Annals of Thyroid Research

Open Access

Austin Publishing Group

Research Article

The Effect of Thyroid Dysfunction on Plasma Creatinine Levels

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Received: November 04, 2016; **Accepted:** November 30, 2016; **Published:** December 02, 2016

Abstract

Introduction: There are conflicting reports on how kidney function is affected in patients with thyroid dysfunction. This study was designed to investigate how hypothyroidism and hyperthyroidism affect the concentration of plasma creatinine in a large patient material.

Methods: Patient results with simultaneous determinations of FT4, FT3, TSH and creatinine were extracted from the laboratory information system. Over an eight year period this yielded more than thousand cases with results from thyroid function tests combined with plasma creatinine concentrations.

Results: Median plasma levels of creatinine differed significantly in hypothyroid and hyperthyroid patients as compared to euthyroid controls. An approximate 20% increase and decrease in median plasma creatinine concentration was found for hypothyroid and hyperthyroid patients, respectively. The differences were statistically significant ($p<0.001$) for both groups and still so when divided according to gender. A correlation analysis showed a significant negative correlation between the biologically active freeT3 and creatinine.

Conclusion: Thyroid hormone correlates significantly to plasma creatinine. It is important to be aware of the relationship between thyroid function and kidney function when interpreting plasma creatinine results and to consider hypothyroidism or hyperthyroidism as a possible cause of an abnormal plasma creatinine level.

Further research is needed in order to uncover the mechanisms behind the relationship between renal function biomarkers and thyroid dysfunction.

Keywords: Thyroid dysfunction; Hypothyroidism; Hyperthyroidism; Euthyroidism; Plasma levels; Creatinine

Abbreviations

EDTA: Ethylenediaminetetraacetic Acid; FT4: Free Thyroxine; FT3: Free Triiodothyronine; GFR: Glomerular Filtration Rate; TRH: Thyrotropin-Releasing Hormone; TSH: Thyroid-Stimulating Hormone

Introduction

There are several aspects of the relationship between the thyroid gland and the kidneys. Thyroid hormones are known to be involved in the development and function of the kidneys and, conversely, kidney function can affect the concentration and metabolism of thyroid hormones [1,2].

The two thyroid hormones Thyroxine (T4) and Triiodothyronine (T3) are produced in the thyroid gland. Production is regulated by Thyrotropin-Releasing Hormone (TRH) from the hypothalamus that activates Thyroid-Stimulating Hormone (TSH) production in the pituitary gland. TSH acts on the thyroid gland where it stimulates secretion of both the prohormone T4 and the biologically active T3. These iodine containing hormones are primarily responsible for regulation of metabolism.

Thyroid hormone deficiency, hypothyroidism, is divided into primary hypothyroidism and central (secondary) hypothyroidism. The most common form, primary hypothyroidism (95%), is mainly caused by either iodine deficiency (globally) or by autoimmune thyroiditis – Hashimoto's thyroiditis. Other causes include congenital thyroid dysgenesis, thyroidectomy, radioiodine treatment and regional radiotherapy. Central hypothyroidism is the result of insufficient secretion of TRH or TSH, which can be caused by tumors (e.g. pituitary adenoma, craniopharyngioma or meningioma), pituitary surgery, radiation, trauma, and infection or ischemic disorders [3].

Hyperthyroidism, which is excessive production of thyroid hormones, is also referred to as thyrotoxicosis. Causes include Grave's disease (60–70%), nodular goiter (multinodulartoxic goiter and toxic adenoma, 30–40%), inflammation of the thyroid, excessive iodine or thyroid hormone intake, and pituitary adenoma [3].

Glomerular Filtration Rate (GFR) is a measure of kidney function and can be determined in different ways. More precisely by measuring plasma clearance of exogenous substances such as 51Cr-EDTA or Iohexol, or by means of endogenous substances like creatinine or cystatin C. The plasma concentration of creatinine is the most common marker used to estimate GFR (eGFR). Creatinine, produced in muscle cells, is eliminated through glomerular filtration.

