ORIGINAL ARTICLE

EVALUATION AND ASSOCIATION OF THYROID PROFILE WITH LIVER FUNCTION PARAMETERS AND LDL LEVELS BEFORE AND AFTER I^{131} THERAPY

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ABSTRACT

BACKGROUND: The pathogenesis of liver function abnormalities and cardiac dysfunction in hyperthyroid patients after I^{131} treatment is still unclear. The aim of this study was to determine the effects of radioiodine I^{131} on liver function parameters, lactate dehydrogenase(LDH) and low-density lipoproteins(LDL) before and after I^{131} therapy in hyperthyroidism patients. **METHOD:** Total 52 patients of hyperthyroidism recommended for I^{131} were involved in this study with age ranging from 12 - 65 years (mean age=38.6 – 14.8 & BMI=11.5 – 3.7). The significance of the differences between the results of 1st, 2nd and 3rd time serum analysis was assessed by unpaired student s t-test. Associations between the parameters were assessed by Spearman correlation analysis. **RESULTS:** Significant variations were observed for thyroid profile FT3 (p=0.04), FT4 (p=0.01), TSH (p=0.005) during the follow-up treatment. Before taking I^{131} (serum analyzed at 1st time), negative correlation of FT3 with AST (r= -0.458, p=0.032) and LDL (r= -0.454, p=0.039) were observed. During 2nd time (after stopping carbimazole) no correlation were assessed. Two months after administration of I^{131} drops, significant negative association of FT3 (r= -0.62, p=0.04) and FT4 (r= -0.61, p=0.02) with ALB were observed. FT3 (r= -0.82, p=0.00) & FT4 (r= -0.71, p=0.00) also showed negative correlation with LDL after I^{131} therapy. Whereas TSH showed significant positive association with ALB (r=0.61, p=0.01) and LDL (r=0.70, p=0.00) respectively. **CONCLUSION:** Our findings suggest that the association of TFTs with biochemical parameters in patients with goiter recommended for iodine therapy is an important diagnostic and therapeutic tool. The increase in transaminases and LDL level after administration of I^{131} therapy may adversely affect heart and liver function.

Keywords: Hyperthyroidism, Carbimazole, Radioiodine I^{131}, liver functions, low-density lipoprotein

Introduction

Hyperthyroidism is an endocrine disorder in which excessive thyroid hormones are synthesized and released by thyroid gland, characterized by normal or higher uptake of radioiodine by thyroid gland also known as thyrotoxicosis with hyperthyroidism or true hyperthyroidism.[1] Thyroid hormones are crucial for

