Correlation of Thyroid Functions, Urinary Iodine Excretion, Tc99m Pertechnetate and I-131 Uptakes in the Patients with Multinodular Goiter After Mandatory Iodinization

Zorunlu İyodinasyon Sonrası Multinodüler Guatr Hastalarının Tiroid Fonksiyonları, İdrar İyot Düzeyleri, Tc99m Perteknetat Uptake'leri, I-131 Uptake'leri Arasındaki İlişki

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ABSTRACT

Objective: The aims of this study are first to evaluate the association between urine iodine levels and thyroid Tc99m pertechnetate uptake (TcPU) levels in multinodular goiter (MNG) patients, second to evaluate TcPU levels in euthyroid, subclinical and clinical hyperthyroid patient groups, and third to compare TcPU and I-131 uptake levels to decide whether TcPU can be use instead of I-131 uptake.

Material and Methods: Twenty-nine patients who were newly diagnosed multinodular goiter were included in the study. After taking blood and urine samples, TcPU tests and thyroid scintigraphies were done. By performing I-131 uptake measurements 4th and 24th hour uptake levels were calculated.

Results: Twenty-one patients (72%) had a urinary iodine level above 100 µg/g creatinine that indicates sufficient iodine intake. There was a significant negative correlation between TcPU levels and urine iodine levels. According to TSH levels, while 18 patients were euthyroid, 11 were hyperthyroid. The TcPU levels were found to be higher in hyperthyroid patients compared to the euthyroid ones, but this difference was not statistically significant. There was a significant positive correlation between the patients' TcPU and I-131 4th and 24th hour uptake values.

Conclusion: TcPU, which is a more practical method, can be used instead of I-131 uptake values. Our results suggest that it would be important to evaluate the relationship between urinary iodine and TcPU levels in larger series of MNG patients after mandatory iodinization.

Key Words: Tc99m pertechnetate, Thyroid function tests, Nodular goiter

ÖZ

Amaç: Çalışmada amaç, 1. multinodüler guatr hastalarında (MNG) idrar iyot düzeyleri ile tiroid Tc99m perteknetat uptake (TcPU) düzeyleri arasındaki ilişkiyi belirlemek, 2. ötiroid, klinik ve subklinik hipertiroidi hasta gruplarında TcPU düzeylerinin değerlendirmek, 3. TcPU ile I-131 uptake düzeylerini karşılaştırarak TcPU'in I-131 uptake yerine kullanılıp kullanılamayacağını belirlemektedir.

Gereç ve Yöntemler: Çalışmaya yeni tanı almış MNG olan 29 hasta dahil edildi. Hastalardan kan ve idrar örnekleri alındıktan sonra TcPU ve tiroid sintigrafisi yapıldı. I-131 uptake ölçümleri yapılarak 4. ve 24. saat uptake değerleri ölçüldü.

Bulgular: Yirmi bir hastanın (%72) idrar iyot düzeyi yeterli iyot alımını gösteren 100 µg/g kreatinin'den yüksek idi. TcPU düzeyleri ile idrar iyot düzeyleri arasında negatif korelasyon saptandı. TSH düzeylerine göre 18 hasta ötiroid, 11 hasta hipertiroid idi. TcPU düzeyleri hipertiroid hastalarda ötiroid olanlardan yüksekti fakat istatistiksel anlamlı değildi. TcPU düzeyleri ile I-131 4. saat ve 24. saat uptake'leri arasında pozitif korelasyon saptandı.

Sonuç: Daha pratik bir yöntem olan TcPU değerleri I-131 uptake yerine kullanılabilir. Zorunlu iyodinasyon sonrası MNG hastalarında idrar iyot düzeyleri ile TcPU düzeyleri arasındaki ilişki daha geniş hasta serilerinde değerlendirilmelidir.

Anahtar Sözcükler: Tc99m perteknetat, Tiroid fonksiyon testleri, Nodüler guatr

INTRODUCTION

Multinodular goiter (MNG) is a common disease in our country and all around the world with the incidence rate as high as 19-67% through thyroid ultrasound (1,2). Along with many factors leading to goiter, it is endemic in areas where iodine deficiency is most common. The best indicator of the presence of iodine deficiency among the community is urinary iodine clearance. An iodine amount of 100-200 µg/L detected in spot urine is considered to be a sign of adequate iodine intake (3).

