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RESEARCH ARTICLE

ARE PARATHYROID FUNCTIONS AFFECTED IN PATIENTS WITH DIFFERENTIATED THYROID CANCER WHO HAVE RECEIVED RADIOACTIVE IODINE THERAPY: TWO-YEAR FOLLOW-UP RESULTS

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ABSTRACT

Background/aim: Administration of external ionizing radiation to the neck may causes hyperparathyroidism (HPT) over the years. Radioactive iodine (RAI) therapy which applied in differentiated thyroid cancers (DTC) exposes parathyroid glands to radiation. This may cause hyperparathyroidism, parathyroid adenoma and hyperplasia. The aim of this study is to determine whether RAI treatment changes the parathyroid gland functions in patients with DTCs. **Methods:** The 2-years parathormon (PTH), calcium (Ca) and phosphorus (P) levels of 145 patients who had previously undergone RAI ablation in our hospital were reviewed retrospectively. Pretreatment PTH, Ca, and phosphorus levels were compared to the at 1st, 6th, 12th, and 24th month results after treatment. **Results:** During the 2-years follow-up, there were not any significant differences between baseline and follow-up PTH, Ca and phosphorus levels ($p > 0.05$). In patients with receiving low dose RAI therapy, 12th month phosphorus level was significantly lower than baseline ($p = 0.015$; $p < 0.05$). In patients with receiving high-dose RAI therapy, 6th month PTH levels were significantly lower than baseline ($p = 0.014$; $p < 0.05$). **Conclusion:** Transient decrease in PTH levels may be observed in patients receiving RAI treatment for DTC at 6 months. However, RAI treatment does not affect PTH functions in two years of follow-up.

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INTRODUCTION

Ionizing radiation exposure to neck causes some side effects in parathyroid gland including increased risk of HPT, parathyroid adenoma, or hyperplasia (Holmberg 2002; Rasmuson 2002; Tisell 1976; Christmas 1998; Kalaghchi 2003; Fujiwara 1994)). Due to anatomically close relationship between thyroid and parathyroid glands, parathyroids may be exposed to ionized radiation during RAI therapy, which is a component of treatment, in DTC patients. Due to this reason, parathyroid functions may be affected. RAI have being performed to eliminate residual thyroidal tissue and microscopic cancer foci in these patients with many years. Hovewer, it has some possible side effects such as radiation exposure of the bladder/gonads, increased risk of secondary cancer, lung fibrosis, thyroiditis, sialadenitis, nausea, vomiting, xerostomia (Pacini 2006; Güven 2009). Iodine is a classical substrate of the thyroid, and parathyroid glands do not utilize iodine. I-131 has been frequently used for many years to ablation or treatment in benign and malignant thyroid diseases. It has approximately 90% beta, and 10% gamma emissions. The penetration of beta emission is about 2 mm. Because of these reasons, parathyroid glands are mainly affected by radioiodine within the thyroid cells (Rasmuson 2006). There are few studies reported that, development of primary HPT after the RAI treatment (Netenbos 1981; Cundiff 2001; Fjalling 1983). The several times higher than normal increased incidence of HPT was demonstrated in children and adolescents with Graves disease following to radioactive iodine therapy (Bondeson 1989; Esselstyn 1982). It was also determined that, significantly increased risk of HPT and parathyroid adenoma in rats expose to radioactive iodine (Berdjis 1972; Triggs 1977). Development of hypoparathyroidism after the RAI treatment also reported (Glazebrook 1987; Eipe 1968; Fulop 1971; Orme 1971; Better 1969; Jialal 1980). On the other hand some other studies reported RAI treatment was not affect parathyroid functions including Ca and phosphorus levels (Hamilton 2005; Zhang 2020).

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The aim of this study is to determine whether RAI treatment changes the parathyroid gland functions in patients with DTCs.

MATERIALS AND METHODS

Patients: University's ethical committee approved this retrospective study before starting. We retrospectively reviewed the data of 145 consecutive patients with pathologically confirmed DTC who, underwent total thyroidectomy and subsequent RAI ablation from May 2016 to March 2018. The mean age of the patients was 47.41 ± 14.69 (19-88 years). All patients signed informed consent forms before each procedure. Exclusion criteria from our study were as follows: Pregnancy, presence of other systemic diseases, the history of previous radiotherapy to the neck region or RAI treatment, parathyroid gland dysfunction before treatment, removal of parathyroid glands during surgery. In addition, therapy of calcium or vitamin D which was recently administered.

