Endocrine (2019) 64:293–298
https://doi.org/10.1007/s12020-018-1807-x

ORIGINAL ARTICLE

Long-term outcomes of renal function after radioactive iodine therapy for thyroid cancer according to preparation method: thyroid hormone withdrawal vs. recombinant human thyrotropin

Yoon Young Cho[1,2,3] · Soo Kyoung Kim[1,2] · Jung Hwa Jung[1,2] · Jong Ryeal Hahm[1,2] · Tae Hyuk Kim[4] · Jae Hoon Chung[4] · Sun Wook Kim[4]

Received: 30 July 2018 / Accepted: 29 October 2018 / Published online: 23 November 2018

Abstract

Purpose Long-term effects of iatrogenic hypothyroidism on renal function from thyroid hormone withdrawal during radioactive iodine therapy (RAIT) have not been studied, especially in subjects with mildly impaired renal function. We compared renal function in thyroid cancer subjects according to preparation method of either thyroid hormone withdrawal (THW) or injection of recombinant human thyrotropin (rhTSH).

Methods This retrospective study enrolled 241 thyroidectomized patients (rhTSH group, $n = 87$ and THW group, $n = 154$). Changes in glomerular filtration rate (GFR) were measured prior to surgery, at the time of RAIT, and during a regular follow-up at least one year after RAIT.

Results Baseline renal function was comparable between the rhTSH group and the THW group (91.4 mL/min/1.73 m^2 vs. 92.4 mL/min/1.73 m^2). At the time of RAIT, GFR was significantly decreased in the THW group (70.6 mL/min/1.73 m^2, −23.6%), whereas renal function was preserved in the rhTSH group (85.4 mL/min/1.73 m^2, −6.6%). In the THW group, renal function was fully recovered within 6 months after RAIT and was maintained up to 24 months, even in subjects with baseline GFR less than 90 mL/min/1.73 m^2.

Conclusions THW for RAIT preparation induced considerable reduction in renal function, but this change was transient. In contrast, injection of rhTSH did not decrease renal function, making it a good option for RAIT preparation for subjects with renal dysfunction.

Keywords Renal function · Radioactive iodine therapy · Thyroid hormone withdrawal · Recombinant human thyrotropin

Introduction

Radioactive iodine therapy (RAIT) is a widely used treatment for differentiated thyroid carcinoma after total or near-total thyroidectomy. The rate of RAIT approaches 50% in thyroid cancer patients [1, 2]. To prepare for RAIT, thyroid hormone withdrawal (THW) or injection of recombinant human thyrotropin (rhTSH) is used to increase serum TSH. As a traditional method, THW induces transient hypothyroidism and stimulates endogenous TSH secretion. Elevated level of TSH promotes radioactive iodine (RAI) uptake in thyroid remnant tissue and metastatic disease. Injection of rhTSH also stimulates RAI uptake with a similar efficacy to THW but has the advantage of avoiding the various changes caused by hypothyroidism during THW [3].

A hypothyroid state causes metabolic effects on every organ system. Decreased hemodynamics in the circulatory

✉ Sun Wook Kim
swkimmd@skku.edu

1 Division of Endocrinology and Metabolism, Department of Medicine, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju, Korea

2 Institute of Health Sciences, Gyeongsang National University School of Medicine, Jinju, Korea

3 Sungkyunkwan University, Graduate School of Medicine, Seoul, Korea

4 Division of Endocrinology and Metabolism, Department of Medicine, Thyroid Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

system influence renal function, especially glomerular filtration rate (GFR). Physiologic changes of water and electrolyte imbalance, reduced renal blood flow, renal plasma flow, and single-nephron GFR resulting in decreased GFR have been reported in severe hypothyroidism [4, 5]. Impaired GFR and increased creatinine (Cr) levels are reversible with thyroid hormone replacement in uncomplicated hypothyroidism [6, 7].

