



# Parathyroid gland function after radioiodine ( $^{131}\text{I}$ ) therapy for toxic and non-toxic goitre

Czynność gruczołów przytarczycznych po leczeniu radiojodem ( $^{131}\text{I}$ ) toksycznego oraz nietoksycznego wola

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## Abstract

**Introduction:** The therapeutic effect of radioactive iodine ( $^{131}\text{I}$ ) on benign goitre consists of the emission of tissue-destructive beta-radiation. Since the range of beta  $^{131}\text{I}$  radiation in tissue can reach 2.4 mm, it can affect the adjacent parathyroid glands. The purpose of this paper is to assess parathyroid function in patients with toxic and non-toxic goitres, up to five years following  $^{131}\text{I}$  therapy.

**Material and methods:** The study sample consisted of 325 patients with benign goitres (220 with toxic nodular goitre (TNG), 25 with non-toxic nodular goitre (NTNG), and 80 with Graves' disease (GD) treated with  $^{131}\text{I}$ . The therapeutic activity of  $^{131}\text{I}$  for each patient was calculated using Marinelli's formula. The serum levels of  $\text{fT}_3$ ,  $\text{fT}_4$ , TSH, iPTH and  $\text{Ca}^{2+}$ , Ca and phosphates were determined one week before  $^{131}\text{I}$  administration, as well as every two months up to a year following the therapy, and then after three and five years post-treatment.

**Results:** After two months following the administration of  $^{131}\text{I}$ , all the treated patients showed a statistically significant above normal increase in iPTH concentrations (amounting to a value almost twice the norm in patients with TNG), which remained stable up to ten months after treatment, to return to normal level in the following months. In all the patients,  $\text{Ca}^{2+}$ , Ca, phosphates concentration remained within normal range throughout the course of the study. The concentrations of  $\text{fT}_3$  and  $\text{fT}_4$  quickly returned to normal after  $^{131}\text{I}$  administration, and remained within normal range until the completion of the study.

**Conclusion:** Radioiodine treatment of benign thyroid disorders results in transient (up to ten months after  $^{131}\text{I}$  administration) hyperparathyroidism. The condition does not influence the level of calcium and phosphates concentration in any significant way.

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**Key words:** hyperparathyroidism, hyperthyroidism, radioiodine therapy

## Streszczenie

**Wstęp:** Efekt terapeutyczny radiojodu ( $^{131}\text{I}$ ) w wolu łagodnym opiera się na emisji niszczącego tkanki promieniowania beta. Maksymalny zasięg promieniowania beta  $^{131}\text{I}$  w tkance wynosi do 2,4 milimetra. Dlatego, też w zasięgu tego promieniowania mogą się znajdować sąsiadujące z tarczycą przytarczycze. Celem pracy była ocena czynności przytarczyc u chorych z wolem nadczynnym i normocynnym poddanych terapii  $^{131}\text{I}$  w okresie do 5 lat od zastosowanego leczenia.

**Materiał i metody:** Badania zostały wykonane u 325 chorych z łagodnym wolem (220 z wolem guzowatym nadczynnym (TNG), 25 z wolem guzowatym obojętnym (NTNG) i 80 z chorobą Gravesa-Basedowa (GD) poddanych leczeniu  $^{131}\text{I}$ . Aktywność lecznicza  $^{131}\text{I}$  dla każdego pacjenta wyliczana była z wzoru Marinellego. W trakcie radiojodoterapii oznaczano stężenia  $\text{fT}_3$ ,  $\text{fT}_4$ , TSH, iPTH,  $\text{Ca}^{2+}$ , Ca i fosforanów w surowicy tydzień przed podaniem  $^{131}\text{I}$ , i następnie w odstępach dwumiesięcznych przez rok po terapii oraz po 3 i 5 latach.