Technetium 99m (Tc99m) pertechnetate and Iodine-131 (I-131) are widely used for thyroid scintigraphy and uptake measurement. Tc99m pertechnetate has some advantages because of its short half-life, and low thyroid gland and total body radiation dose due to the lack of ß radiation. Moreover, it is easily accessible and cheap. I-131 has the disadvantage of ß radiation and a long half-life. Studies have reported the comparison of I-131 and Tc99m pertechnetate uptake (TcPU) in the evaluation of thyroid function and that Tc99m pertechnetate can be used instead of I-131 (4-7).

The aims of this study was first to determine whether adequate iodine intake occurred by observing urinary iodine levels of MNG patients in a region where mild/moderate iodine deficiency existed before mandatory iodination (8) and to evaluate the associated urine iodine levels and TcPU levels in MNG patients, second to evaluate TcPU levels in euthyroid, hyperthyroid and subclinical hyperthyroid patient groups, and third by comparing TcPU and I-131 uptake levels to decide whether TcPU can be used instead of I-131.

MATERIALS and METHODS

Twenty-nine patients (23 women, 6 men) aged 24-74 years (mean 52.8 ± 11.2 years) who had been referred to the Endocrinology department of our hospital for goiter complaints were included in this study. Patients who were diagnosed as MNG by thyroid ultrasonography and had not been treated at least for three months were included. Blood and spot urine samples were taken for sT4/TSH measurements and urinary iodine levels respectively. Subsequently, TcPU, thyroid scintigraphy and I-131 uptake measurements and biological half-life estimation were performed. I-131 uptake calculation was performed 3-5 days after TcPU.

This study was approved by the Ethics Committee of the Akdeniz University School of Medicine. Written informed consents were obtained for all patients.

Technetium 99m Pertechnetate Thyroid Uptake

After injecting 5 mCi Tc99m pertechnetate into a 2 cc injector, injector full (EF) images were obtained for 2 seconds from a 9 cm height using a Toshiba GCA 602 gamma camera with parallel-hole collimator. After injection of the radioactive substance, injector blank (EB) images were obtained. The anterior thyroid images were taken from patients with the neck hyperextended at a position of 9 cm away from the gamma camera 20 minutes after injection. The images were taken in 2 frames as 100 Kcounts and 200 Kcounts in the 128x128 matrix. Uptake values were estimated for each of the images by using the "Thyroid Uptake" program. During computation, region of interest (ROI) illustrations for the background and thyroid gland were drawn. The thyroid uptake value was obtained by an automated program using the following formula:

Uptake=C/DX100

D=Attenuation-corrected radioisotope dose

C=Background-corrected thyroid gland count

Thyroid Scintigraphy

After obtaining thyroid uptake images from the patients, 200 Kcount or 10-minute thyroid scintigraphy images were obtained with pin-hole collimator 5 mm aperture.

Iodine-131 Thyroid Uptake

I-131 thyroid uptake measurements were obtained via the Atomlab 950 thyroid uptake counter. 20-30 µCi I-131 in liquid form added to water and was given to the patients. 60 second-counts were taken from the neck and right elbow (used as background) of the patients at the 4^{th} and 24^{th} hour, and 3^{rd} and 5^{th} days. Thyroid uptake values were then obtained using an automated program, and the biological half-life calculation was performed.

Statistical Analysis

The paired T-test was used for comparison of the TcPU and I-131 uptake values. "Independent samples t-test" and "Mann-Whitney U test" were used for other analyzes. Correlation and regression analysis were performed between 100 and 200 Kcount uptakes and between TcPU and I-131 uptake values. $p < 0.05$ was considered statistically significant.

RESULTS

According to the results of the thyroid function tests 18 patients were euthyroid, 6 patients were subclinical hyperthyroid and 5 patients were clinical hyperthyroid. No hypothyroid case was detected.

The mean TcPU values for all patients were 0.95 ± 0.52 (0.28-2.33) and 0.99 ± 0.53 (0.29-2.38) for 100 and 200 Kcount, respectively. There was a correlation between Tc100 and 200 Kcount uptake values as a result of the correlation analysis (r: 0.998, $p < 0.05$) and 100 Kcount uptake values were used for the statistical evaluation.