Recent studies have reported similar changes in renal function during THW preparation for RAIT as those observed in chronic hypothyroidism. Coura-Filho et al. found an 18–22% decrease in GFR using a ^{51}Cr-EDTA radioisotope assay in 14 patients prepared by THW and preservation of GFR in 14 patients treated with rhTSH [8]. Duranton et al. reported a reversible impairment of GFR in iatrogenic hypothyroidism ($n = 21$), whereas renal function was enhanced in euthyroid patients injected with rhTSH ($n = 20$) [9]. These two prospective studies had limitations of a small number of participants and a limited follow-up period (less than three months) for renal function.

Thus, we investigated the acute and long-term effects of transient hypothyroidism during THW preparation for RAIT on renal function and compared them with those of euthyroid patients by rhTSH preparation. We aimed to demonstrate the reversibility of renal function especially in subjects with decreased GFR.

Materials and methods

Subjects

This retrospective study included patients undergoing RAIT after thyroid surgery for thyroid cancer at Samsung Medical Center between July 2011 and August 2014. Exclusion criteria were as follows: younger than 18 years, multiple RAITs within less than one year, follow-up duration less than one year, a history of using contrast media during the study period, known renal disease, known distant metastasis, hypothyroid state before RAIT, or insufficient laboratory data. We enrolled 241 individuals composed of 154 subjects prepared by THW and 87 subjects prepared by rhTSH injection. All patients were followed longer than two years, and the mean ± SD duration was 3.1 ± 1.0 years. Gender, age, height, weight, systolic and diastolic blood pressures, heart rate, presence of hypertension or diabetes, pathology and stage of thyroid cancer, tumor size, and baseline and follow-up data of GFR were reviewed using medical records. Among 241 subjects, 23 individuals (10%) had hypertension and 12 (5%) had diabetes. Most of them were treated for hypertension or diabetes at outside hospitals. Four patients with hypertension were prescribed with angiotensin II receptor blocker (ARB) at our hospital and they had been taking stable doses of ARBs more than one year before RAIT. We also checked the use of pain killers such as NSAIDs or herbal medication, and subjects denied the use of the drugs. This research was approved by the Institutional Review Board of Samsung Medical Center.

RAIT preparation methods

THW was performed as per the following protocol in our institution: four weeks before the date of RAIT, subjects discontinued levothyroxine (LT4) and switched to liothyronine (LT3) for two weeks, followed by withdrawal of LT3 for an additional two weeks. The rhTSH group continued LT4 medication and visited our institution two consecutive days before RAI administration to receive rhTSH intramuscularly at a dose of 1.1 mg per day. All patients were instructed to start a low-iodine diet for one week before the date of RAIT. All subjects stopped any iodine-containing drugs (i.e., lithium, amiodarone). A structured program for the low-iodine diet was delivered by trained nurses and dieticians for all individuals preparing for RAIT.

On the day of RAIT, subjects were asked to collect the first urine in the morning for measuring urine iodine concentration. Blood sampling was also performed for measurement of common blood counts (CBC) and blood chemistry including renal function, thyroid function, and thyroglobulin (Tg) level.

Measurement of GFR

Blood samples were drawn for a renal function test in the preoperative period (before RAIT) for baseline, at the time of RAIT, and at 6-month intervals during the first year after RAIT, followed by yearly check-up. GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as follows: $\mathrm{GFR} = 141 \times \mathrm{minimum}\ (\mathrm{creatinine}/\kappa,\ 1)^{\alpha} \times \mathrm{maximum}\ (\mathrm{creatinine}/\kappa,\ 1)^{-1.209} \times 0.993^{\mathrm{age}} \times 1.018$ (if, female), where κ is 0.7 for women and 0.9 for men, and α is −0.329 for women, and −0.411 for men [10].