**Wyniki:** U wszystkich chorych po 2 miesiącach od momentu rozpoczęcia leczenia zaobserwowano znamieny statystycznie wzrost stężenia iPTH ponad normę (do wartości prawie dwukrotnie powyżej normy u pacjentów z TNG), który utrzymywał się aż do 10 miesięcy, a następnie ulegał normalizacji. Stężenia  $\text{Ca}^{2+}$ , Ca i fosforanów u wszystkich leczonych pozostawały w zakresie normy w trakcie całego badania. Stężenia  $\text{fT}_3$  i  $\text{fT}_4$  w surowicy po podaniu  $^{131}\text{I}$  szybko się normalizowały i pozostawały w zakresie normy do końca badania.

**Wnioski:** Radiojodoterapia łagodnych schorzeń tarczycy prowadzi do powstania przejściowej (trwającej maksymalnie do 10 miesięcy od podania radiojodu) nadczynności przytarczyc. Stan ten istotnie nie wpływa na stężenia wapnia i fosforanów w surowicy.

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**Słowa kluczowe:** nadczynność przytarczyc, nadczynność tarczycy, radiojodoterapia

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## Introduction

It is widely known that the therapeutic effect of the radioiodine isotope  $^{131}\text{I}$  for both non-toxic and toxic

goitres is based on the fact that it emits strong ionising beta radiation, which causes damage to thyrocytes. As is known from physics, the maximum range of beta radiation from  $^{131}\text{I}$  decay is 2.4 mm [1-3]. That is why

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radiation affects not only the thyroid gland tissue but also reaches over 2 mm beyond it, and its effect increases with the magnitude of radiation dose. It is known from anatomy and histology that parathyroid glands are situated in the immediate vicinity of the thyrocytes, on the posterior lobe of the thyroid, and thus can be permeated by beta radiation from  $^{131}\text{I}$  absorbed by the thyroid gland.

It seems worth considering whether this type of radiation might lead to any parathyroid malfunction. Although the issue has been investigated by various researchers, the available conclusions — mostly based on a limited number of patients — are often widely discrepant or even contradictory [1–4, 6, 10–12]. Some authors maintain that radiation from thyroid-absorbed  $^{131}\text{I}$  causes temporary damage to parathyroid glands, resulting in their transient hypofunction, whereas others, on the contrary, believe that the same radiation causes parathyroid hyperfunction [4, 5]. There are also studies whose authors claim that the radiation from thyroid-absorbed  $^{131}\text{I}$  may lead to the development of parathyroid adenoma, as well as those which do not contain any evidence of increased risk for such a development [6–9].

For this reason, the purpose of this paper is to assess the parathyroid gland function in patients with toxic and non-toxic goitres after  $^{131}\text{I}$  therapy up to five years post-treatment.

## Material and methods

The sample encompassed 325 patients with benign goitres, including 220 patients (180 women and 40 men) with toxic nodular goitres (TNG), 80 (70 women and ten men) with Graves' disease (GD), and 25 (22 women and three men) with non-toxic nodular goitres (NTNG). The average age of the studied population was  $45 \pm 10$  years. All the patients underwent radioiodine ( $^{131}\text{I}$ ) treatment at the Nuclear Medicine Department Clinic of the Medical University of Białystok between 2006 and 2012. The primary aim of the treatment was to eliminate hyperthyroidism and/or to reduce the size of goitre. Before the administration of therapeutic activity of  $^{131}\text{I}$ , all the patients were routinely qualified for the study: they had undergone physical examination and their past medical histories had been investigated. Further, the patients' serum levels of thyroid-stimulating hormone (TSH) were measured by means of immunoradiometric assay, free thyroxine ( $\text{fT}_4$ ) and free triiodothyronine ( $\text{fT}_3$ ) were evaluated using the radioimmunological method (RIA). All the nodules were biopsied (in order to exclude cancer), USG examinations of the thyroid glands were performed, as were 24-hour ( $T_{24}$ ) and 48-hour ( $T_{48}$ ) radioactive iodine uptake tests and the

scintigraphic evaluation using a gamma camera (Nucline™ Th, Mediso). Moreover, serum concentrations of iPTH were determined by means of the immunoluminescence assay (ICMA), the ionised calcium method ( $\text{Ca}^{2+}$ ) using ion-selective electrodes, corrected for possible pH variations whereas total calcium (Ca) and phosphates (P) by means of chemical methods. It should be stressed that patients with diseases that might affect calcium-phosphorus homeostasis were excluded from the study.