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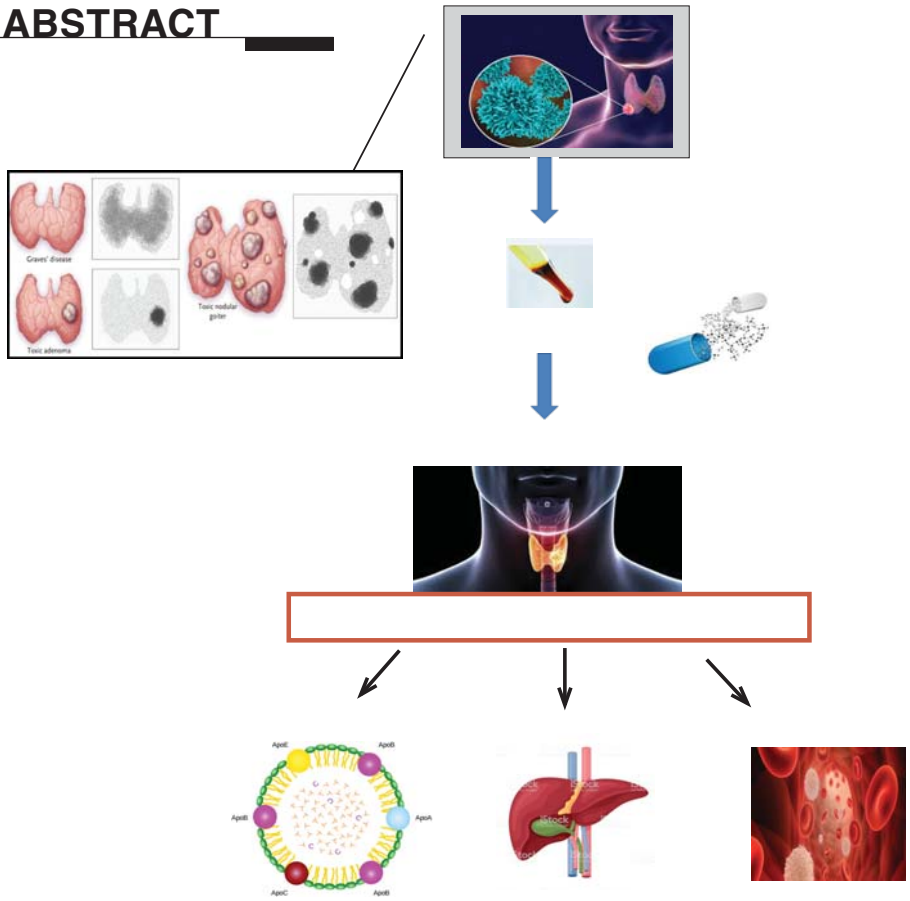
GRAFICAL ABSTRACT



Parameters	Level
Low-density lipoproteins	⇧
Albumin	⇧
Alkaline phosphates	⇩
Aminotransferases	⇧
Lactate dehydrogenase	⇧

development, neuronal growth, reproduction and regulation of energy metabolism; they affect the working of all body organs, tissues and cells.[2] In iodine sufficient areas Graves disease accounts 70 to 80% of patients associated with hyperthyroidism whereas, in iodine deficient areas it accounts ~50% of patients with hyperthyroidism and other half attributable to nodular thyroid disorder.[3] Thyroid goiter disorders can be categorized into toxic, non-toxic, local or non-endemic and diffuse or nodular goiter. Because of endocrine disorders 500-600 million peoples are affected with nodular goiter around the world.[4,5] Most prevalent 90% of cases of hyperthyroidism are associated with multi-nodular goiter, diffuse toxic goiter, and toxic adenomas.[6,7] The higher prevalence rate of goiter has been documented in females (94.7%) and less prevalent in males (5.26%).[8] The extent of hyperthyroidism is lower as compared to hypothyroidism in Pakistan and their prevalence rate was 5.1% and 5.8% respectively.[9,10]

Graves disease affects numerous organs such as gastrointestinal cardiovascular and hepatic systems.[11] The liver is the key organ where thyroid hormones metabolism takes place.[12] Hepatic dysfunction is common in patients with Graves disease.[13] Hyperthyroidism induced liver function abnormalities or liver failure may occur due to excess release of thyroid hormones or autoimmune injuries. Previous studies

showed that the elevated level of free thyroid hormone had a deleterious effect on hepatic cells.[14,15] The liver is the main organ plays an important role in metabolizing thyroid hormones and regulates their systemic effects.[16,17] Hyperthyroidism may also be responsible for cholestatic jaundice due to decreased bilirubin and bile excretion.[18]

Liver dysfunctions are common in patients with thyrotoxicosis including hepatocellular injuries, increased level of liver enzymes AST and ALT, cholestasis, and also increased level of alkaline phosphatase (ALP), GGT and bilirubin. The risk of coexisting autoimmune hepatitis has also been considered in hyperthyroidism associated patients.[19]

