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ORIGINAL ARTICLE

Comparison of Outcome in Radioiodine Induced Euthyroid and Hypothyroid Patients

Shekholeslami F, Ataie L, Hedayati M, Mehrabi Y, Azizi F.

Endocrine Research Center and the Division of Cardiology, Taleghani Medical Center, Shaheed Beheshti University of Medical Sciences, Tehran, I.R. Iran

The major consequence of radioiodine therapy for thyrotoxicosis is hypothyroidism and long-term precise management of hypothyroidism may be problematic. In this study, the long-term outcomes were compared in radioiodine treated euthyroid and hypothyroid patients on thyroid hormone treatment.

Materials and Methods: One hundred and thirty eight patients with diffuse toxic goiter were treated with radioactive iodine. One hundred and seven patients (78%) returned for follow up visits for up to 11.5±0.8 years. Numbers of occurrences of thyroid dysfunction in each patient were recorded and a total cost of management was calculated.

Results: At the end, 41 patients (38%) were still euthyroid (group 1) and 66 (62%) became hypothyroid (group 2). Serum, FT4, FT3, TSH, thyroid antibodies, lipid profile, calcium, phosphorus, and PTH were measured and bone mineral density, ECG and echocardiography were performed. There was no significant difference in age, sex, duration of symptoms and thyroid function between the 2 groups. The cost of treatment was lower in group 1 than in group 2. During 11.5 years of follow up, percentage of elevated and suppressed TSH in groups 1 and 2 were 0.02 and 20.5, p<0.001 and 7.9 and 13.4, p<0.001, respectively. At the end of 10 years, goiter rate, serum T4, T3, thyroid antibodies, lipids, Ca, P and PTH and bone mineral density and echocardiography data were not signifanctly different between two groups. However, mean serum TSH and number of TSH above 5 mU/L was greater in group 2 than 1 (p<0.01).

Conclusion: It is concluded that thyroid derangements frequently occur in patients who become hypothyroid after radioiodine therapy, while on replacement therapy.

Keywords: Radioiodine, Hyperthyroidism, Hypothyroidism, Bone mineral density

Introduction

Radioactive iodine has been used for the treatment of hyperthyroidism for more than six decades,[1] and has proved clinically efficient, safe and cost-effective.[2] Radioiodine has been used as a first-line therapy for thyrotoxicosis, and its use is increasing among younger patients.[3]

Hypothyroidism has been considered an inevitable consequence of radioiodine therapy rather than a side effect.[4] Over the past few decades, much attention has been focused on achieving euthyroidism and avoiding hypothyroidism by adjusting the radioiodine dose. However the biological response of the gland remains unpredictable[5] and despite numerous associations found between thyroid failure

Correspondence: Fereidoun Azizi, Endocrine Research Center, P.O.Box: 19395-4763, Tehran, I.R. Iran
E-mail: Azizi@erc.ac.ir

and some pretreatment variables, no single variable or combination of variables has been shown to predict the outcome after radioiodine therapy to justify the use of a mathematical formula in determining the dose individually.[5-7] In recent decades the frequency of hypothyroidism after radioiodine therapy has increased, appearing sooner after therapy[8,9] probably because of the use of higher doses and the increased ease of detection of hypothyroidism by serum TSH measurements.

It has been alleged that although lifelong thyroxine therapy is not a major problem, the risk of overreplacement on the heart[10,11] and bones[12,13] in particular in menopausal women, exists. In addition the potency, uniformity and reproducibility of thyroxine preparations, even the best brands, may be dubious[14,15] and 20-50% of patients are noncompliant.[16,17] All of these factors make long-term precise management of hypothyroidism somewhat problematic.

Little is known of the effects of less precise management of hypothyroidism in radioiodine treated patients on the heart and bones and the blood biochemical variables. We therefore studied the long-term outcomes in radioiodine treated hyperthyroid patients who remained euthyroid and compared them with those who became hypothyroid and were treated with levothyroxine.

Materials and Methods

This controlled cohort study was performed between July 1990 and October 2003 in Tehran, Iran. All patients with hyperthyroidism due to diffuse toxic goiter who agreed to radioiodine treatment were selected consecutively for this study. Patients presenting with overt symptoms and signs of hyperthyroidism including fatigue, weakness, nervousness, weight loss, tachycardia, hyperactivity, diffuse goiter, tremor, warm and moist skin, stare and lid lag were enrolled into the study. The diagnosis was based on elevated levels of T4 (>12.5 μg/dL) and/or T3 (>200 ng/dL) in the presence of a decreased serum TSH (<0.3 mU/L) and a diffuse uptake on a technetium scintigram.