100 Kcount TcPU values and I-131 uptake values of the patients are summarized in Table I. The mean TcPU value of the patients with clinical hyperthyroidism was higher than euthyroid and subclinical hyperthyroid patients but this was not statistically significant (p>0.05). There was no significant difference between the 4th, 24th hour I-131 uptake values of the clinical and subclinical hyperthyroid patients and euthyroid patients (p>0.05).

There was a statistically significant positive correlation between the TcPU and 4th and 24th hour I-131 uptake values (r: 0.598, p<0.05 and r: 0.881, p<0.01) (Figure 1A,B). Correlation between TcPU and I-131 uptake values according to the regression analysis was formulated at a 95% confidence interval as follows:

I-131 4th hour uptake=(5.03xTcPU)+4.47

95% confidence interval; upper limit=(6.83xTcPU)+6.13

lower limit=(3.23xTcPU) +2.81

I-131 24th hour uptake=(13.11xTcPU)+6.43

95% confidence interval; upper limit=(16.81xTcPU)+9.83

lower limit=(9.71xTcPU) +3.03

When the thyroid scintigraphies of the patients were evaluated, hyperactive MNG (hyper-hypoactive in 16 patients, only hyperactive in 2 patients) was observed in 18 patients and hypoactive MNG was observed in 11 patients. Nine patients with hyperactive nodules were subclinical or clinical hyperthyroid. TcPU values were significantly higher in patients with hyperactive nodules compared to patients with hypoactive nodules (1.1 ± 0,6 and 0,3 ± 0,1) (p <0.05). Although I-131 uptake values were higher in patients with hyperactive nodules, this difference was not statistically significant (p> 0.05).

Urinary iodine values evaluated with both urinary iodine (microgram (µg)/L) and prorated creatinine iodine (µg/gcreatinine (cr)) were measured for patients. There was a correlation between these two values (r: 0.436, p <0.05) and iodine µg/g cr levels were used in the statistical evaluations. Urinary iodine levels in patients ranged from 24 to 266 µg/gcr (mean 150 ±72, median 130). It was observed that eight of 29 patients (28%) had urinary iodine lower than 100 µg/g cr, which was considered inadequate iodine intake.

TcPU values were significantly higher in patients with urinary iodine levels less than 100 µg/gcr than ones with that of greater than 100 µg/g cr (p <0.05). There was no statistically significant difference between I-131 uptake values and biological half-lives between the groups (Table II). There was also a statistically significant negative correlation observed between urinary iodine and TcPU values (r:-419, p <0.05) (Figure 2). There was no significant correlation between urinary iodine levels and I-131 uptake

Table I: TcPU values, 4th and 24th hour uptake values of I-131 and biological half-life for the euthyroid, clinical and subclinical hyperthyroid patient groups.

Thyroid functions	TcPU %		I-131 4th hour uptake %		I-131 24th hour uptake %		Biological half-life (day)
	Mean%	Range	Mean	Range	Mean	Range	
Euthyroid (n=18)	0.82±0.44	0,28-1.7	8.3±2.6	4.6-12.5	18.2±5.4	9.2-24.9	29±12 (n=16)
Subclinical hyperthyroid (n=6)	0.98±0.48	0.44-1.6	10.7±2.8	7.2-14.2	20.9±6.7	13-26.2	45±13 (n=4)
Clinical hyperthyroid (n=5)	1.37±0.73	0.61-2.3	11.7±4.7	6.4-17.6	21.8±7	13-28.5	18±12 (n=4)

TcPU: Tc99m pertechnetate uptake

Table II: TcPU and I-131 uptake values, biological half-life values in patients with urinary iodine levels less than 100 µg/g creatinine and higher than 100 µg/g creatinine.