Citation: Englund FI, Berggren K, Usener B, Broberg H, Larsson A and Brattsand G. The Effect of Thyroid Dysfunction on Plasma Creatinine Levels. Annals Thyroid Res. 2016; 2(2): 82-86.

Table 1: Reference intervals for the laboratory analyses used in the study.

	P-Triiodothyronine (T3)	P-Thyroxine (T4)	P-Thyroid-stimulating hormone (TSH)	P-Creatinine
Reference range	3.3 – 6.0 pmol/L	10.0 – 22.0 pmol/L	0.4 – 4.0 mIU/L	50 – 90 µmol/L (females) 60 – 100 µmol/L (males)

However, when kidney function decline, tubular secretion influence the clearance rate of creatinine. The level of creatinine in blood is also individually affected by muscle mass, diet and various drugs [4].

Dysfunctionality of the thyroid can affect renal structure and blood flow, glomerular filtration rate and tubular transport, as well as water and electrolyte balance [1,2]. Explanations to this may involve changes in cardiac output and peripheral vascular resistance by thyroid hormones. In hypothyroidism, cardiac output is reduced due to lack of inotropic and chronotropic effect of thyroid hormones. A decrease in cardiac output and increased vascular resistance would diminish renal blood flow and reduce GFR. In hyperthyroidism the relation would be the reverse [5-7].

It has been described that thyroid dysfunction can cause a change in the rate of glomerular filtration of certain substances that are present in the blood, for example creatinine [1,8]. Changes in creatinine concentration in blood during thyroid dysfunction can also be a result of either myopathy or rhabdomyolysis present in hypothyroidism, or decreased muscle mass in hyperthyroidism [7,9].

Relations between thyroid disease and kidney function were initially described as clinically subtle and random, but to date there are several reports of increased serum creatinine in hypothyroid patients, and it has even been suggested that overt and subclinical hypothyroidism can be associated with increased risk of chronic kidney disease [5,9,10]. Studies that measured 51Cr-EDTA-clearance in thyroid disorders are consistent with reduced GFR in hypothyroidism [11,12]. There is also evidence of hyper filtration in hyperthyroid patients [4,13,14]. Most previous studies, however, have investigated small patient groups, often focusing on differences in creatinine levels before and after treatment of hyper- or hyperthyroidism. The results indicate that there is a difference in creatinine that to some extent is reversible upon treatment and normalization of the thyroid hormone axis [5,7,15]. One larger study suggests a relationship between elevated TSH and decreased estimated GFR based on creatinine concentration, as well as between decreased TSH and increased GFR [2]. Studies on cystatin C implies that this marker is not suitable for calculating GFR and monitoring kidney function in the clinical situation of thyroid dysfunction. This since, in contrast to creatinine, cystatin C concentration has been reported to be normal or lower in hypothyroidism with reduced GFR and higher in hyperthyroidism with normal GFR [1,16,17].

The aim of the current study was to assess plasma creatinine levels in well-defined hypo- hyper- and euthyroid patients based on FT3, FT4 and TSH utilizing a large patient cohort. This was done in order to determine whether there is a significant difference in plasma creatinine concentrations in hypothyroid and hyperthyroid patients as compared to euthyroid patients. If significant differences can be observed in thyroid dysfunction versus euthyroidism, this will be important to consider when clinically interpreting creatinine laboratory results and when handling patients with abnormal kidney or thyroid function.