I-131 ablation theraphy: According to routine procedure of our clinic, TSH levels must above 30 mIU/mL for RAI therapy. This was achieved by thyroid hormone withdrawal. In addition, low iodine diet was applied to the patients. Thyroid scintigraphy, I-131 uptake study, neck ultrasonography and non-contrast lung radiography/tomography were performed. When deciding to the I-131 dosage; American Thyroid Association (ATA) criteria (Araque 2020), our own clinical experience, and patient' preferences were taken into consideration. 30-200 mCi of I-131 were given orally to the patients and they were hospitalized in nuclear medicine department for 1-3 days.

Biochemical analysis: Thyroid stimulating hormone (TSH), thyroglobulin (Tg), PTH, serum calcium (Ca) and phosphorus levels were measured in the blood samples while patient was fasting. These tests were also performed in the 1st-6th-12th and 24th months of ablation. PTH (pg/ml), Tg (ng/ml) and TSH (mIU/L) levels were measured with Roche reagents by a Cobas 801 analyzer (Roche Diagnostics, Germany) with electrochemiluminescence immunoassay method. Serum calcium (mg/dl) and phosphorus (mg/dl) levels were measured by electrochemiluminescence method with Roche reagents by a Cobas 702 analyzer (Roche Diagnostics, Germany). The reference ranges were as follows: TSH (0.27-4.2 mIU/L), Tg (3.5-77 ng/ml), PTH (15-65 pg/ml), serum calcium (8.6-10.3 mg/dl), phosphorus (2.6-4.5 mg/dl).

Statistical Analysis: Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, in addition to descriptive statistical methods (average, standard deviation, median, frequency, ratio, minimum, maximum), the distribution of the data was evaluated using the Shapiro-Wilk Test. Friedman test in comparing periodic quantitative data with three or more cases that do not show normal distribution. Wilcoxon test was used to determine the differences, $p < 0.05$ was accepted statistically significant.

RESULTS

The characteristics of 145 patients were shown in Table 1. The mean Thyroglobuline (Tg), TSH, and 24th hour 131I uptake rate of patients were 16.28±39.40 mIU/L, 42.70±68.41 mIU/L, and 8.20±10.36%, respectively. TSH levels were: 0.56±1.00 mIU/L at 1st month, 0.05±0.09 mIU/L at 6th month, 0.15±0.40 mIU/L at 12th month, and 0.24±0.52 mIU/L at 24th month. Table 2 shows the two-year follow-up results of PTH, Ca, phosphorus levels of patients who received radioactive iodine therapy. When all patients were taken into consideration, there were not any statistically significant differences at 1st, 6th, 12th and 24th months PTH, Ca and phosphorus levels from the baseline ($p > 0.05$). In patients with receiving low dose RAI therapy (<100mCi), there was not any statistically significant differences in PTH and calcium levels($p > 0.05$).

On the other hand, we found statistically significant differences between phosphorus values. ($p = 0.015$; $p < 0.05$). Phosphorus levels at the 12th month was significantly lower than baseline (**Friedman test, $p = 0.001$; $p < 0.01$) (Table 3). In patients with receiving high dose RAI therapy (≥ 100mCi), levels of PTH at 6th month were significantly lower than the baseline ($p = 0.014$; $p < 0.05$); (** Friedman test, $p = 0.001$; $p < 0.01$). On the other hand, there were not any statistically significant differences in calcium and phosphorus ($p > 0.05$), (Table 4).

DISCUSSION

In patients with received RAI treatment for DTC, we could not find any significant differences in PTH levels at 2-years follow-up. Many of studies reported that, temporary or permanent hyperparathyroidism after the RAI treatment for benign or malignant thyroid diseases (Netenbos 1981; Cundiff 2001; Fjalling 1983; Bondeson 1989; Esselstyn 1982; Berdjis 1972; Triggs 1977; Rosen 1984; Prinz 1982; Pauwels 2000). Szumowski et al. (2013) found transient HPT after the RAI therapy. The authors reported that, this finding mostly occured between 4 to 20 years after the RAI treatment.