Thyroid dysfunctions have intense effect on lipoprotein metabolism.[20] Hyperthyroidism may also increase the heart rate and contractility along with bone turnover, osteopenia, osteoporosis, and fractures, hyperactivity, anxiety, excessive sweating, weight loss, palpitations, muscle weakness, reduced fat mass, tachycardia, stare, eyelid lag, irritability, and menstrual irregularity.[21] Thyroid hormones directly regulate lipoprotein consumption by decreasing low-density cholesterol via the activation of LDL gene receptors.[22] Thyroid hormones also involved in the stimulation of cholesteryl ester transfer proteins (CETP) that convert the HDL into VLDL and triglycerides.[23] Transitory alterations in thyroid hormones disturb both efflux and influx of lipid metabolism and may also disturb the cholesterol homeostasis.[24] Thyroid function abnormalities may have great impact on lipids metabolism as well as various cardiovascular risk factors.

Radioiodine (RIA) therapy considered as common treatment of hyperthyroidism. Radioiodine treatment may periodically be administered in patients with subclinical hyperthyroidism.[26] Radioiodine iodine therapy recommended as safe, simple and effective treatment and relatively inexpensive method as compared to other therapeutic practices.[27] Anti-thyroid drugs: Carbimazole, Methimazole and propylthiouracil considered as primary treatment of thyrotoxicosis (goiter disease) or use for preparing the patients for definitive therapy with surgery or radioiodine treatment.[28]

Radioiodine I^{131} treatment may cause worsen liver damage due to the massive release of stored thyroid hormones into the bloodstream, which may also lead to temporary exacerbation of thyrotoxicosis.[29] The purpose of the present study was to evaluate the association of thyroid function tests (TFTs) with liver function tests (LFTs), LDH and LDL before and after radioiodine I^{131} therapy in hyperthyroid patients. Therefore, this study evaluated the potential effect of RAI therapy on liver function, LDL and LDH with emphasis on BMI, sex, age, smoking, accumulated dose and type of goiter (DG, DTG, MNG, TNG, nodule in right lobe, cold nodule in right lobe isothymus, nodule in left lobe and left lobe genigin thyroid tissue).

Methods

Study Subjects:

This is a longitudinal hospital based cohort study in which 52 patients were involved associated with Goiter disease (hyperthyroidism). They were living in the region of southern Punjab of Pakistan and recruiting to Outpatient Clinics of Multan Institute of Nuclear Medicine and Radiotherapy (MINAR Cancer Hospital), Nishtar Hospital Multan during the period of 10 months from September 2019 to June 2020. Study was approved by ERC of MINAR, Multan.

Inclusion criteria:

All the clinically tested thyroid function tests (TFTs) patients of hyperthyroidism with age ranging from 12-65 years were selected for taking first time radioiodine I^{131} therapy. Sample size (n=52) was determined by serum samples collected 3 times from the same patient: 1st time when patient came for taking time of Iodine I^{131} (taking Carbimazole), 2nd time before taking Iodine I^{131} drops (after 15 days off of Carbimazole) and 3rd time after 2 months of taking iodine 131.

Exclusion criteria:

Any known case of hypothyroidism and euthyroidism on treatment, supplementation with vitamin D or patients that took medications which affected thyroid functions, liver functions and lipid metabolism such as, Statins, diabetic medicines, oral contraceptives, estrogen, glucocorticoids were excluded from the study after taking proper medical history.

Anthropometric Measurements

Subjects accomplished a planned form concerning demographic characteristics at the primary visit. All procedures performed in this study involving human participants were in accordance with the ethical standards of the Institutional Ethics Committee of MINAR and Informed consent was obtained from all individual participants included in the study. The height and weight of the subjects were measured twice and then average calculated by employing a digital scale. Body mass index (BMI) was calculated by using the subsequent formula: weight in kilogram divided by the sq. in height in meters (kg/m^2). All data including age, gender, BMI, material status, Smoking, Goiter duration, Amount of I^{131} dose, thyroid scan and region were recorded on a standard form. Different types of goiter: diffused goiter, diffused toxic goiter, multinodular goiter, toxic nodular goiter, nodule in right lobe, cold nodule in right lobe isothymus, nodule in left lobe and left lobe benign thyroid tissue were defined by thyroid scan. (Fig.4)