Required therapeutic activity (A) of  $^{131}\text{I}$  was calculated using Marinelli's formula [10]:

$$A = \frac{25 \cdot m \cdot D}{T_{24} \cdot T_{\text{eff}}}$$

where

**A** —  $^{131}\text{I}$  therapeutic activity (MBq)

**25** — unit conversion coefficient

**m** — mass of thyroid gland calculated from USG (g)

**D** — absorbed dose of  $^{131}\text{I}$  (Gy)

**$T_{24}$**  — 24-h  $^{131}\text{I}$  uptake (%)

**$T_{\text{eff}}$**  — effective  $^{131}\text{I}$  half-life in thyroid gland (days) =  $T_{\text{biolog}} \times T_{\text{phys}} / (T_{\text{biolog}} + T_{\text{phys}})$ , where  $T_{\text{biolog}}$  (rate of iodine excretion from the thyroid),  $T_{\text{phys}}$  (physical half-life of radioactive iodine)

The choice of thyroid absorbed  $^{131}\text{I}$  radiation dose depended on the type of hyperthyroidism and was consistent with the recommendations made by the European Association of Nuclear Medicine [11]. For toxic nodular goitre, the absorbed dose was 260Gy, for Graves' disease it was 140Gy, while for non-toxic nodular goitre it was 180Gy.

Throughout the first year following radioiodine therapy, all the subjects were re-examined every two months, and additionally after three and five years post-treatment. The check-ups involved  $\text{fT}_3$ ,  $\text{fT}_4$ , TSH, iPTH,  $\text{Ca}^{2+}$ , Ca and P blood serum tests.

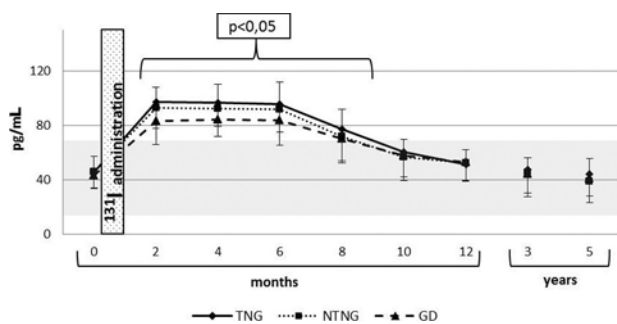
The study was approved by the Ethics Committee for Medical Research, Medical University of Białystok, and is in accordance with GCP (good clinical practice). Informed consent was given by all patients participating in the study.

## Statistical analysis

All statistical analyses were performed using the software package Statistica 10 (Stat Soft, Tulsa, OK, USA).

The Friedman test was used for assessment of the differences between pre- and post-treatment levels of  $\text{fT}_4$ ,  $\text{fT}_3$ , TSH, iPTH,  $\text{Ca}^{2+}$ , Ca and P.

The extent to which variations of the thyroid-absorbed dose of  $^{131}\text{I}$  influence the iPTH serum levels was determined by means of linear regression function.



**Figure 1.** Variations of native parathyroid hormone (iPTH) serum levels in patients with TNG, GD and NTNG within one year and after 3 and 5 years following radioiodine administration. Part of the graph marked by clip corresponds statistically significantly ( $p < 0.05$ ) with elevated iPTH concentrations above normal in all patients. (The grey area indicates normal concentrations of iPTH in blood serum)