Statistics

Statistical analyses were performed using SPSS Statistics 18 (SPSS Inc., Chicago, IL, USA). Descriptive statistics (mean, SD, median, interquartile ranges) were tabulated for baseline characteristics and renal function test results during follow-up measurements. We performed the Mann–Whitney *U*-test to compare nonparametric variables, such as renal function, between the two groups categorized by preparation method for RAIT. For parametric measures, the independent *t*-test was used. We regarded p-value < 0.05 as significant.

Results

Baseline characteristics of two groups with rhTSH ($n = 87$) or THW ($n = 154$) are presented in Table 1. All parameters were comparable between the two groups, except age ($p = 0.04$) and thyroid function during RAIT ($p < 0.001$). The median and interquartile ranges of GFR at baseline were 91.4 (81.6, 106.1) mL/min/1.73 m^2 in the rhTSH group and 92.4 (84.1, 104.0) mL/min/1.73 m^2 in the THW group. Variables for cancer pathology, tumor size, and cancer stage showed no difference in the two groups.

Table 1 Baseline demographics in groups according to rhTSH and THW

Parameter	rhTSH ($n = 87$)	THW ($n = 154$)	p-value
Gender, female	63 (72)	107 (69)	0.63
Age (years)	48 ± 13	45 ± 12	**0.04**
Height (cm)	163 ± 8	163 ± 9	0.89
Weight (kg)	63 ± 13	63 ± 12	0.83
Systolic BP (mmHg)	121 ± 14	119 ± 13	0.19
Diastolic BP (mmHg)	75 ± 12	74 ± 11	0.44
Heart rate (bmp)	78 ± 12	78 ± 13	0.67
Hypertension	10 (11)	13 (8)	0.45
Diabetes	5 (6)	7 (4)	0.69
Baseline GFR (mL/min/1.73 m^2)	91.4 (81.6, 106.1)	92.4 (84.1, 104.0)	0.45
Range	54.2–142.1	49.5–146.9	
Thyroid function at RAIT			
TSH (mIU/L)	41.5 (26.1, 55.3)	85.8 (65.0, 112.2)	**<0.001**
Free T4 (ng/dL)	1.87 (1.63, 2.10)	0.07 (0.04, 0.10)	**<0.001**
T3 (ng/dL)	98 (77, 114)	38 (25, 53)	**<0.001**
Pathology			0.86
Papillary	85 (98)	151 (98)	
Follicular	1 (1)	1 (1)	
Poorly differentiated	1 (1)	2 (1)	
Tumor size (cm)	1.3 ± 1.0	1.4 ± 1.1	0.53
AJCC stage			0.10
I or II	38 (44)	83 (54)	
III or IV	49 (56)	71 (46)	

rhTSH recombinant human TSH, *THW* thyroid hormone withdrawal, *BP* blood pressure, *GFR* glomerular filtration rate, *RAIT* radioactive iodine therapy, *TSH* thyrotropin, *free T4* free thyroxine, *T3* triiodothyronine, *AJCC* American Joint Committee on Cancer, *SD* standard deviation, *IQR* interquartile range

Variables are presented as number (percentage), mean ± SD, median (IQR), or range

Changes in renal function at the time of RAIT and during follow-up measurements are shown in Table 2. In the rhTSH group, GFR was not significantly changed around RAIT, with a 6.6% GFR decrease during RAIT preparation. In the THW group, GFR was reduced at the time of RAIT, with a 23.6% change from baseline ($p < 0.001$). Renal impairment was recovered within 6 months after RAIT, and the median time to recovery was 160 days in the THW group.

Renal function in subjects with mildly decreased GFR (less than 90 mL/min/1.73 m^2) was analyzed according to RAIT preparation method (Table 3). The median GFR before RAIT was similar in the two groups (81.1 mL/min/1.73 m^2 vs. 81.8 mL/min/1.73 m^2). All patients showed a GFR between 60 and 89 mL/min/1.73 m^2 at baseline except two subjects with a GFR of 49.5 (in the THW group) and 54.2 (in the rhTSH group) mL/min/1.73 m^2. During RAIT, GFR was decreased in the THW group (−20.3%), whereas renal function was preserved in the rhTSH group (−3.6%) compared to baseline. Renal function returned to baseline within 6 months after RAIT, and the recovery was maintained at the last follow-up (up to 24 months).