Laboratory Measurement:

Blood samples were drawn in fasting. Samples were taken into K2-EDTA [30] and BD gel vacutainer for TFTs analysis and plain red top vials with no additives used for biochemical parameters analysis. Thyroid function tests FT3, FT4 and TSH (reference range; TSH: 0.2-5.5miU/L, FT4: 10-24.5pmol/L, FT3: 3.1-6.8pmol/L)were measured with an electro chemilumine scence immunoassay (Hitachi Modular E411; Roche Diagnostics, Mannheim, Germany) and by radio immunoassay (RIA) kits provided by Immunotech, Beckman coulter, Czech Republic. Liver function parameters (ALB, ALP, ALT, AST & Total Bilirubin), LDL and LDH were measured by Chemistry Analyzer (P500 Diatron).

Statistical Analysis:

Statistical analysis was performed with SPSS version 26 (SPSS Inc., Chicago, IL, USA). The level of significance of 3 different time points; 1st 2nd and 3rd time (hormonal and biochemical parameters of a same individual) were assessed by unpaired independent Student's t-test after checking for normality by the Shapiro-wilk test.[31] As non-normal distribution was found for TFT s, Albumin, LFTs, LDL and LDH results were assessed by Wilcoxon ranked pairs test. The level of statistical significance was set at P<.05. Finally, the relationship of TFT s with Albumin, LFTs, LDL and LDH were assessed by Spearman correlation analysis.

Results

Total fifty-two (52) patients of hyperthyroidism were diagnosed with diffused goiter (DG) 9(17.3%), diffused toxic goiter (DTG) 13 (25%), multinodular (MNG) 20 (38.4%), Toxic Nodular Goiter (TNG) 3 (5.7%), Nodule in right lobe 2 (3.8%), Nodule in left lobe 3 (5.7%), cold Nodule in right lobe isothymus 1 (1.9%) and left lobe benign thyroid tissue 11 (1.9%) with age ranging from 12-65 years. The patients were diagnosed on the basis of Tc-99m pertechnetate thyroid scan (Fig.4). The mean age of patients was 38.6 – 14.8 years with BMI 11.5 – 3.7. In which 42 (80%) females and 10 (20%) males associated with different types of hyperthyroidism. The amount of dosage I^{131} (5 mci-29 mci) and duration of goiter ranges from 2 months to 15 years. Patients demographic data represented in (Tab.1).

The comprehensive results of thyroid function tests (TFTs), liver function tests (LFTs), LDH, and are shown in (Tab.2) The significance of the differences between the results of 3 time points (1st, 2nd, 3rd time) serum analysis were recorded by unpaired independent student-t test. When we compared the 1st time results with 2nd time results significant difference were observed in ALB (p=0.000), ALP (p=0.003), ALT (p=0.002), AST (p=0.002), Bilirubin Total (p=0.002), LDH (p=0.020) and LDL (p=0.001). And when we compared 2nd time results with 3rd time