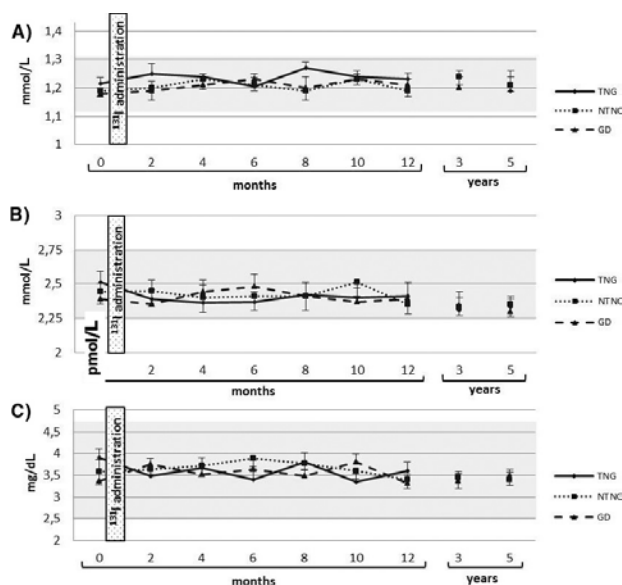
**Rycina 1.** Zachowanie się stężeń natywnej postaci parathormonu (iPTH) w surowicy krwi u pacjentów z TNG, GD, NTNG poddanych radiojodoterapii w okresie do 1 roku oraz po 3 i 5 latach od podania izotopu. Część wykresu objęta kłamrą odpowiada istotnie statystycznie ( $p < 0,05$ ) podwyższonym powyżej normy wartościom iPTH u wszystkich pacjentów (Obszar zaznaczony szarym kolorem pokazuje zakres norm stężenia PTH w surowicy krwi)

## Results

Two months after the administration of therapeutic radioiodine, all the patients showed statistically significant ( $p < 0.005$ ) increases in above-normal iPTH serum levels. The highest (slightly over two-fold) rise in serum levels of iPTH occurred in TNG patients, a little lower — in NTNG ones, and relatively the lowest — in GD patients. In the next four months, iPTH concentrations remained similarly high in all the patients. Six months after radioiodine administration, the hormone level started to decrease, to come back to normal in the tenth month post-treatment. The follow-up examinations — three and five years following radioiodine therapy — revealed that the concentrations of iPTH,  $Ca^{2+}$ , Ca and P did not exceed normal limits in any of the patients (Figs. 1 and 2).

As can be seen from Figure 2, the differences between blood serum concentrations of  $Ca^{2+}$ , Ca and P pre- and post-treatment were very small in all the patients, and thus statistically insignificant.

Analysis of iPTH concentrations in the blood serum of patients who underwent radioiodine therapy leads to the conclusion that, depending on the thyroid absorbed dose, the most significant increase in iPTH above the upper normal range (starting from the 2<sup>nd</sup> month post-administration, and persisting as long as until the 10<sup>th</sup> month) occurred in those patients whose thyroids absorbed the highest accumulated dose, i.e. 260Gy. With the thyroid absorbed



**Figure 2.** Variations of serum levels of **A)  $Ca^{2+}$** , **B) Ca**, **C) P** in patients with TNG, GD and NTNG within one year and after 3 and 5 years following radioiodine administration. (The grey area indicates normal concentrations of above factors in blood serum)

**Rycina 2.** Zachowanie się stężeń **A)  $Ca^{2+}$** , **B) Ca**, **C) P** w surowicy krwi u pacjentów z TNG, GD, NTNG poddanych radiojodoterapii w okresie do 1 roku oraz po 3 i 5 latach od podania izotopu. (Obszar zaznaczony szarym kolorem pokazuje zakres norm stężenia  $Ca^{2+}$  w surowicy krwi)