Study protocol

In women, pregnancy was excluded by tests. Radioiodine was delivered to 138 patients in doses calculated using the following formula:

$$\frac{(100\ \mu ci\ ^{131}I/g\ of\ thyroid) \times thyroid\ weight\ (g)}{24\ h\ radioidoine\ uptake}$$

Patients received methimazole 20-40 mg/day, before and 1-3 months after radioiodine therapy. The mean dose of radioiodine was 7.6±4.8 with the range of 4.9 to 13.3 mCi. 107 patients (78%) returned for follow up visits for 11.5±0.8 years (range 9.1-12.8).

After monthly visits for the first 3 months of therapy, all patients were visited every 3 months for the first year and, if stable every 6 months thereafter. At each visit, complete history was taken, physical examination was performed and side effects of treatment were ascertained. A blood sample for the measurement of serum T_4, T_3, FT_4, FT_3 and TSH concentrations was obtained from each patient. Numbers of events of thyroid dysfunction during years of follow up were recorded. Diagnoses of hyper-or hypothyroidism, both overt and subclinical, were made according to following criteria: euthyroid (TSH level within the normal range, 0.3-5.0 mU/L, inclusive); hypothyroid (TSH>5.0 mU/L and T4 level <4.5 μg/dL); subclinically hypothyroid (TSH>5.0 mU/L; T4 ≥ 4.5 μg/dL); hyperthyroid (TSH level < 0.03 mU/L, T_4 > 12.5 μg/dL and/or T_3>200 ng/dL) and subclinically hyperthyroid (TSH level ≤ 0.01 mU/L, $T_4 \leq 12.5$ μg/dL and $T_3 \leq 200$ ng/dL). If hyperthyroidism recurred or persisted, patients were treated with calculated doses of radioiodine, as described in the study protocol. At each visit, patients who had serum TSH levels between 5.1-10.0 mU/L were requested to repeat TSH measurement every 6

months until serum TSH declined to below 5.0 or increased to above 10 mU/L. In patients with serum TSH over 10 mU/L, levothyroxine treatment was started and the dosage of levothyroxine was adjusted to keep serum TSH concentration within the normal range.

Final visit: At the end of the study, weight and height were measured and body mass index (BMI) was calculated. The level of calcium intake was estimated by a research dietitian using dietary recall. A questionnaire was completed to assess the status of cigarette smoking and the history of age at menarche and menopause in women. Physical activity was assessed by the Lipid Research Clinic questionnaire[18] and the quality of life was evaluated by the specific questionnaire SF-36.[19] Thorough physical examination was performed and goiter was graded according to WHO classification.[20] A blood sample after 12 hr fast and a 24 hour urine sample were obtained for measurement of variables cited in "measurements", and bone mineral density, EKG and echocardiography, were performed.

The Human Research Review Committee of the Shaheed Beheshti University of Medical Sciences approved the study, and verbal informed consent was obtained.

Measurements

Serum bilirubin, alkalin phosphatase, creatinine, calcium and phosphorus measurements were done by routine methods. Serum cholesterol and triglycycerides were assayed using enzymmtic calorimetric tests with cholesterol esterase and cholesterol oxidase and glycerol phosphate oxidase, respectively. HDL-C was measured after precipitation of the apolipoprotein B containing lipoproteins with phosphotungistic acid. LDL-C was calculated using the Friedwald formula. LDL-C was not calculated when triglyceride concentration was over 400 mg/dL. Excretion of free deoxypyridinoline in 24h urine sample was measured by radimmunoassay using Gamma BCT DPD kit from Immunodiagnostic Systems Limited, Boldon, UK.