Urinary iodine	TcPU %	I-131 4th hour uptake %	I-131 24th hour uptake %	Biological half-life (day)
≥100 µg/g creatinine n=21	0,8±0,5	9,5±4	19.7±7.4	29±14
<100 µg/g creatinine n=8	1,3±0,5	10±2.6	20.7±4.7	32±14
p	0.018*	0.274	0.525	0.739

TcPU: Tc99m pertechnetate uptake, ***:** p<0.05

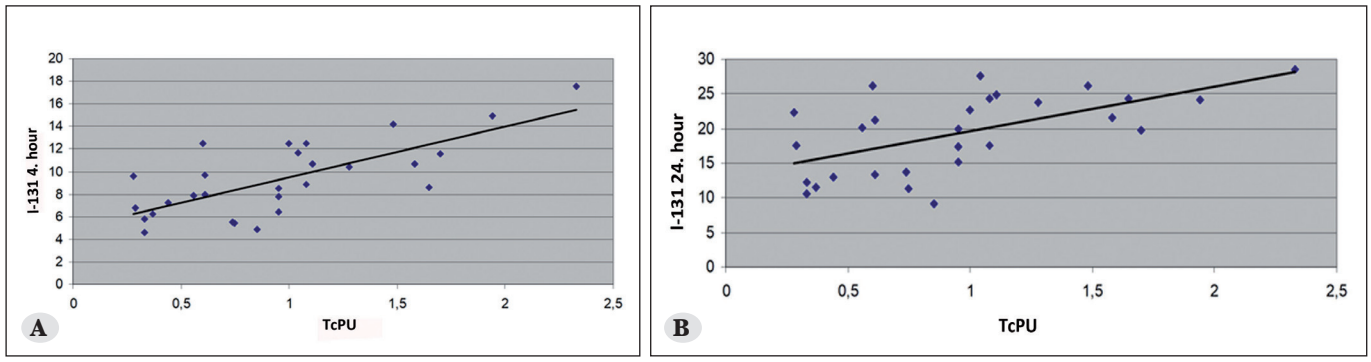

Figure 1: Positive correlation between TcPU and 4th hour **(A)**, 24thhour **(B)** hour I-131 uptake values (r: 0.598, p <0.05 and r: 0.881, p<0.01).

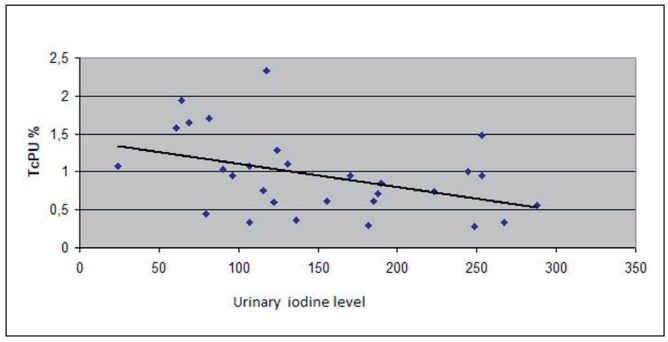

Figure 2: Negative correlation between TcPU and urinary iodine levels (r:-419, p<0.05).

values and biological half-lives. There was no statistically significant difference between euthyroid and clinical/subclinical hyperthyroid patients regarding urinary iodine levels (p> 0.05).

DISCUSSION

Apart from other factors in the development of goiter, the primary factor is the inadequacy of iodine intake. The best indicator of iodine deficiency is the decreased urinary iodine levels. In a study, the optimal median urinary iodine levels have been reported to be 100-199 µg /L as an indicator of optimal iodine intake in school children and adults (3). It was found in a study performed on 605 children aged 6-11 years in the same region as this study that goiter was detected at a rate of 35% through inspection and palpation and the median urinary iodine level was found to be 62.8 ± 21.8 and 64.9 ± 19.1 µg/gcr in the groups with and without goiter respectively (8). Median urinary iodine level in the MNG patients was 130 µg/g cr in this study which was performed about seven years after the beginning of mandatory iodinization. Urinary iodine levels were found to be more than 100 µg/gcr in 76% of the cases which indicated adequate iodine uptake. Despite the limited number of cases, this result can be regarded as a parameter indicating that iodine intake was not low after mandatory iodinization in this region.

Determination of the thyroid scintigraphic activity of the thyroid nodules is essential in the follow-up of patients. Active nodules observed during scintigraphy do not always indicate clinical hyperthyroidism. Restriction of the iodine salt and no use of thyroid hormone preparations in the monitoring of nodules may be sufficient for the treatment of such patients. In this study, 9 out of 18 patients who had a scintigraphically hyperactive nodule were euthyroid. This result suggests that thyroid scintigraphy is an important method for the follow-up and treatment of MNG patients.