Discussion

We found a 24% decrease in GFR in the THW group at the time of RAIT. However, renal function was restored within 6 months, and the recovery persisted up to 24 months in this study. No patient suffered from renal dysfunction, even those with a mild decrease in baseline GFR (less than 90 ml/min/1.73 m^2). The rhTSH group showed a 7% decrease in GFR at the time of RAIT ($p > 0.05$) and preserved renal function at baseline GFR in the long-term follow-up.

The underlying mechanism of GFR impairment has not been fully explained in hypothyroid subjects. Montenegro et al. reported a decreased GFR in 41 patients with primary

Table 2 Comparison of renal function before and after radioactive iodine therapy according to rhTSH and THW

GFR (mL/min/1.73 m^2)	rhTSH ($n = 87$)	THW ($n = 154$)	p-value
Before RAIT	91.4 (81.6, 106.1)	92.4 (84.1, 104.0)	0.45
At RAIT	85.4 (77.9, 97.1)	70.6 (65.1, 79.3)	**<0.001**
<6 months after RAIT	90.9 (81.6, 105.2)	91.6 (82.2, 104.7)	0.79
6–12 months after RAIT	87.4 (76.6, 99.2)	87.3 (78.9, 99.9)	0.65
12–24 months after RAIT	90.0 (76.2, 103.4)	88.6 (80.5, 99.4)	0.82
Percentage change before and at the time of RAIT	−6.6 (−12.7, +3.5)	−23.6 (−28.5, −17.1)	**<0.001**

rhTSH recombinant human TSH, *THW* thyroid hormone withdrawal, *GFR* glomerular filtration rate, *RAIT* radioactive iodine therapy

Values are presented as median (interquartile range)

Table 3 Comparison of renal function before and after radioactive iodine therapy according to rhTSH and THW in subjects with baseline GRF less than 90 mL/min/1.73 m^2

GFR (mL/min/1.73 m^2)	rhTSH ($n = 41$)	THW ($n = 63$)	p-value
Before RAIT	81.1 (75.2, 84.6)	81.8 (75.0, 86.5)	0.45
At RAIT	78.2 (70.3, 83.8)	65.2 (57.6, 68.9)	**<0.001**
<6 months after RAIT	80.4 (72.0, 88.7)	81.8 (75.2, 89.3)	0.79
6–12 months after RAIT	79.8 (72.2, 87.6)	78.9 (73.3, 87.1)	0.65
12–24 months after RAIT	76.2 (68.5, 87.0)	79.9 (72.9, 85.2)	0.82
Percentage change before and at the time of RAIT	−3.6 (−8.8, +5.9)	−20.3 (−25.6, −13.4)	**<0.001**

rhTSH recombinant human TSH, *THW* thyroid hormone withdrawal, *GFR* glomerular filtration rate, *RAIT* radioactive iodine therapy

Values are presented as median (interquartile range)

hypothyroidism, and half of patients showed increased serum creatinine level; these changes were recovered after thyroid hormone supplement [11]. Hataya et al. demonstrated an improvement in GFR even in chronic kidney disease (CKD) patients with GFR 30–60 mL/min/1.73 m^2 within a six-month treatment period for primary hypothyroidism [12]. Restoring renal function with thyroid hormone replacement indicates that renal dysfunction is caused by transient functional changes rather than permanent pathologic damages [13]. Hypothyroidism leads to changes in metabolic rate set, including decreased cardiac output and circulating blood volume with impaired renin-angiotensin-aldosterone activities, resulting in decreased renal perfusion, which are generally accepted mechanisms elucidating renal dysfunction in hypothyroidism [4, 5]. Some authors have suggested a relationship between hypothyroidism and endothelial dysfunction, as hypothyroidism causes low concentrations of insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF), which can be normalized by thyroid hormone replacement [14]. Although not widely accepted, some authors have reported relevance between hypothyroidism and renal tubular damage [15, 16].