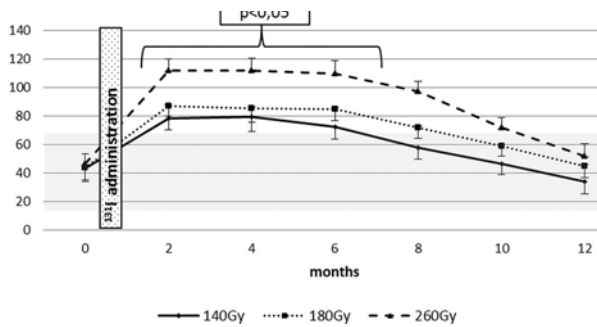
dose of  $^{131}I$  at 180Gy, the rise in iPTH above normal levels is slightly lower, and its concentration returns to normal more rapidly. In thyroids with the lowest absorbed dose (140Gy), iPTH levels were found to increase to the least extent, and the time necessary for achieving normal parameters was the shortest: only six months after the administration of  $^{131}I$ . The increase in iPTH was statistically significant at  $p < 0.005$  for all the three absorbed doses (Fig. 3).

Using the linear regression model, it has been proved that there exists a correlation between the absorbed dose and the level of iPTH, which is expressed by the formula below:

$$iPTH = 0.54 \text{ absorbed dose} + 10.24 \quad r^2 = 0.97 \quad p < 0.05$$

From the formula it can be seen that the higher the absorbed dose, the greater the rise in the concentration of iPTH in blood serum.

As far as the hormonal function of the thyroid is concerned, only TNG patients showed statistically significant ( $p < 0.001$ ) alterations in levels of hormones after radioiodine treatment: mean levels of  $fT_3$  and  $fT_4$  returned from above the upper limit to normal as a result of treatment. In all the patients, the blood serum levels of  $fT_3$  and  $fT_4$  remained within normal limits for a year following radioiodine administration, i.e. throughout the period covered by this study (Figs. 4 and 5).



**Figure 3.** Variations of native parathyroid hormone (iPTH) serum levels depending on absorbed dose of  $^{131}\text{I}$  in patients after radioiodine therapy within one year following radioiodine administration. Part of the graph marked by clip corresponds statistically significantly ( $p < 0.05$ ) with elevated iPTH concentrations above normal irrespectively of absorbed dose. (The grey area indicates normal concentrations of PTH in blood serum)

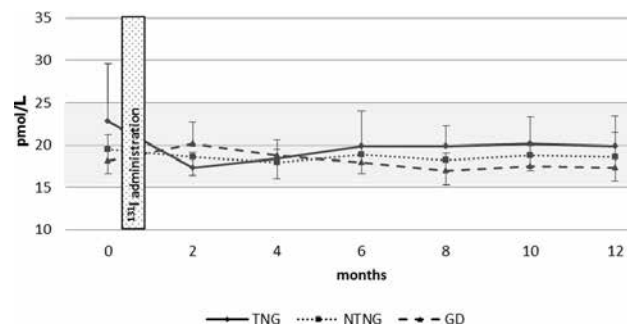
**Rycina 3.** Zachowanie się stężeń natywnej postaci parathormonu (iPTH) w surowicy krwi w zależności od dawki pochłoniętej  $^{131}\text{I}$  w tarczycy u pacjentów poddanych radiojodoterapii w okresie do 1 roku od podania izotopu. Część wykresu objęta klamrą odpowiada istotnie statystycznie ( $p < 0,05$ ) podwyższonym powyżej normy wartościom iPTH bez względu na dawkę pochłoniętą (Obszar zaznaczony szarym kolorem pokazuje zakres norm stężenia PTH w surowicy krwi)

## Discussion

The abovementioned figures prove that the use of radioactive isotope of iodine ( $^{131}\text{I}$ ) in the treatment of benign thyroid disease (i.e. hyperthyroidism and large, euthyreotic goitre) not only normalises hormonal function of thyroid but also has an influence on the hormonal function of parathyroid glands. In the therapeutic process, the transitory hyperparathyroidism was observed (independently of the type of hyperthyroidism); however, it usually subsided ten months after administration of I-131. A statistically significant increase in the level of iPTH in all patients does not change the concentrations of calcium and phosphate in the blood.