Materials and Methods

Data collection

This observational retrospective data base study was carried out at the Skaraborg Hospital Department of Laboratory Medicine, Unilabs, Skövde, including a large patient material of 1141 cases. Data was obtained from the laboratory data base CGM Analytix Laboratory Information System (version 5.5). The data base contains laboratory results from patients in both non-institutional care and institutional care (district health care centers and Skaraborg Hospital). All tests were analyzed in lithium heparin plasma. Chemiluminescence methods were used for determination of FT4, FT3, TSH3-Ultra on the Advia Centaur XP/XPT Immuno assay System (Siemens Healthcare, Upplands Väsby, Sweden), while creatinine was analyzed with an enzymatic method (ECRE_2) on the Advia1800/2400Chemistry System (Siemens Healthcare); All analytical methods used in the study were the same during the 8years study period and subjected to regular standard quality controls. Reference intervals are presented in Table 1. Crystal Reports (version10.0.0.533, SAP, Walldorf, Germany) was used to extract sample-ID, test results, date of sampling, age (20–65years) and gender (females and males) from the laboratory information system. Data was collected from 2008–2015, i.e. from 8 consecutive years. Since no complete personal identification numbers or medical records were displayed during data management, no ethical approval was required for the study. Microsoft Excel (2010) was used to extract cases that had results for free T3, free T4, TSH and creatinine with identical sample-ID.

Data processing

Normal thyroid function was defined as FT3 3.3-6.0 pmol/L, FT4 10.0-22.0 pmol/L and TSH 0.4-4.0 mIU/L. From the data sets sorted as normal, 400cases (200 females and 200 males) were randomly chosen to form the reference group for statistical analysis. Hypothyroid disease was defined as FT3<3.3pmol/L, FT4<10pmol/L and TSH>4.0mIU/L (n=162). Hyperthyroid disease was defined as FT3 >6.0 pmol/L, FT4 >22 pmol/L and TSH<0.4 mIU/L (n=579). This generated three groups: euthyroidism (reference group), hypothyroidism, and hyperthyroidism. When divided by gender, six groups in total were created.

Statistical analysis

The data obtained was analyzed using IBMSPSS Statistics (version 22and24). In all six groups, the median values were calculated for creatinine, FT3, FT4 and TSH. The non-parametric Mann-Whitney test was used for comparison and significance testing. A p value<0.05 was considered significant. Spearman's rank correlation was used to study correlation between FT3 and creatinine.

Results

Significant differences in creatinine medians

A total number of 1141 patient results were selected for investigation in the present study. Table 2 presents number of cases, age, thyroids function tests and creatinine concentration. The results

Table 2: Demographic and laboratory features for the three groups of hypothyroidism, hyperthyroidism and euthyroidism (CG = Control Group). *n* = number of patients. Clinical quantitative variables are expressed as median, and the creatinine range in min-max values.

	Hypothyroidism			Euthyroidism (CG)			Hyperthyroidism		
	All	Females	Males	All	Females	Males	All	Females	Males
n	162	106	56	400	200	200	579	457	122
Age median (years)	48	46	53	44	44	44	44	44	46
T3 median (pmol/L)	2.25	2.10	2.35	4.70	4.40	4.90	11.30	11.40	10.95
T4 median (pmol/L)	7	7	6	16	15	16	32	32	33
TSH median (mIU/L)	77.50	75.50	83.50	1.50	1.45	1.60	<0.01	<0.01	<0.01
Creatinine median (µmol/L)	83	76	96	70	61	79	53	50	66
Creatinine Min-Max (µmol/L)	28–314	30–247	28–314	37–162	37–92	44–162	21–128	21–128	39–110
p value	***1	***2	***3	-	-	-	***1	***2	***3

****p*< 0.001

1) Level of significance for median creatinine when compared to all euthyroid subjects (control group).

2) Level of significance for median creatinine when compared to female euthyroid subjects.

3) Level of significance for median creatinine when compared to male euthyroid subjects.