Iatrogenic hypothyroidism while preparing for RAIT in thyroidectomized subjects also deteriorates renal function transiently, whereas the use of rhTSH helps to maintain renal function. Coura-Filho et al. observed changes in mean GFR from 94 mL/min/1.73 m^2 to 76 mL/min/1.73 m^2 after THW ($n = 14$, $p = 0.009$) and from 91 mL/min/1.73 m^2 to 93 mL/min/1.73 m^2 after rhTSH ($n = 14$, $p = 0.613$) in a prospective study [8]. The decrease in GFR was 18.5% with ^{51}Cr-EDTA (mL/min/1.73 m^2) and 22.5% with modified MDRD (mL/min) in the THW group, with a modest positive correlation between the two methods. Their study had the advantage of measuring GFR by ^{51}Cr-EDTA, which is considered the gold standard for GFR measurement rather than creatinine-based equations. However, they followed up GFR only until the day of a whole body image scan (one week after RAIT); thus, a longer duration for complete recovery of renal function was not described. We presented a comparable decline in GFR of 23.6% after THW using the creatinine-based CKD-EPI equation (from 92 mL/min/1.73 m^2 to 71 mL/min/1.73 m^2). Among numerous equations, the CKD-EPI equation has become the most accurate GFR estimating equation validated in various populations [17, 18]. Although we did not use a direct method of GFR measurement, the CKD-EPI equation is the most widely used equation in clinical practice. In addition, we presented GFR changes for at least two years in all subjects and documented the long-term safety of RAIT preparation for renal function.

In our study, no patient progressed to CKD, defined as a GFR less than 60 mL/min/1.73 m^2 for at least three months [19]. At baseline, two-fifths (43%) of our population showed mildly decreased GFR (60−90 mL/min/1.73 m^2), including two subjects with GFR less than 60 mL/min/1.73 m^2 (GFR 49.5 and 54.2 mL/min/1.73 m^2). The decrease in GFR was from 82 mL/min/1.73 m^2 to 65 mL/min/1.73 m^2 after THW. In CKD patients, GFR less than 60 mL/min/1.73 m^2 is related to major adverse outcomes, such as impaired renal function, progression to kidney failure, and cardiovascular mortality [19]. Moreover, both decreasing and increasing GFR changes are associated with risk of all-cause mortality in a community-based longitudinal cohort study [20]; thus, fluctuations in GFR during repeated RAIT preparation with THW might have potential hazard on renal function, although we did not address this issue. Renal dysfunction was transient, and all patients were fully recovered; however, clinicians need to be cautious in preparing for RAIT with THW, especially in patients with GFR near 60 mL/min/1.73 m^2, considering the substantial decrease in GFR.

Prior studies reported slightly increased GFR of 4% using rhTSH [8, 9], but a 7% decrease was observed in our data. Some authors suggest that rhTSH may enhance renal function [9]. Although the mechanism of the increase in GFR after rhTSH has not been elucidated, various measurement methods of GFR and studied populations may contribute to non-significant changes in renal function. We cautiously assumed that a low-iodine diet might be one of the reasons for transient decline in GFR in subjects

preparing for RAIT, based on a preclinical study showing that iodine deficiency can change the protein expression of rat kidney, leading to renal damage [21].

This study has some limitations. First, due to the retrospective design of our study, some detailed clinical information was not available. For example, we cannot obtain information regarding medications in subjects with hypertension or diabetes who were treated at outside hospitals. We had two patients with a baseline GFR less than 60 mL/min/1.73 m^2. They had no history of hypertension, diabetes, or renal disease, however preoperative evaluation for renal disease have not been conducted; thus, the exact cause of a decrease in renal function did not be assessed. Second, we did not investigate the underlying pathophysiological mechanisms for renal dysfunction during iatrogenic hypothyroidism, although which is beyond the scope of our study and generalized hypodynamic status of the circulatory system is widely accepted as mechanisms of renal effects in hypothyroidism.