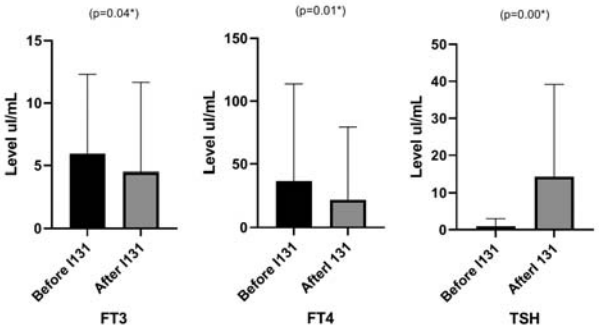


Figure 1: Comprehensive results of free TFTs before and after I^{131}

Correlation graphs before I131

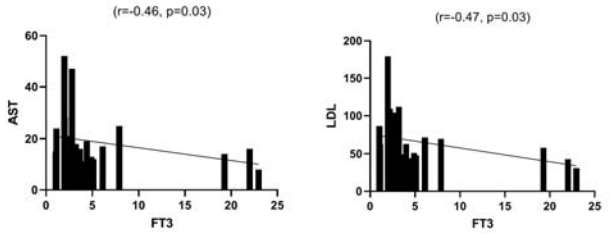


Figure 2: Correlation of FT3 with AST and LDL before I^{131} therapy

results significant differences were recorded in ALP (p=0.000) and LDH (p=0.031). And by the comparison of 1st time results with 3rd time results significant differences were recorded in FT3 (p=0.04), FT4 (p=0.010), TSH (p=0.005), ALB (p=0.000), ALP (p=0.007), ALT (p=0.001), AST (p=0.000), and LDL (p=0.000) after completion of patient s visits during treatment (before and after taking I^{131} therapy) (Tab.2). Before I^{131} therapy, significant negative association of FT3 with AST (r=-0.458, p=0.032) and LDL (r=-0.454, p=0.039) was observed in hyperthyroid condition (Tab.3) by using Spearman correlation analysis. Whereas, there was no correlation found in FT4 and TSH with biochemical parameters.

Correlation graphs after I^{131}

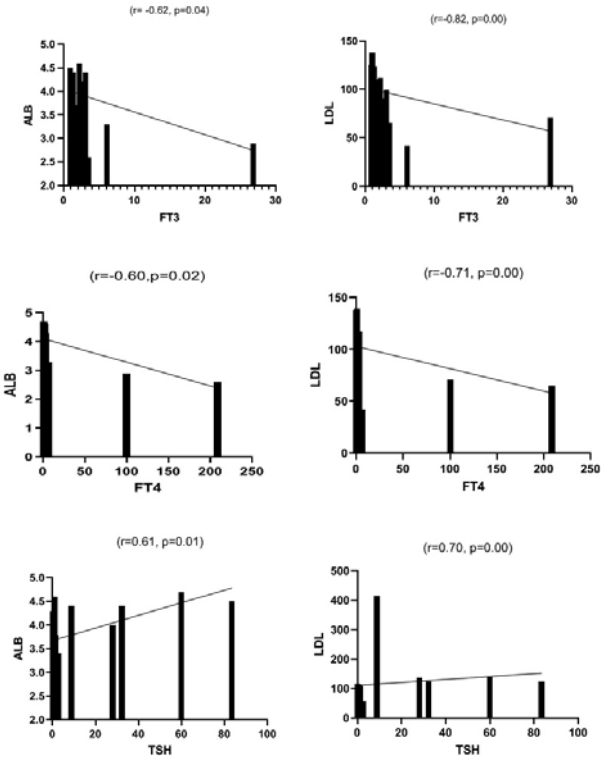


Figure 3: Correlation of TFTs with ALB and LDL after I^{131}

After the I^{131} treatment of radioiodine significant negative association of FT3 with ALB (r=-0.62, p=0.04) (Fig.1) and LDL (r=-0.820, p=0.00) (Fig.2) was observed. FT4 also showed negative association with ALB (r=-0.621, p=0.041) (Fig.3) and LDL (Fig.4) (r=-0.71, p=0.00). Meanwhile TSH showed positive correlation with ALB(r=0.610, p=0.016) and highly strong positive correlation with LDL (r=0.707, p=0.003) by using spearman correlation analysis after I^{131} therapy (Tab.3).