Thyroid uptake studies performed with the use of radioactive iodine are widely used in the diagnosis of hyperthyroidism, distinguishing different causes of hyperthyroidism, determining the radioactive iodine treatment dose and detecting intrathyroidal iodine metabolism defects. While the uptakes in the early period (first 30 min) show mainly iodine capture function (trapping) of the thyroid, uptakes at the 2nd-6th hours show both trapping and organic binding properties. The 24th hour or later uptake values also give the secretion ratio of iodine from gland (9). Radioactive iodine uptake values are found to be increased in cases such as hyperthyroidism and iodine deficiency; on the contrary, these values are low in primary and secondary hypothyroidism and in many cases such as excessive iodine intake. Radioactive iodine uptake values in toxic MNG were normal or slightly elevated (10). In this study, there was no statistically significant difference between hyperthyroid and euthyroid patients regarding the I-131 uptake values.

Tc99m pertechnetate has been used for the dosimetric studies and scintigraphic evaluation of thyroid due to its advantages such as short half-life, lack of ß radiation, and short retention time in the thyroid gland (11-13). In this study, TcPU was calculated similarly to the method used by Ramos et al. (14). However, apart from this study, 5mCi Tc99m pertechnetate was used considering the radiation dose. To determine the effect of the count statistics, two separate images were taken as 100 and 200 Kcount. Because of the high correlation between these uptake values, 100

Kcount images using 5mCi Tc99m pertechnetate is enough to calculate TcPU.

Meller et al. used Tc99m pertechnetate uptake to determine the radioactive iodine dose in patients with toxic MNG and treatment success was achieved at a rate of 97% in patients with unifocal thyroid autonomy and 81% in those with multifocal/disseminated autonomy after the 18 months follow-up period (12). In a previous study for the standardization of TcPU values for the thyroid gland, Ramos et al. found TcPU ranged from 0.4% to 1.7% in 47 euthyroid volunteers (14). TcPU values were 0.28-1.7% (mean 0.82 ± 0.44) in euthyroid MNG patients in this study. In another study, the authors evaluated thyroid function by TcPU and they showed the correlation coefficient between the TcPU and the 24th hour I-131 uptakes of the euthyroid patients was 0.71(15). In this study, there was a significant correlation between the TcPU values and I-131 uptake values at both the 4^{th} (r=0.725) and the 24^{th} hour (r= 0.598). According to these results, I-131 uptake values can be obtained by calculating the TcPU which is a much more practical method. This estimation can be performed by the calculation of the lower and upper limits within the 95% confidence interval.

Various studies show the relationship between TcPU and urinary iodine levels. Kreisig et al. have shown a significant negative correlation between the TcPU and urinary iodine levels in the normal thyroid, goiter with euthyroidism and thyroid autonomy in an area of iodine deficiency (16). In another study, Reinhardt et al. showed a negative correlation between TcPU and urinary iodine levels in all cases including euthyroid, functional autonomy and Graves patients in a region where iodinization was provided. They also showed that TcPU is low in the patients with euthyroid goiter regardless of urinary iodine, whereas the uptake values are high in functional autonomy and Graves patients with urinary iodine level below 50-100 iodine/gcr. However, when urinary iodine levels were between 100-500 iodine/g cr, they did not observe any significant change (17). In this study, urinary iodine values were negatively correlated with TcPU in all patients. A significant correlation was also observed in euthyroid patients but there was no correlation in the hyperthyroid patients. TcPU values were significantly higher in patients with urinary iodine levels less than 100 µg/g cr compared to those with values greater than 100 µg/g cr.

The major limitation of the present study was the small number of the cases. Due to incomplete data, we could only evaluate the association between thyroid uptake values and thyroid function tests and urinary iodine levels in twenty-nine patients.

In conclusion, median urinary iodine levels are sufficient in MNG patients after mandatory iodinization. There was a significant negative correlation between urinary iodine levels and TcPU in accordance with the literature. It has been shown that TcPU, which is a more practical method, can be used instead of I-131 uptake values. Studies including a larger number of patients are needed to evaluate the relationship between urinary iodine, TcPU and I-131 uptakes in different patient series.

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