In conclusion, we found a significant reduction in renal function in the THW group at the time of RAIT, whereas renal function was preserved in the rhTSH group. Although GFR in the THW group showed full recovery within several months, patients with GFR around 60 mL/min/1.73 m^2 might benefit from rhTSH considering the deterioration of renal function during THW for RAIT preparation.

Funding This study was supported by a grant from the Institute of Health Sciences [#IHS GNU-2017-04].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The study was approved by the institutional research committee but informed consent was not mandatory due to our retrospective design.

References

1. N.G. Iyer, L.G. Morris, R.M. Tuttle, A.R. Shaha, I. Ganly, Rising incidence of second cancers in patients with low-risk (T1N0) thyroid cancer who receive radioactive iodine therapy. Cancer **117**, 4439–4446 (2011). https://doi.org/10.1002/cncr.26070
2. Y.Y. Cho, J. Lim, C.M. Oh, J. Ryu, K.W. Jung, J.H. Chung, Y.J. Won, S.W. Kim, Elevated risks of subsequent primary malignancies in patients with thyroid cancer: a nationwide, population-based study in Korea. Cancer **121**, 259–268 (2015). https://doi.org/10.1002/cncr.29025
3. U. Mallick, C. Harmer, B. Yap, J. Wadsley, S. Clarke, L. Moss, A. Nicol, P.M. Clark, K. Farnell, R. McCready, J. Smellie, J.A. Franklyn, R. John, C.M. Nutting, K. Newbold, C. Lemon, G. Gerrard, A. Abdel-Hamid, J. Hardman, E. Macias, T. Roques, S. Whitaker, R. Vijayan, P. Alvarez, S. Beare, S. Forsyth, L. Kadalayil, A. Hackshaw, Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. N. Engl. J. Med. **366**, 1674–1685 (2012). https://doi.org/10.1056/NEJMoa1109589
4. C. Villabona, M. Sahun, M. Roca, J. Mora, N. Gomez, J.M. Gomez, R. Puchal, J. Soler, Blood volumes and renal function in overt and subclinical primary hypothyroidism. Am. J. Med. Sci. **318**, 277–280 (1999)
5. S.E. Bradley, J.B. Coelho, J.E. Sealey, K.D. Edwards, F. Stephan, Changes in glomerulotubular dimensions, single nephron glomerular filtration rates and the renin-angiotensin system in hypothyroid rats. Life. Sci. **30**, 633–639 (1982)
6. S.H. Kreisman, J.V. Hennessey, Consistent reversible elevations of serum creatinine levels in severe hypothyroidism. Arch. Intern. Med. **159**, 79–82 (1999)
7. J.G. den Hollander, R.W. Wulkan, M.J. Mantel, A. Berghout, Correlation between severity of thyroid dysfunction and renal function. Clin. Endocrinol. (Oxf.). **62**, 423–427 (2005). https://doi.org/10.1111/j.1365-2265.2005.02236.x
8. G.B. Coura-Filho, J. Willegaignon, C.A. Buchpiguel, M.T. Sapienza, Effects of thyroid hormone withdrawal and recombinant human thyrotropin on glomerular filtration rate during radioiodine therapy for well-differentiated thyroid cancer. Thyroid **25**, 1291–1296 (2015). https://doi.org/10.1089/thy.2015.0173
9. F. Duranton, A. Lacoste, P. Faurous, E. Deshayes, J. Ribstein, A. Avignon, G. Mourad, A. Argiles, Exogenous thyrotropin improves renal function in euthyroid patients, while serum creatinine levels are increased in hypothyroidism. Clin. Kidney J. **6**, 478–483 (2013). https://doi.org/10.1093/ckj/sft092
10. A.S. Levey, L.A. Stevens, C.H. Schmid, Y.L. Zhang, A.F. Castro 3rd, H.I. Feldman, J.W. Kusek, P. Eggers, F. Van Lente, T. Greene, J. Coresh, A new equation to estimate glomerular filtration rate. Ann. Intern. Med. **150**, 604–612 (2009)
11. J. Montenegro, O. Gonzalez, R. Saracho, R. Aguirre, O. Gonzalez, I. Martinez, Changes in renal function in primary hypothyroidism. Am. J. Kidney Dis. **27**, 195–198 (1996)
12. Y. Hataya, S. Igarashi, T. Yamashita, Y. Komatsu, Thyroid hormone replacement therapy for primary hypothyroidism leads to significant improvement of renal function in chronic kidney disease patients. Clin. Exp. Nephrol. **17**, 525–531 (2013). https://doi.org/10.1007/s10157-012-0727-y
13. G. Capasso, G. De Tommaso, A. Pica, P. Anastasio, J. Capasso, R. Kinne, N.G. De Santo, Effects of thyroid hormones on heart and kidney functions. Miner. Electrolyte Metab. **25**, 56–64 (1999). https://doi.org/10.1159/000057421
14. C. Schmid, M. Brandle, C. Zwimpfer, J. Zapf, P. Wiesli, Effect of thyroxine replacement on creatinine, insulin-like growth factor 1, acid-labile subunit, and vascular endothelial growth factor. Clin. Chem. **50**, 228–231 (2004). https://doi.org/10.1373/clinchem.2003.021022
15. E. Algun, C. Topal, M. Ozturk, M.R. Sekeroglu, A. Durmus, Urinary beta-2 microglobulin in renal dysfunction associated with hypothyroidism. Int. J. Clin. Pract. **58**, 240–243 (2004)
16. G. Karanikas, M. Schutz, M. Szabo, A. Becherer, K. Wiesner, R. Dudczak, K. Kletter, Isotopic renal function studies in severe hypothyroidism and after thyroid hormone replacement therapy. Am. J. Nephrol. **24**, 41–45 (2004). https://doi.org/10.1159/000075628
17. M.P. Cristelli, F. Cofan, N. Rico, J.C. Trullas, C. Manzardo, F. Aguero, J.L. Bedini, A. Moreno, F. Oppenheimer, J.M. Miro, Estimation of renal function by CKD-EPI versus MDRD in a cohort