Hormone and antibody measurements: Serum T_4 and T_3 were measured by radioimmunoassay, and serum TSH by immunoradiometric assay by kits from Orion Diagnostica, Finland. We measured free T4 (fT_4) and free T_3 (fT_3) by saturation analysis using kits from Diagnostic Products Co., U.S.A.; intact PTH by the Elisa method by kits from Diagnostic Systems Laboratories, Inc. U.S.A.; antithyroperoxidase antibody (TPOAb) and antithyroglobulin antibody (TgAb) by immunoenzymometric assay, Radim, Italy and urinary iodine levels by a digestion method.[21]

Reference ranges of serum parameters for euthyroid adult subjects are: T_4, 4.5-12.5 μg/dL; T_3, 80-200 ng/dL; TSH, 0.1-5.0 mU/L (μU/mL); fT_4, 0.7-2.0 ng/dL; fT_3, 2.2-5.0 pg/mL; PTH, 8.8-76.6 pg/mL; TPOAb, <100 IU/mL; TgAb, <100 IU/mL. To convert values to SI units, for T_4, T_3 and PTH multiply by 12.87, 0.01536 and 0.80, respectively. Interassay and intraassay coefficent of variations for all tests were less than 8 and 10%, respectively.

Bone mineral density: Bone mineral density (BMD) was measured by DEXA (dual-energy- xray absorptiometry) with Lunar DPX device, U.S.A. Densitometry was performed on L1-L4 vertebral regions, femur (neck, trochanter, ward and total) and forearm (mid shaft, upper distal part and total radius). BMD was expressed in units of gram per square centimeter and as Z scores. The Z score was calculated as the number of standard deviations between the patients' BMD and the age and sex matched reference mean value. Precision errors established with a local normal population were less than 1.46% for all locations (spine, hip and radius). The colleague interpreting the BMD results was blinded to the treatment modalities of patients.

Echocardiographic and Doppler measurements: Complete M-mode and two dimensional Doppler echocardiographic analysis

was performed with an ultrasound mechanical system equipped with a 3.5 MHZ transducer (Kontron Instruments Sigma 44 hvcd). M-mode and two dimensional recordings were acquired with the patients in the lateral recumbent position. A single experienced echocardiographer read all the echoes and was blinded to the treatment modalities of patients.

Costs

Costs were calculated from the actual expenses during 11.5 years of follow up for each of the two groups. The costs of each radioiodine treatment (including radioiodine uptake before therapy), propranolol (20-40 mg/day for 1-3 months), outpatient specialist visits (mean 26) and the costs of laboratory tests and hormone measurements during the acute phase and maintenance periods were calculated; in radioiodine-induced hypothyroid patients, the cost of levothyroxine from the time of occurance of thyroid failure to the end of study was added. Hospital and ambulatory costs for thyroid related events and illnesses, such as evaluation of complications related to thyroid dysfunction or side effects of medications, were calculated and added to the total costs for each patient. All costs were actual and when obscure (less than 15%), were estimated from the perspectives of the health care system. They are expressed both in Iranian rials and US dollars. Non-health care costs such as losses in productivity or costs outside the health system (e.g. family time) were not included.

Statistical Analysis

Base-line and outcome variables were compared with the use of Student's t, chi square, and Fisher's exact tests. For testing associations between variables Pearson and Spearman correlation coefficients were employed. In order to avoid multiple testing false positive finding, Bonferroni correction was employed. The values of $p<0.05$ were considered significant. Statistical analysis was performed using SPSS 9.05 software (SPSS Inc., Chicago, IL).

Results

Of 138 patients who entered the study, 79 patients (57%) had been treated with methimazole for 3-12 months, which was discontinued 5 days before radioiodine therapy. Flow chart of patients treated with radioiodine is seen in Fig. 1. One hundred and seven patients (78%) completed a mean of 11.5 years of follow up. Nineteen required additional 1-3 doses of radioiodine to become either eu-or hypothyroid. Ultimately, 41 patients (38%) remained euthyroid (Group 1) and 66 patients (62%) became hypothyroid, 3 months to 9 years after receiving radioiodine treatment (Group 2).