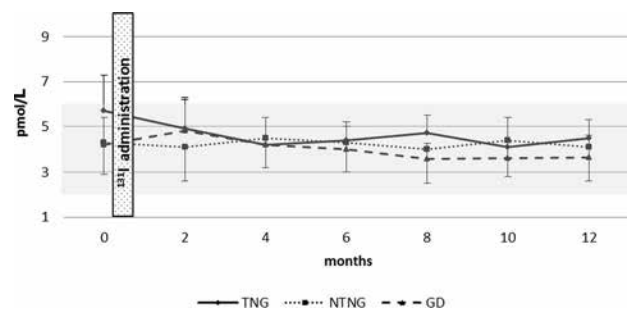
As in other scientific studies into the issue, our sample consisted of patients with thyroid goitres (toxic: in the case of TNG and GD, or non-toxic). Before the administration of  $^{131}\text{I}$ , the concentrations blood serum of calcium and iPTH in all our patients were within normal limits, as in studies conducted by other authors [4, 5, 13]. This makes it possible to conclude that hyperthyroidism usually does not affect the levels of calcium and iPTH in blood serum. Admittedly, it is an established fact that hyperthyroidism may lead to hypercalcaemia (in 20-30% of hyperthyroid patients), which consequently contributes to decreased serum levels of iPTH [14].

Apart from two papers, one by Ross and Nussbaum (1985) and the more recent one by Komorovsky and Raghavan, the literature does not offer any assessment



**Figure 4.** Variations of mean concentrations of  $fT_4$  in patients, from before radioiodine administration to 12 months post-dose. (The grey area indicates normal concentrations of  $fT_4$  in blood serum)

**Rycina 4.** Zachowanie się średnich stężeń hormonu  $fT_4$  u chorych w okresie od momentu przed podaniem radiojodu do 12 miesięcy po podaniu. (Obszar zaznaczony szarym kolorem pokazuje zakres norm stężenia  $fT_4$  w surowicy krwi)



**Figure 5.** Variations of mean concentrations of  $fT_3$  in patients, from before radioiodine administration to 12 months post-dose. (The grey area indicates normal concentrations of  $fT_3$  in blood serum)

**Rycina 5.** Zachowanie się średnich stężeń hormonu  $fT_3$  u chorych w okresie od momentu przed podaniem radiojodu do 12 miesięcy po podaniu. (Obszar zaznaczony szarym kolorem pokazuje zakres norm stężenia  $fT_3$  w surowicy krwi)

of the early effects of  $^{131}\text{I}$  radiation used for the treatment of benign thyroid diseases on parathyroid function [4, 5]. Similarly to Ross and Nussbaum, we observed an above normal rise in the levels of iPTH as soon as two months post-dose. Nevertheless, our further results and their interpretation are markedly different. Ross and Nussbaum associated increased iPTH levels with the drop in blood serum calcium caused by  $^{131}\text{I}$ -induced hypothyroidism, since thyroid hormones have resorptive properties and thus, by leading to high bone turnover, contribute to higher concentrations of serum calcium. They also found that exogenous thyroxine normalises the levels of thyroid hormones and TSH, which leads to a rise in calcium and a drop in iPTH. Therefore, the authors emphasise the impact of the thyroid hormones and iPTH on bone metabolism, and thus on the level of calcium in the body. Meanwhile, our study showed that elevated iPTH did not result from impaired hormonal

function of the thyroid gland, since in most patients treated with radioactive iodine (except several cases of GD patients where hormonal supplementation with thyroxine was necessary post-therapy), the thyroid glands functioned normally. Moreover, elevated iPTH levels were observed up to approximately the eighth month post-dose, to return to normal limits and remain within them until the end of the period covered by this study (five years post-dose), with regular thyroid function throughout the period. Interestingly, the serum concentrations of calcium were stable throughout the study, in spite of temporary increases in iPTH, even up to twice the upper normal limit. Similar stability was observed as far as the serum concentration of phosphates was concerned. This is probably because the elevated iPTH acted for too short a time, and also because other regulatory mechanisms of calcium homeostasis could have been involved [15]. The temporary increase in iPTH in all our patients can presumably be explained by post-radiation inflammation of the parathyroid glands, which, in the initial stage, caused excessive release of iPTH accumulated in the main parathyroid cells. In the next stage, such excessive release continues also as a result of the stimulation of the remaining, undestroyed, main cells, which are prompted to hypersecretion of iPTH [16]. We have also noticed that the higher the thyroid-absorbed dose of  $^{131}\text{I}$ , the greater the impact on the parathyroid glands, and the higher the secretion of iPTH due to parathyroid inflammation. Precise interdependence between iPTH concentration and absorbed dose has been described by means of a linear regression model. That is why, in our study, the rise in iPTH was the highest in toxic nodular goitre patients, who had received the largest absorbed dose, whereas in the case of NTNG and GD (where the absorbed doses were accordingly lower), the above normal increase in iPTH was smaller and the time needed for it to return to normal limits was shorter.

