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Evaluation of a Number of Blood Biochemical Markers after Radioiodine Therapy in Papillary Thyroid Cancer Patients

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Abstract

Background: This study aimed to assess several biochemical and oxidative stress parameters before and after radioiodine therapy in patients with well-differentiated thyroid cancer who consumed a low iodine diet and withdrawal of levothyroxine after total thyroidectomy.

Methods: We enrolled 40 candidates for radioiodine therapy. Blood sampling was performed prior to as well as 72 h after consumption of 125-200 mCi of 131I. Total protein, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and creatinine were measured. Oxidative stress parameters that included malondialdehyde and protein carbonyl levels were also assessed.

Results: There were significantly decreased total protein, creatinine, aspartate aminotransferase, and alanine aminotransferase levels ($P<0.001$) after treatment. However, malondialdehyde levels increased significantly ($P<0.05$) over the studied time.

Conclusion: We found that radioactive iodine absorption in peripheral tissues due to a low-iodine diet and levothyroxine withdrawal could relieve iodine deficiency in the liver and kidneys which resulted in reduced total protein, aspartate aminotransferase, alanine aminotransferase, and creatinine levels. However, it induced oxidative stress by increasing malondialdehyde levels in the blood.

Keywords: Biochemical parameters, Oxidative stress, Well-differentiated thyroid cancer, Radioiodine therapy

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Introduction

Thyroid cancer is the most common endocrine malignancy with an increasing incidence in Iran. Recent reports show a higher incidence in women compared to men. Thyroid cancer is the seventh most common cancer among Iranian women and fourteenth among Iranian men. Although there are different

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types of thyroid cancers, the papillary type is most frequently seen in Iranian patients.[1] The prognosis of the papillary type is good;[2] 88% of Iranian patients survive at least five years after diagnosis and treatment.[1] Common treatments include total thyroidectomy, radioactive iodine (RAI), and thyroid suppression therapy. In metastatic cases, radiotherapy may be used. Radioactive 131I is administered after a total thyroidectomy.[3] In order to promote RAI uptake, patients undergo levothyroxine (L-T4) withdrawal which produces hypothyroidism symptoms along with increased liver and muscle enzyme levels.[4,5] In RAI treatment, a low-iodine diet is also essential to increase I-131 uptake into the remaining normal thyroid tissue and tissues of the thyroid carcinoma.[6] This diet causes increased RAI absorption by other body organs.[7]

Most information about iodine deficiency has been reported by a study of people who live in low-iodine areas. In adults, it has been shown that mild to moderate iodine deficiency results in hypothyroidism and goiters.[8] There are no other studies on the effects of iodine deficiency in patients who consume a low-iodine diet along with L-T4 withdrawal. It is of interest to people who have iodine deficiency or live in low iodine areas.

Patients with low-risk tumors receive low doses (30-100 mCi) of RAI, whereas those with intermediate to high risk cancers receive high doses (120 -200 mCi).[3] Studies have shown that thyroid cancer patients treated by radioactive 131I (100-200 mCi) had significantly decreased salivary superoxide dismutase enzyme (SOD), total protein, and albumin concentrations after at least one year. These results have elucidated the cause of 131I dependent damage to the salivary gland and oral cavity by increased oxidative stress due to reductions in salivary antioxidant status, SOD enzyme and uric acid concentrations.[9] Radioiodine therapies not only kill tumor cells but also cause damage to normal tissues by the generation of reactive oxygen species (ROS). The SOD enzyme is responsible for ROS inactivation; it has radio-protective effects on tissues, as well as at the cellular and molecular levels. Lipid peroxidation is one damage that occurs at the molecular level.[10] An imbalance between ROS generation and elimination of ROS results in a state of oxidative stress.[11] Another study on rats has shown that low level microwave radiation exposure increased malondialdehyde (MDA) levels as a marker of lipid peroxidation and protein carbonyl as a marker of protein oxidation in the blood.[12]

This study intended to determine the effects of radioiodine therapy on iodine deficient patients who consumed a low-iodine diet along with L-T4 withdrawal. In this study, we evaluated a number of biochemical and oxidative stress markers in patients' blood samples prior to and 72 h after administration of 125-200 mCi 131I. Total protein, aspartate aminotransferase (AST), alanine amino-transferase (ALT), alkaline phosphatase (ALP), creatinine (Cr), MDA, and protein carbonyl levels were measured in patients' sera.