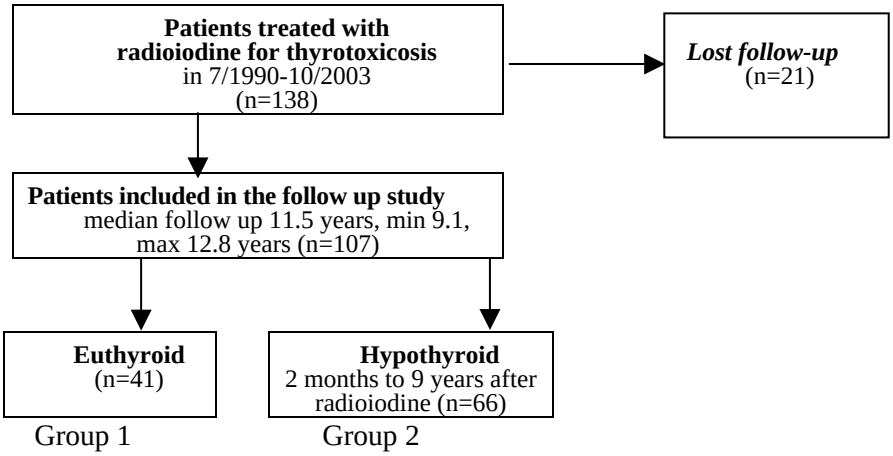

Fig. 1. Flow chart and follow-up times in 138 patients with hyperthyroidism treated with radioactive iodine.

Table 1. Clinical and Biochemical variables at the end of study in 2 groups of patients with thyrotoxicosis treated with radiodione*

Variable	Group 1 (n=41)	Group 2 (n=66)
Clinical variables		
Age (yr)	58±8†	61±9
Body mass index (kg/m2)	28.0±4.3	27.9±3.7
Prior treatment with antithyroids (%)	25	22
Current smoking (% of patients)	15	17
Daily consumption of calcium (mg)	501±286	490±264
Systolic blood pressure (mmHg)	132±16	138±20
Diastolic blood pressure (mmHg)	79±10	81±12
Pulse rate (n/min)	78±12	78±13
Total goiter rate (%)	24	26
Biochemical variables		
Serum T4 (μg/dL)	8.8±2.9	9.1±3.8
Serum T3 (ng/dL)	158±21	162±40
Serum free T_4	1.62±0.36	1.68±0.60
Serum free T_3	3.11±0.58	3.66±0.84
Serum TSH (mU/L)	2.71±2.10	5.4±8.1‡
Antithyroperoxidase antibody (IU/mL)	45±69	49±74
Antithygoglunbuline antibody (IU/mL)	256±229	235±271
Cholesterol (mg/dL)	217±53	228±47
Triglyderides (mg/dL)	158±74	162±69
LDL-C cholesterol (mg/dL)	128±52	133±45
HDL-C cholestrol (mg/dL)	56±14	60±13
Serum creatinine (mg/dL)	0.91±0.65	0.99±0.23
Serum calcium (mg/dL)	9.08±0.65	9.12±0.59
Serum phosphorus (mg/dL)	4.26±0.61	4.16±0.54
Serum PTH (nmol/l)	39±18	47±24

* Groups 1 and 2, euthyroid and hypothyroid (on levothyroxine therapy), respectively.
† Plus-minus values are means ± SD. To convert values to SI units; for cholesterol, triglycerides, T4 and T3 multiply by 0.02586, 0.01129, 12.87 and 0.01536, respectively. LDL denotes low-density lipoprotein, HDL high density lipoprotein and PTH parathyroid hormone.
‡ $p<0.01$, compared to group 1.

There was no statistical difference in age, sex, duration of symptoms, size of goiter and thyroid function tests among patients who remained in the study and those who lost follow up. In addition, there were no significant differences in basal characteristics between those who became hypothyroid and patients who remained euthyroid after radioiodine treatment.

Thyroid status during follow up

During 11.5 years of follow up of the 41 patients in group 1, no serious thyroid related events, such as storm, congestive heart failure, or atrial fibrillation, occurred. Patients in group 1 had 657 measurements of thyroid function tests. In 12 patients (0.02%) TSH was above 5.0 and in 52 (7.9%) TSH was below 0.3 mU/L. For patients in group 2, a total of 1161 measurements of thyroid function tests were performed. Serum TSH above 5.0

and below 0.3 mU/L was observed in 238 (20.5%) and 155 (13.4%) occasions respectively; both p<0.001, as compared to group 1.

Costs

The overall costs of management of hyperthyroidism and related complications of each patient was 5,660,000±23,000 rials ($708±28) in group 1 and 6,420,000±37,000 rials ($802±45) in group 2 (p<0.001).

Quality of life

Mean scores of the questionnaires were 37±12 and 43±9 for mental components and 48±6 and 45±87 for physical components in groups 1 and 2, respectively. The difference was not statistically significant.