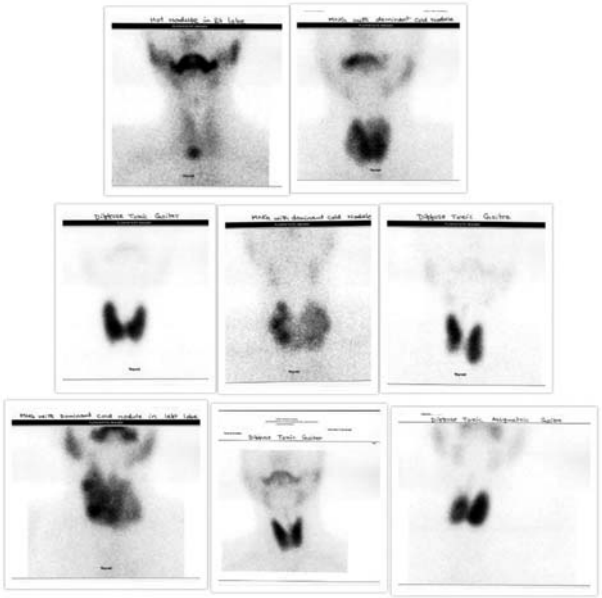


Figure 4:

Total Number of Patients (n = 52)	
Female	42 (80%)
Male	10 (20%)
Age	12 – 65 years
Goitre duration	02 months - 15 years
BMI (Mean ± SD)	11.5 ± 3.7
Dose (Mean ± SD)	5mci--29mci
Smokers	17 (32.6%)
Diffused Goitre	9 (17.3%)
Diffused Toxic Goitre	13 (25%)
Multinodular Goitre	20 (38.4%)
Toxic Nodular Goitre	3 (5.7%)
Cold Nodule in right lobe isothymus	1 (1.9%)
Nodule in right lobe	2 (3.8%)
Nodule in left lobe	3 (5.7%)
Left lobebenign thyroid tissue	1 (1.9%)

Table 1: Demographic data of patients

Para meters	1st Time mean ± std	2nd Time mean ± std	3rd Time mean ± std	P-Value Summery (1st Vs 3rd Time)	P-Value Summery (2nd Vs 3rd Time)	P-Value Summery (1st Vs 3rd Time)
FT3	5.9 ± 6.3[b]	-	4.4 ± 7.1[b]	-	-	**0.04***
FT4	36.8 ± 76.6[b]	-	21.8 ± 57.5[b]	-	-	**0.01***
TSH	1.0 ± 2.0[b]	-	14.4 ± 24.7[b]	-	-	**0.00***
ALB	2.6 ± 0.9[a]	3.9 ± 0.8[b]	3.8 ± 0.6[a]	**0.00***	0.88	**0.00***
ALP	81.6 ± 60.4[a]	148.5 ± 96.0[a]	44.4 ± 48.6[b]	**0.00***	**0.00***	**0.00***
ALT	12.9 ± 7.4[a]	23.2 ± 16.9[b]	42.0 ± 82.5[b]	**0.00***	0.57	**0.00***
AST	18.4 ± 11.1[b]	29.4 ± 13.4[b]	42.9 ± 42.4[a]	**0.00***	0.20	**0.00***
Bilirubin.T	0.2 ± 0.3b	3.11 ± 11.9[b]	0.2 ± 0.1[b]	**0.00***	0.00	0.38
LDH	324.3 ± 402.0[b]	318.7 ± 107.1[a]	568.9 ± 482.8[a]	**0.02***	**0.03***	0.91
LDL	59.8 ± 33.7[a]	95.7 ± 38.9[a]	119.1 ± 87.1[a]	**0.00***	0.31	**0.00***

[a] normal distribution, [b] non-normaldistribution
*P-value represents significance from unpaired non-parametric test sum statistical analysis) Significance level: <0.05