of HIV-infected patients: a cross-sectional analysis. BMC Nephrol. **18**, 58 (2017). https://doi.org/10.1186/s12882-017-0470-4

18. R.J. MacIsaac, E.I. Ekinci, E. Premaratne, Z.X. Lu, J.M. Seah, Y. Li, R. Boston, G.M. Ward, G. Jerums, The Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation does not improve the underestimation of Glomerular Filtration Rate (GFR) in people with diabetes and preserved renal function. BMC Nephrol. **16**, 198 (2015). https://doi.org/10.1186/s12882-015-0196-0
19. L.A. Stevens, J. Coresh, T. Greene, A.S. Levey, Assessing kidney function—measured and estimated glomerular filtration rate. N. Engl. J. Med. **354**, 2473–2483 (2006). https://doi.org/10.1056/NEJMra054415
20. T.C. Turin, J. Coresh, M. Tonelli, P.E. Stevens, P.E. de Jong, C.K. Farmer, K. Matsushita, B.R. Hemmelgarn, Change in the estimated glomerular filtration rate over time and risk of all-cause mortality. Kidney Int. **83**, 684–691 (2013). https://doi.org/10.1038/ki.2012.443
21. Y.H. Dai, J. Zhang, C.J. Liu, H. Fang, [Expression of AP-1 and TGF-beta1 in kidney of iodine deficient rats and its significance]. Xi. Bao. Yu. Fen. Zi. Mian. Yi. Xue. Za. Zhi. **25**, 813–815 (2009)