Variables at final visit

The clinical and biochemical data of 107 patients at the end of study are summarized in Table 1. Mean age, BMI, percent of smokers, history of antithyroid terapy, amount of daily consumption of calcium, systolic and diastolic blood pressure, pulse rate and serum concentrations of ceratinine, cholesterol, triglycerides, LDL-C, HDL-C, calcium, phosphorus, alkaline phosphatase and PTH were not significantly different between the 2 groups. In addition, there was no significant difference in physical activity, age of menarche and start and duration of menopause in women between the 2 groups.

Before randomization, goiter was present in 81% of the cases. At the end of the study, goiter rate was 24 and 26% in groups 1 and 2, respectively. Mean serum concentrations of T_4, T_3, fT_4I, fT_3, and thyroid antibody concentrations were not significantly different between the 2 groups (Table 1); serum TSH however, was increased in group 2, as compared to group 1 (p<0.01). Serum TSH was above 5 mU/L in 19 (29%) patients of group 2, with normal serum T_4 and T3 levels. Serum TSH was less than 0.3 mU/L in 2 and 7 patients in groups 1 and 2 respectively; 4 of 7 patients with suppressed TSH in group 2 had elevated serum T_4 with normal serum T_3 levels.

At the end of study, there was no difference in mean of Z scores between two groups in hip, radius and vertebral locations (Table 2). The number of patients with Z scores equal or below 1.5 SD was 23.8% and 29.1% in groups 1 and 2, respectively.

Urinary concentration of free deoxypyridionoline was 30.4±19.9 and 29.6±32.3 mmol per mmol of creatinine in groups 1 and 2, respectively, not statistically significant.

Table 2. Bone mineral density at the end of study *

Variables	Group 1 (n=41)	Group 2 (n=66)
Hip		
Total	-0.35±1.06†	-0.64±0.87
Neck	-0.38±0.87	-0.64±1.00
Trochanter	-0.43±1.20	-0.80±0.84
Radius		
Total	-1.61±0.93	-1.74±1.20
Distal	-0.97±0.80	-1.74±1.17
Midshaft	-1.40±0.89	-1.63±1.09
Vertebra (L2-L4)	-0.05±1.26	-0.42±1.15

* Group 1 euthyroid and group 2 hypothyroid (on levothyroxine therapy) after radioiodine treatment.
† Plus-minus are mean±SD of Z scores.

Table 3. Echocardiographic and Doppler data in the two groups studied*

Variables	Group 1† (n=41)	Group 2 (n=66)
LVEDD (mm)†	47.8±5.0	47.2±5.1
IVST (mm)	9.07±1.41	8.66±1.43
LVPWT (mm)	9.08±1.41	8.76±1.38
EF (%)	69±8	66±10
LVMI (g/m2)	97±22	99±31
IVRT (ms)	79±13	80±14
E/A	0.94±0.26	0.95±0.29

* Group 1 euthyroid and group 2 hypothyroid (on levothyroxine therapy) after radioiodine treatment.
† Values are mean±SD. LVEDD, left ventricular end diastolic dimension; IVST, interventricular septal thickness; LVPWT, left ventricular posterior wall nickness; EF, ejection fraction; LVMI, left ventricular mass index; IVRT, isovolumic relaxation time; E/A, ratio of peak velocity of early diastolic filling (E) to peak velocity of atrial contraction (A).

Table 3 demonstrates echocardiographic data in patients of two groups. No significant difference is seen in various parameters between groups 1 and 2.

There was negative correlation between serum T_3 and TSH ($r=-0.526$, $p<0.001$) and positive correlation between serum fT3 and fT4 ($r=0.422$, $p<0.008$). Z scores of the neck and midshaft of femur and distal radius inversely correlated with serum T3 ($r=0.441$, $p<0.006$, $r=0.385$, $p<0.017$ and $r=0.478$, $p<0.002$, respectively).

Discussion

In the present study, we compared thyroid function tests, costs, and data on echocardiography, bone mineral density and serum concentrations of some blood constituents in patients rendered euthyroid by radioiodine and those who became hypothyroid after radioactive iodine therapy and were maintained on levothyroxine. All parameters were comparable between 2 groups; however, the rate of elevated TSH during follow-up and the cost of treatment were increased in group 2, as compared to those in group 1.