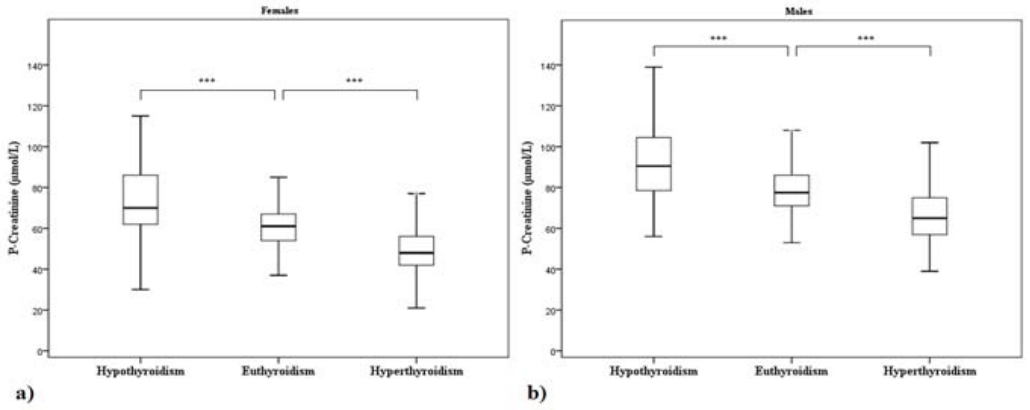

Figure 1: Median creatinine by group for (a) females and (b) males. ***p<0.001. The box represents median and inter quartile range (25%-75%). Whiskers represent 1.5 IQR. Outliers are not plotted.

are summarized for the hypothyroid, euthyroid and hyperthyroid groups. There are significant differences in median creatinine concentration between the three thyroid function groups, and this difference remains after separating each group according to gender. The median creatinine concentration in the hypothyroid group was 19 % higher than the median creatinine concentration in the euthyroid group. The median creatinine concentration in the hyperthyroid group was 24% lower than the median creatinine concentration in the euthyroid group. All median creatinine concentrations in the groups fall within the reference interval. However, 345 creatinine results were below the lower reference interval limit (all but 33 from the hyperthyroid group) and 61 creatinine results were above the upper reference interval limit (all but 19 from the hypothyroid group). As expected, plasma creatinine concentrations are higher in males than in females. The median age is similar in all groups, with the exception of hypothyroid males who are older. The box plot in Figure 1 visually illustrates the differences in creatinine concentrations between the hypothyroid, euthyroid and hyperthyroid groups.

Significant correlations

Spearman's correlation test revealed a significant (at the 0.01level) negative correlation between FT3 and creatinine concentration for both females (r=–0.672) and males (r=–0.518). When split by group and gender, correlation was strongest in the hyperthyroid group and weakest in the euthyroid group. Regression scatter plots (Figure 2) show the relationship between FT3 and creatinine concentration for females and males. Analysis of the relationship between FT4 and creatinine concentration as well as TSH and creatinine concentration showed correlation coefficients – 0.572 and 0.587, respectively.

Discussion

In a large patient material, this study confirms previously described relations between thyroid dysfunction and plasma creatinine concentration. Hypothyroidism is associated with increased plasma creatinine concentration and hyperthyroidism with decreased plasma creatinine concentration. The definition of hypothyroidism and hyperthyroidism in the present study rely entirely on laboratory analysis of FT3 and FT4 in combination with TSH. This approach has the strength of well defined thyroid function groups compared to most other similar studies that investigate only one thyroid hormone in relation to kidney function. Clinical thyroid hormone testing, however, may be based on TSH and FT4 only, particularly in hypothyroidism. The number of cases in the