Table 2: Comprehensive Results of TFT S, LFTs, LDH, LDL & Serum electrolytes

Para meters	ALB r-value (p-value)	ALP r-value (p-value)	ALT r-value (p-value)	AST r-value (p-value)	Bilirubin.T r-value (p-value)	LDH r-value (p-value)	LDL r-value (p-value)
FT3	-0.18 (0.42)	0.21 (0.32)	-0.32 (0.14)	**-0.52 *(0.03)**	0.25 (0.26)	-0.13 (0.56)	**-0.47*(0.03)**
FT4	0.07 (0.70)	0.04 (0.80)	-0.03 (0.85)	0.03 (0.84)	0.02 (0.91)	-0.06 (0.74)	0.09 (0.63)
TSH	0.08 (0.64)	-0.23 (0.20)	0.24 (0.19)	0.31 (0.09)	-0.21 (0.25)	0.05 (0.77)	0.12 (0.52)
After I131 therapy (3rd time)							
FT3	**-0.62 *(0.04)**	0.08 (0.80)	0.00 (1.00)	0.07 (0.83)	0.45 (0.19)	0.05 (0.87)	**-0.82 **(0.00)**
FT4	**-0.609 *(0.02)**	0.11 (0.69)	-0.05 (0.85)	-0.15 (0.60)	0.26 (0.38)	-0.05 (0.86)	**-0.71 **(0.00)**
TSH	**0.610 *(0.01)**	0.01 (0.95)	0.05 (0.84)	0.16 (0.55)	-0.20 (0.47)	-0.03 (0.88)	**0.70 **(0.00)**

*correlation and significant values, non-normal distribution (Spearman correlation),

Table 3: Correlation of TFTs with Biochemical parameters and BMI (before I[131] therapy)

Discussion

Administration of iodine I[131] causes variations in liver function parameters and Lipid profile. Radioiodine radiations had a great effect on hepatocellular enzymes and growth factors and also cause the mutations in DNA or RNA at the molecular level.[32] This study has been shown that FT3 negatively correlates with LDL in a hyperthyroid state, as Ferdos A. Alterihy, et al. (2012) proved that level of low-density lipoprotein (LDL) decreased in hyperthyroid patients than those of control group. Another study proved that hyperthyroidism causes a reduction in serum cholesterol concentrations.[34] Hyperthyroidism is inversely related to low-density lipoprotein as FT3 or FT4 level increases LDL level decreases due to increased hepatic uptake because of greater affinity for the LDL receptor and regulatory triglycerides protein.[35] Excess amount of T3 causes hepatic dysfunction by inducing apoptosis via activation of a mitochondrial-dependent pathway,[14] another study also indicates that the serum-free T3:T4 ratio negatively correlates with the severity of the liver disease and has prognostic value.[33]

After I[131] therapy significant increase in TSH level and decrease in FT3 and FT4 level were observed in patients, converting the status of disease from hyperthyroidism to hypothyroidism or euthyroidism as Shakhreet, B., et al. (2015) proved in his study.[36] A similar study also proved that strongly significant changes were observed for TFT s (FT3=0.012, T4=0.017, and TSH=0.001) during the follow-up treatment (before and after taking iodine I131).[37] Our results showed that ALP level significantly decreases after taking I[131] therapy. Similar to Alavi, et al.[38] but their results are not significant. Our results confirmed that ALP level decreases and ALT level increases after taking iodine I[131] therapy as Papachristos et al. proved in his study.[39] The prognosis of hepatic dysfunction is closely correlated with the consequences of hyperthyroid Graves disease after iodine I[131] therapy.[40] Our results suggest that ALT and AST levels continuously increases during the follow up treatment. Conversely, Alavi, et al.[38] mentioned that ALT and AST levels decrease after radioiodine therapy in hyperthyroidism. However, they evaluated the results after 72 hrs of iodine I[131] intake whereas we have evaluated the biochemical parameters after 2 months of I[131] therapy. Previous studies showed that hepatic enzymes or liver function parameters altered after I[131] therapy which demonstrated that RAI therapy affects the liver functions as Renfei Wang, et al. (2017) also proved that hepatic dysfunctions closely associated with outcomes of iodine I[131] treatment in patients with thyrotoxicosis.[40]

