 8± 1 (F), JP
3	LVIDD (mm)	47		48± 4(M); 44 ± 3 (F), JP
4	LVIDS (mm)	29		30± 4(M); 28 ± 3 (F), JP
5	LVmass (g)	113		133± 28(M); 105 ± 22 (F), JP
6	LVMi (g/m^2)	78		76± 16(M); 70± 14 (F, JP
7	EF%	69		64 ± 5 (M), 66 ± 5 (F), JP
8	FS%	38		35 ± 4
9	E (cm/s)	72		74 ± 14 (M); 88±13 (F), JP
10	A (cm/s)	38		43 ± 10 (M); 45 ±11 (F), JP
11	E/A	1.89		1.8 ± 0.5 (M); 2.0 ± 0.6 (F), JP
12	IVRT (msec)	88		83 ± 9
13	mVCF(circ/sec)	1.21		1.21± 0.14
14	a ms (IVRT+ET+ICRT)	400		400 ± 35
15	Ejection time (ms) (b)	298		306 ± 36
16	Tei Index (a-b/b)	0.34		0.35± 0.10 (M), 0.32 ± 0.09 (F), JP
17	Deceleration time (msec)	170		186± 34 (M), 175 ± 33 (F), JP
18	Peak aortic velocity (cm/s)	98		90 ± 10
19	E_m cm/sec (lateral)	19		16± 3.10 (M), 16.7 ± 3.1 (F), JP
20	A_m cm/sec	9		8.2 ± 2.8 (M), 7.2 ± 2.3 (F), JP
21	E/ Em	3.7		4.8 ± 2.8 (M), 5.5± 1.3 (F), JP
22	$a^/$ ms	396		426 ± 25; Turkey
23	$b^/$ ms	295		316 ± 36; Turkey
24	Modified Tei index ($a^/$- $b^/$ / $b^/$)	0.34		0.33 ± 0.05; Turkey

Patients name: ** **Reg no: Volun *2**

Exercise Tolerance Test:		
	First visit Date:17/02/08	Second visit Date:
Rest		
Pulse (bpm)	78	
SBP/DBP mmHg	110/75	
Exercise		
Pulse bpm	162	
SBP/DBP mm Hg	140/90	
METS	10.4	
Duration of exercise time	10 min	
Double products	$22.64X\ 10^3$	
ECG change	No abnormality	

চিকিৎসা ও গবেষনা কর্মে অংশগ্রহণে রোগীর সম্মতিপত্র

আমি এই মর্মে ঘোষণা করছি যে, আমাকে আমার থাইরয়েড কারসিনমা রোগের চিকিৎসা এবং পরবর্তি ফলোআপ সম্পর্কে অবহিত করা হয়েছে। আমাকে জীবন রক্ষাকারী ঔষুধ থাইরক্সিন সারাজীবন খেতে হবে। তবে এর কিছু কার্ডিয়াক পার্শ্বপ্রতিক্রিয়া এবং এর প্রতিকারের উপায় সম্বন্ধে বিস্ড়রিত জানানো হয়েছে। আমি ডাঃ ফাতিমা বেগম পরিচালিত গবেষণামূলক চিকিৎসা কার্যক্রমে অংশগ্রহন করলাম। আমাকে উক্ত গবেষণায় অংশগ্রহণ ঝুঁকি সম্পর্কে বলা হয়েছে। আমাকে আরও আশস্ড় করা হয়েছে যে, আমি কোন প্রকার শারীরিক, মানসিক ও সামাজিক ক্ষয়ক্ষতি সম্মুখীন হব না এবং সংশিষ্ট বিষয়ে গোপনীয়তা রক্ষা করা হবে। এই গবেষণামূলক কার্যক্রমের মাধ্যমে আমার চিকিৎসা পাশাপাশি চিকিৎসা বিজ্ঞানে নতুন অগ্রগতির সম্ভবনার কথা বলা হয়েছে। গবেষণা কার্যক্রমের জন্য আমি আমার বিভিন্ন নমুনা সংগ্রহ, ব্যবহার ও সংরক্ষণের অনুমতি দিলাম। তাছাড়া প্রয়োজনে আমি ইকোকার্ডিওগ্রাফি ও ই টি টি প্রোগাম অংশগ্রহণ করার অনুমতি দিলাম। যে কোন সময়ে নিজেকে এই চিকিৎসা ও গবেষণা কার্যক্রম থেকে প্রত্যাহার করার অধিকার সংরক্ষণ করলাম। এই চিকিৎসা এবং গবেষণা কজে অংশগ্রহণের জন্য আমি কখনও কোন আর্থিক সুবিধা দাবি করব না।

আমি স্বজ্ঞানে, স্বেচ্ছায়, সানন্দে এই সম্মতিপত্র স্বাক্ষর করলাম।

স্বাক্ষর/টিপসহি

নামঃ

ঠিকানাঃ

গবেষনা কর্মে অংশগ্রহণে সুস্থ স্বেচ্ছাসেবীর সম্মতিপত্র

আমি এই মর্মে ঘোষণা করছি যে, ডাঃ ফাতিমা বেগম পরিচালিত গবেষণা সম্পর্কে বিস্ড়রিতভাবে আমাকে অবহিত করা হয়েছে। আমি ডাঃ ফাতিমা বেগম পরিচালিত গবেষণামূলক চিকিৎসা কার্যক্রমে অংশগ্রহন করলাম। আমাকে উক্ত গবেষণায় অংশগ্রহণে ঝুঁকি সম্পর্কে বলা হয়েছে। আমাকে আরও আশস্ড় করা হয়েছে যে, আমি কোন প্রকার শারীরিক, মানসিক ও সামাজিক ক্ষয়ক্ষতি সম্মুখীন হব না এবং সংশিষ্ট বিষয়ে গোপনীয়তা রক্ষা করা হবে। এই গবেষণামূলক কার্যক্রমের মাধ্যমে চিকিৎসা বিজ্ঞানে নতুন অগ্রগতির সম্ভবনার কথা বলা হয়েছে। গবেষণা কার্যক্রমের জন্য আমি আমার বিভিন্ন নমুনা সংগ্রহ, ব্যবহার ও সংরক্ষণের অনুমতি দিলাম। তাছাড়া প্রয়োজনে আমি ইকোকার্ডিওগ্রাফি ও ই টি টি প্রোগাম অংশগ্রহণ করার অনুমতি দিলাম। যে কোন সময়ে নিজেকে এই গবেষণা কার্যক্রম থেকে প্রত্যাহার করার অধিকার সংরক্ষণ করলাম। এই গবেষণা কজে অংশগ্রহণের জন্য আমি কখনও কোন আর্থিক সুবিধা দাবি করব না।

আমি স্বজ্ঞানে, স্বেচ্ছায়, সানন্দে এই সম্মতিপত্র স্বাক্ষর করলাম।

স্বাক্ষর/টিপসহি

নামঃ

ঠিকানাঃ