Our follow-up period was relatively short, and longer follow-up periods may change these results. Similar results to our study were reported in the literature. (Hamilton 2005; Zhang 2020; Glazebrook 1987; Mortensen 2005). There are several hypotheses about why RAI does not affect the parathyroid cells. The first is that parathyroid cells cannot take to the iodine. The second is low mitotic activity of these cells. In addition, parathyroid cells are not exposed to a pituitary stimulus. In addition, minimum residual thyroid tissue remains after the surgery in DTC patients. Although the doses of radioiodine are high, low volume of residual tissue causes decreasing cumulative uptake.

This may cause the lower radiation exposure of the parathyroid cells. In this study we also found that, patients with low-dose RAI treatment have had significantly lower phosphorus levels at 12 months compare to baseline. we could not find any clear knowledge about that in the literature. According to our findings, the decreasing of phosphorus level was within normal limits. We think that, there was not any clinical significance of this finding. On the other hand, levels of the PTH at 6th month in patients who, received high-dose RAI treatment (≥ 100mCi) were significantly lower than baseline. In some studies mentioned that, transiently decreased parathyroid function. (Guven 2009; Tighe1952).

Table 1. Characteristics of the Patients

Category		(n)	Percent (%)
Number of patients		145	100
Sex			
	Female	130	90
	Male	15	10
Age			
	Mean±SD	47.41 ± 14.69	
	Range	19-88 (47) years	
Pathological type			
	PTC	136	94
	FTC	6	4
	HCC	3	2
I-131 dosage(mCi)			
	30	39	27
	75	13	9
	100	71	49
	125	10	7
	150	9	6
	200	3	2

PTC: Papillary thyroid cancer, FTC: Follicular thyroid cancer, HCC: Hurtle cell carcinoma,

Table 2. Comparison of PTH, Ca, P values before and after ablation for two years

	PTH (pg/ml)	Ca (mg/dl)	P (mg/dl)
Reference range	15-65	8.6-10.3	2.6-4.5
Pre-ablation	55.67±28.89	9.36±0.94	3.81±0.75
1st month	47.57±24.12	9.30±0.49	3.82±0.72
6th month	47.62±22.18	9.4±0.54	3.68±0.54
12th month	53.54±29.33	9.5±1.28	3.60±0.6 2
24th month	52.82±28.97	9.37±0.48	3.56±0.69
P value	0.084	0.106	0. 663

Table 3. Comparison of two-year PTH, Ca, P values with baseline values after ablation in patients with DTC receiving low-dose RAI therapy (<100 mCi)

	PTH (pg/ml)	Ca (mg/dl)	P (mg/dl)
Reference range	15-65	8.6-10.3	2.6-4.5
Pre-ablation	63.09±29.51	9.23±1.27	3.79±0.82
1stmonth	43.89±29.20	9.31±0.74	4.18±0.68
6th month	53.07±21.69	9.16±0.60	3.81±0.56
12th month	55.30±26.50	9.95±1.97	3.62±0.54
24th month	62.05±31.82	9.34±0.44	3.61±0.86
P value	0.910	0.637	*0.015**

Table 4. Comparison of two-year PTH, Ca, P values with baseline values after ablation in patients with DTC receiving high-dose RAI therapy (≥100 mCi)

	PTH (pg/ml)	Ca (mg/dl)	P (mg/dl)
Reference range	15-65	9.44-0.67	2.6-4.5
Pre-ablation	51.06±27.89	9.30±0.34	3.83±0.71
1st month	49.23±22.35	9.31±0.74	3.64±0.68
6th month	44.4±22.08	9.55±0.45	3.60±0.52
12th month	52.55±31.02	9.26±0.52	3.59±0.63
24th month	47.66±26.17	9.39±0.39	3.55±0.62
P value	*0.014**	0.077	0.725

Güven et al. (2009) reported that, development of transient asymptomatic hypoparathyroidism at 6th month after the RAI ablation. According to their results, parathyroid hormone levels increased to baseline levels at the end of the 12th month. The cause of transient hypoparathyroidism is unclear. However, edema secondary to the RAI may be a factor. Another possible factor is that, increased Ca turn over in the bones. This may cause higher levels of calcium in the blood, resulting in lower parathyroid hormone levels. (Utiger 2001).

Conclusion

Parathyroid functions are not affected by RAI administration for ablation. Transient hypoparathyroidism may occur in patients receiving high-dose RAI. Parathyroid functions of patients receiving RAI therapy should monitored carefully.

Conflicts of interest: Authors declared no conflict of interest.

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