An interesting observation was a continuous increase in albumin level after Iodine-131 oral administration. After taking I[131] therapy elevation in albumin level may lead to kidney problem as Rubaida mehmood et al. (2019) mentioned that the increased in creatinine

and chloride after administration of I^{131} therapy of patients leading to kidney problems.[37] However they evaluate the results of serum electrolytes and creatinine before and after iodine I^{131} administration. Our study also confirmed that FT3 and FT4 negatively correlate with albumin after I^{131} treatment. As previous study proved that FT3 positively correlates with Albumin in untreated hyperthyroid patients.[41] Another study also shown that albuminuria positively correlates with FT4 in chronic kidney disease[42] as well as our study also showed that FT4 positively associated with Albumin but this association becomes negative after iodine 131 therapy, however, the previous studies are not available that confirmed the direct effect of I131 therapy on Albumin level.

This study confirmed that low-density lipoprotein (LDL) levels increase after the treatment of iodine I^{131}, as F. Azizi, et al.[43] proved that LDL-cholesterol concentrations were increases in radioiodine I^{131} treated patients as compared to anti-thyroid drugs treated patients. A study also has been reported that total cholesterol and LDL levels constantly decreases in hyperthyroidism state and increased in hypothyroidism condition.[25] Another remarkable observation was a negative association of FT3 with LDL after Iodine I^{131} treatment, as Muls, et al. (1982)[44] proved that lipoproteins (HDL & HDL) level significantly increased with the decrease of FT3 and FT4 and increased in TSH level after treatment as compared to untreated hyperthyroid patients. F. Costantini et al. (1998) also indicates that decreased level of thyroid hormones not only increases the quantity of low-density lipid particles, but also stimulates LDL oxidability.[45] The lipid metabolism dysfunction may results in the development of atherosclerotic coronary artery diseases(CAD) in patients associated with overt hypothyroidism.[46,47] In addition hypothyroidism may also affect cardiovascular (CVD) risk factors as well as increasing the risk of coronary artery diseases. However our finding suggests that radioiodine 131 may adversely affect the lipid metabolism and contributing to increasing the risk of cardiovascular and coronary artery diseases.

This study also evidences that TSH positively associates with albumin and low-density lipoprotein in I^{131} treated patients. This study shows that LDL level increases with the increase of TSH level similar with previous studies which showed that a steady increase in total cholesterol, low-density lipoprotein (LDL) and triglycerides and a gradual decrease in high-density lipoprotein cholesterol (HDL-C) level have been observed with elevating TSH level.[48,49] Thyroid function abnormalities have a great influence on lipids as well as various cardiovascular risk factors. The increase in low-density lipoprotein (LDL) in serum after administration of Iodine 131 therapy is an alarming situation for coronary artery diseases or heart disorders. However, future studies are needed to determine the potential adverse effects of Iodine 131 therapy on lipid metabolism and serum albumin level.

Conclusion

Our study suggest that the association of thyroid functions with liver function parameters LDH and LDL level in patients recommended for iodine therapy gives a new idea of diagnostic and therapeutic tool. This study indicates that radioiodine 131 may have adverse effect on hepatocellular enzymes and had a great impact on lipid metabolism. The increase in liver enzymes & LDL levels after administration of I^{131} therapy is an alarming situation for liver and heart disorders. As well as increase in albumin level may cause kidney problems. However, future studies are needed to confirm our results.

Abbreviations:

TFTs: Thyroid function tests; FT3: Free triiodothyronine; FT4: Free thyroxine; TSH: Thyroid stimulating hormone; LFTs: Liver function tests; LDL: Low density lipoprotein; LDH: Lactate dehydrogenase enzyme; ALT: Alanine aminotransferase; ALB: Albumin; AST: Aspartate transaminase; ALP: Alkaline phosphate, BiT: Total Bilirubin; BMI: Body mass index.

Conflict of Interest: None

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