Material and Methods

Patients

A total of 40 patients consented to participate and enrolled in this study. The study was conducted according to the Declaration of Helsinki. All patients had documented evidence of well-differentiated, papillary thyroid carcinoma and underwent total thyroidectomy. There were 28 females and 12 males between the ages of 14 and 78 years. All participants, two to five months after surgery, began their iodine therapy regime for the first time as follows. Patients received replacement of L-T4 with liothyronine at a daily dose of 50 mg for 2 weeks, followed by 2 weeks of total withdrawal before radioiodine therapy to 3 days after with a thyroid-stimulation hormone level (TSH) >30 mIU/L. The thyroid remnants were ablated by administration of 125 mCi (15 patients), 150 mCi (24 patients), and 200 mCi (1 patient) oral131I. Patients received information about the need for a low-iodine diet and allowed foods. We encouraged patients to follow this diet from 2 weeks before radioiodine therapy until they underwent the 131I whole-body scan, 72 h after treatment. Patients did not take salicylates or other antioxidants that influenced the oxidative

Table 1. Biochemical and oxidative stress parameters before and 72 h after radioactive iodine therapy (RAI).

Parameters	Before	After	*P*-value
AST (<35 IU/L)	70.94±44.59	34.16±19.43	0.000004
ALT (<35 IU/L)	37.64±28.48	20.81±14.23	0.000154
Total protein (6.0-8.0 g/dL)	8.81±0.75	8.10±0.53	0.0000007
Cr (0.6-0.2mg/dL)	1.23±0.28	1.04±0.19	0.0000007
ALP (41-133 IU/L)	174.86±62.33	166.49±63.07	0.163695
Protein carbonyl (nmol/mg)	9.7±7.3	11.2±6.3	0.153123
MDA (nmoles/ml)	1.35±0.50	1.60±0.7	0.01237

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; Cr: Creatinine; MDA: Malondialdehyde

state for 3 weeks before the study. Exclusion criteria were: patients with more than one cancer or the presence of other systematic diseases such as diabetes mellitus, liver, or kidney diseases. All radioiodine therapies were performed in the Nuclear Medicine Department of Nemazee Hospital according to a standard protocol. We carefully monitored the patients during the admission period. Patients were discharged from the hospital 3 days after radioiodine therapy treatment. Blood samples (5 ml) were collected just prior to as well as 72 h after 131I administration. The Ethical Committee of Shiraz University of Medical Sciences approved the study.

Biochemical and oxidative stress parameters

We measured total protein, AST, ALT, ALP, and Cr levels in patients' sera before and 72 h after RAI therapy. Measurements were taken in duplicate with Pars Azmoon kits (Tehran, Iran) using calorimetric methods.

Protein carbonyl was measured in serum as a marker of protein oxidation by spectrophotometric[13] analysis using 2,4-dinitrophenylhydrazine (DNPH). Reactive carbonyl derivatives were calculated using the DNPH molar extinction coefficient at 370 nm and expressed as nmol/mg of protein. Lipid peroxidation in serum was assayed as TBARS using a colorimetric method.[14] Serum (0.5 mL) was added to 2 mL of TBA reagent that contained 0.375% TBA, 15% trichloroacetic acid, and 0.25 mol/L HCl. The mixture was boiled for 15 min, cooled, and centrifuged at 1700×g for 15 min at 4°C. The absorbance of the supernatant was measured at 532 nm. The TBARS concentration was calculated using 1,1,3,3-tetramethoxypropane as the standard with results expressed as nmol/ml of plasma. Each test was repeated twice for confirmation of reproducibility.

Statistical analysis

All parameters were compared using the two-tailed paired student's t-test. The values were presented as mean±SD. The chi-square test was used to determine possible associations between parameter changes and age, sex, and RAI doses. Statistical analyses were performed using SPSS software (version 18.0). A *P*-value of less than 0.05 was considered statistically significant.

Results

This study enrolled 40 well-differentiated thyroid cancer patients, with an average age of 45±17 years. Table 1 lists the mean±SD of all biochemical and oxidative stress parameters. The paired samples t-test results demonstrated that total protein, Cr, ALT, and AST levels decreased significantly ($P<0.001$) in patients' blood within 72 h after iodine therapy to their normal ranges. ALP nonsignificantly decreased. There were no associations between changes to biochemical parameters and clinicopathological features of age, sex, RAI doses, and whole body RAI scan results.

We evaluated the early side effects of 131I therapy on oxidative stress after three days of 131I administration. The oxidative stress marker for lipid, MDA, levels increased significantly in patients' sera ($P=0.01$). However, protein peroxidation had a slight, nonsignificant increase during the study period (Table 1). We observed no effects on MDA levels in terms of dose (125, 150

or 200 mCi) as well as patient age and sex after RAI therapy.