The most obvious objective in the treatment of hyperthyroidism is to render the patient euthyroid and off drug therapy. However, all of the three forms of treatment of thyrotoxicosis, i.e. antithyroid drugs, surgery and radioiodine therapy, fail to achieve this objective. Nearly 60 years ago, ablative treatment of thyrotoxicosis with radioiodine was introduced.[1,21] This mode of therapy was first employed for those with recurrence of thyrotoxicosis after discontinution of antithyroid therapy. However reports of low remission rate with thionamide therapy[22,23] and ease, effectiveness and low expense of radioiodine therapy,[24,25] led to waning enthusiasm for antithyroid drug therapy, and the increasing reliance of radioiodine treatment for hyperthyroidism. In fact, more than two thirds of the members of the American Thyroid Association choose radioiodine as the treatment of choice for virtually all patients with Graves' disease with the exception of the very young or pregnant patients.[26] This practice is not common in members of European Thyroid Association, since two thirds of these prefer antithyroid drugs as the first approach to the treatment of hyperthyroidism.[27]

Radioiodine is increasingly considered the treatment of choice because of its safety and ease of administration.[28] Different authors have described several protocols, each attempting to reduce the incidence of long-term hypothyroidism while maintaining an acceptable rate of control of hyperthyroidism[29,34] Some centers have administered variable doses depending on estimates of size of goiter and/or uptake and turnover of radioiodine

[29-31,33] while others have advocated the use of fixed low doses of radioiodine.[24,32] Yet other authors have given fixed high doses of radioiodine, to ablate the thyroid and induce early hypothyroidism, so that follow-up of thyroid function is not required.[34] The major event resulting from each of these approaches is thyroid failure; hypothyroidism may develop many years after the patients has been rendered euthhyroid by radioiodine,[31] so that long-term follow up of thyroid function is essential.

In the present study we observed that a number of abnormal serum TSH values occurring during 11.5 year of follow-up, and serum TSH concentrations at the end of follow-up were significantly higher in patients with hypothyrodism after radioiodine therapy who were on levothyroxine as compared to those rendered euthyroid by radioiodine therapy. In a retrospective study, 32% of patients receiving levothyroxine replacement had abnormal TSH concentrations, while 92% of them had seen a health care provider the previous year.[34] In the Colorado Thyroid Disease Prevalence Study, of patients who reported taking thyroid medication, nearly 40% had an abnormal serum TSH level, with 0.7 and 0.9% having clinical hypo- and hyperthyroidism and 17.9 and 20.7% subclinical hypo-and hyperthyroidism, respectively.[17] These data, therefore, show that there is an excess of patients under replacement therapy who are not within the normal range of thyroid function and may be at risk of organic consequences of under and overtreatment treatment.

Altered thyroid status profoundly affects hemodynamic regulation. The thyrotoxic state induces an increase in total blood volume, a decrease in total systemic vascular resistance and shortened circulatory time, causing an increase in cardiac work that leads, in time, to cardiac hypertrophy.[35] Lack of thyroid hormones results in deprived heart function with reduced heart rate, stroke volume, and thus, cardiac output, and increased systemic vascular resistance.[35,36] Bone metabolism also is affected by thyroid hormone status. Bone turnover is increased in favor of resorption and the rate of resorption is associated with the serum levels of thyroid hormones in hyperthyroidism.[37] Thyroid hormone exerts its effect on osteoblasts via nuclear receptors to stimulate osteoclastic bone resorption.[38] Even a slight increase in thyroid hormones to a level of subclinical hyperthyroidism results in accelerated bone turnover and calcium excretion.[39] In the present study cardiovascular hemodynamic data were within normal range and comparable in both study groups and parameters of bone mineral density were not significantly different between the 2 groups. The assumption may be that although many patients with radioiodine induced hypothyroidism, experienced alterations in thyroid status, in particular subclinical hypo- and hyperthyroidism, the duration of thyroid derangements were short and corrected during six monthly visits. Therefore, the effects on cardio-vascular hemodynamic and bone changes were short lived.

This study had a few limitations. Firstly, the number of patients available for study was not powered to detect significant differences in cardiovascular, bone and lipid alterations between treatment groups. Secondly, lack of compliance of patients and incidence of thyroid derangement may be different in other settings, because the extent of this problem dedends on the proper replacement therapy and patient education, as well as cultural and social behaviors.

Despite these constraints, the magnitude of thyroid dysfunction in patients taking thyroid medications is of concern. Nearly 34% of subjects taking levothyroxine had less than desirable TSH levels during follow-up. Such patients may be at risk of organic consequences of under- or overtreatment. Thyroidologist must search for an alternative optimal treatment of hyperthyroidism and/or more desirable and effective mode of therapy for hypothyroidism.

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