It should also be added that not taking into account the distribution of the absorbed radiation dose in thyroid on parathyroid function was a certain limitation of our study. This is due to the fact that a thorough evaluation of the relation between parathyroid function and distribution of the absorbed dose of  $^{131}\text{I}$  in the thyroid gland requires knowledge of the exact location of the parathyroid glands. It is widely known that pinpointing this exact location is very difficult, and in clinical practice turns out to be nearly impossible.

Komorovsky and Raghavan describe the case of a child suffering from GD who underwent radioiodine therapy and, at three months post-treatment, developed hypocalcaemia [4]. The authors' conclusions as regards the assessment of calcium concentrations in patients after  $^{131}\text{I}$  therapy aimed at establishing the

possibility of post-radiation hypoparathyroidism have not been confirmed by our data. Perhaps this is due to the difference between study samples. Our sample consisted of patients whose average age was  $45 \pm 10$ , while Komorovsky and Raghavan analysed the case of a child.

The majority of other researchers have only examined the possibility of delayed effects of ionising radiation of therapeutic  $^{131}\text{I}$  on the adjacent parathyroid glands. So any comparisons between those studies and ours are far more difficult and must, to a large extent, be based on assumptions. Our research was concluded after a five-year observation period of the hormonal function of parathyroid glands after radioiodine administration. Throughout that time, apart from elevated iPTH levels in the first months post-dose, no abnormalities were discovered in either the hormonal function of the parathyroid glands or the serum concentrations of ionised calcium. Notwithstanding the first ten months post-treatment, we can agree with the authors who have studied late effects of radiation (some of them describe patients at 35 years post-dose) that radioiodine therapy for benign thyroid disease does not affect the parathyroid function [6, 7, 17]. Mortensen et al. chose an interesting methodology to assess the secretory function of the parathyroid glands after radiation [7]. They emphasise that merely measuring iPTH serum levels is not sufficient for adequate assessment of the glands' function. Additional stimulation tests are necessary to examine the secretory reaction of the parathyroids to a pharmacologically achieved decrease in ionised calcium levels by using EDTA, which binds to calcium. Also these authors concluded that radioiodine radiation does not alter the parathyroid function.

It is also necessary to mention those authors who have conducted research among patients treated (up to over a decade prior to studies) for benign thyroid diseases with ionising radiation and found evidence for increased likelihood of parathyroid adenoma in those cases [13, 18, 19]. In addition, Colaco claims that the risk of parathyroid adenoma grows with age [8].

To sum up, one must bear in mind that in order to determine the cause of hyperparathyroidism, it is essential to consider whether a patient's past medical history includes radioiodine therapy. It seems that this thesis will be an important factor that aims at improving the diagnosis of hyperparathyroidism.

## Conclusions

- Radioactive iodine therapy for benign thyroid diseases contributes to temporary (up to ten months post-treatment) hyperparathyroidism.

- The resultant above normal iPTH levels in the blood serum of treated patients does not significantly affect the concentration of calcium and phosphates in the body.
- Above normal increase in serum iPTH has a positive correlation with thyroid absorbed dose of radioactive iodine.
- In the diagnostic process, radioiodine therapy should be taken into consideration as one of the potential causes of hyperparathyroidism.

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