Discussion

Numerous studies have assessed biochemical parameters in thyroid cancer patients who underwent L-T4 withdrawal and a whole body RAI scan as evaluation of residual/recurrent malignant disease. These studies confirmed significant increases in total protein, liver enzymes (ALT and AST), muscle enzymes (creatine kinase and serum Cr) levels after L-T4 withdrawal due to acute hypothyroidism.[4,5,15-17] It has been reported that preparation of patients for RAI therapy by using recombinant human TSH (rhTSH) instead of L-T4 withdrawal prevented symptoms of hypothyroidism as well as liver and renal dysfunctions by maintaining normal AST, ALT, and serum Cr levels within the normal ranges. Their increases were not likely clinically significant in cancer patients.[5,17,18] In addition, rhTSH reduces the amount of radiation in the entire body, and effective half-life and residence times of RAI in most body organs by approximately one-third[17,19] in comparison to preparation situation with L-T4 withdrawal.[20] On the other hand, dietary iodine restriction stimulates 131I uptake to the thyroid and other organs.[6,7] However, in this setting it has been shown that rhTSH stimulation increased the iodine pool and the iodine excretion around 50% higher than L-T4 withdrawal due to the deiodination of L-T4.[21] Physiological uptake of radioiodine in the salivary glands, thymus, breasts, liver, kidneys, gastrointestinal tract, and urinary tract has been shown in thyroid cancer patients after RAI therapy.[22] These observations confirm that patients who consume a low-iodine diet and undergo L-T4 withdrawal are iodine deficient; hence, their liver and kidneys absorb more RAI than patients who received rhTSH. Our results showed that after iodine absorption in peripheral tissues due to RAI therapy, the biochemical parameters of total protein, ALT, AST, and Cr levels decreased significantly to the reference range levels after 72 h. These changes showed no association with patients' age and sex as well as the administered RAI doses. These results revealed that the main reason for such changes was iodine deficiency in the body organs rather than hypothyroidism, as patients still had hypothyroidism and began L-T4 after the whole body RAI scan. However, the RAI could replace the normal iodine in the liver and kidneys and relieve the adverse effects of iodine deficiency in the liver and kidneys. This treatment might improve the function of these organs. We have not found any report that explained the mechanism which causes biochemical changes in patients who consume a low-iodine diet and undergo L-T4 withdrawal. It is well known that iodine deficiency is the main cause of hypothyroidism.[8] For the first time, we have suggested that the cause of increase in biochemical parameters such as liver enzymes, total protein, Cr. in patients' sera during a low-iodine diet and L-T4 withdrawal is iodine deficiency, rather than hypothyroidism. The total protein levels in these patients have agreed with the results by Vrndic et al.[27] The significant decrease in total protein 3 days after 131I therapy could be correlated with oxidative stress. Protein oxidation and oxidative damage[23] might be another reason for decrease in plasma protein concentrations in these patients

Common adverse effects of radioiodine treatment include dry mouth, mouth pain, salivary gland swelling, altered smell and taste, conjunctivitis, and fatigue. In addition, RAI therapy can increase the risk of developing secondary malignancies, in particular hematologic malignancies or less often kidney, breast, bladder, skin, and salivary gland cancers compared to the general population.[3,24] Another report has shown that the more common short-term adverse effects 96 h after radioiodine therapy included gastrointestinal complaints (65.2%), salivary gland swelling with pain (50%), changes in taste (9.8%) and headaches (4.4%).[25] It has been confirmed that exposure to radiation leads to damages in cells and body fluids as a result of free radical attack.[26] Our data confirmed that treatment with 131I for thyroid cancer caused oxidative stress with a significant increase in the oxidative stress

parameter of lipid peroxidation (MDA) within 72 h, independent of the dose. This indicated that RAI therapy had a short-term adverse effect on lipid peroxidation in serum. The 125-200 mCi dose range did not cause any difference in oxidative intensity. The results of the present study on MDA have supported similar studies of the plasma and erythrocytes in thyroid cancer patients.[27,28] Malondialdehyde can be the result of ROS generation by RAI and low levels of antioxidants such as SOD enzyme, glutathione peroxidase, and catalase in tissues after 131I therapy.[9,10,29] Reactive oxygen species can interact with lipids that form aldehydes which bind to thiobarbituric acid. These reactive substances have been quantified in numerous studies that measured MDA levels, which is an important indicator of oxidative stress and DNA damage by ROS. The patients in the current study had hypothyroidism with TSH were more than 30 mIU/L. However, TSH is not an interfering factor for the MDA assay.[30,31] Malondialdehyde can react with the free amino groups of proteins and nucleic acids, which leads to additional cell damage.[27,28,32] It has been shown that supplementation with vitamins E and C could reduce MDA levels in oxidative stress situations.[33,34] Both vitamins play an important role in protection against free radical-induced damage and have potent antioxidant properties.[35,36] Therefore, dietary vitamin C and E supplementation can reverse the short-term adverse effects of radiotherapy.

We found that RAI uptake in non-thyroid organs such as the liver and kidneys during iodine deficiency and hypothyroidism caused significant decreases to serum levels of liver enzymes, total protein, and Cr. However, the 125-200 mCi doses of RAI used to treat thyroid cancer patients could increase lipid oxidation due to induction of oxidative stress.

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Conflict of interest

No conflict of interest is declared.

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