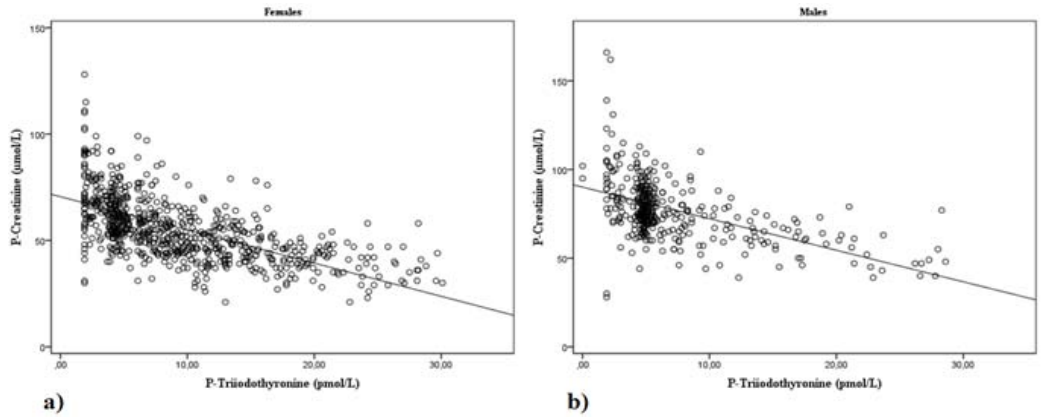

Figure 2: Association between creatinine and FT3 for (a) females and (b) males. Extreme values not plotted. Creatinine is significantly (at the 0.01level) and negatively correlated with FT3: r=–0.672 (females) and r=– 0,518 (males).

hypothyroid and hyperthyroid groups would have been larger if selection criteria without requirement of FT3 were applied, but this has not been investigated in the present study. We chose to include FT3 as selection criteria and in the correlation analysis since free T3 is the biologically active thyroid hormone. Reference interval limits were used as cut offs between the thyroid function groups. Median TSH in the hyperthyroid group is > 75 mIU/L combined with median FT3 and FT4 clearly below the reference intervals and the median TSH in the hyperthyroid group is < 0.01 mIU/L combined with median FT3 and FT4 clearly above the reference intervals (Table 2). We therefore conclude that the majority of cases can be considered as clinically overt disorders in both groups. Most of the patient results in the hypothyroid group and hyperthyroid groups originate from women. This was expected since the incidences of both disorders are higher in women than in men according to the follow up of the Whickham survey [18]. Unexpectedly, the number of cases defined as hyperthyroid in the present study outnumbered the cases defined as hypothyroid in the present study. In contrast, the Wickham survey found higher incidence of hypothyroid disease than hyperthyroid disease [18]. We speculate that the inconsistency may be explained by repeated sampling in the follow up of hyperthyroidism and/or that the selection criteria of cases based on FT3 in the present study may give a selection bias toward hyperthyroid cases.

Regression and correlation analyses showed a significant inverse relation between FT3 and plasma creatinine concentration. The correlation is strongest in the hyperthyroid group, which has the highest number of patient results and for that reason might influence the overall appearance of the regression model. FT4 and plasma creatinine concentration showed a similar inverse relation and TSH and plasma creatinine concentration shoved a similar positive relation. This further strengthens a proportional inverse relation between thyroid hormone activity and plasma creatinine concentration.

Several case reports and small case series report increased levels of serum creatinine in patients with hypothyroidism [19,20]. The main strengths of the study at hand are that it includes a large sample size, the selected age span, and the clear definition of the three thyroid function groups. Where most other similar studies only investigate one thyroid hormone in relation to kidney function, patient results in this study are required to fall within the defined ranges for all three thyroid tests. The present studies suffer from some weaknesses. Hypothyroid males were older than euthyroid males. The number of unique patients in the thyroid function groups is unknown since results from repeated sampling in the same patient are not excluded. It is not known what patient results are from samples taken at health care centers or at the hospital and this may vary between the three thyroid function groups. There was no possibility to identify the cause of hypo-or hyperthyroidism, or possible medical treatment. Hypothyroid and hyperthyroid results may represent primary thyroid disorder but may also represent poorly compliant patients that are on thyroid hormone replacement therapy. Endocrine abnormalities and thyroid dysfunctions are described to be more common in chronic kidney disease and this may result in a bias when selecting cases with combined thyroid function tests and plasma creatinine concentration [20]. None of these remarks, however, disqualifies the observed relation between thyroid disorders and plasma creatinine concentration. It is important to be aware of this relationship when interpreting plasma creatinine results. The possibility that hyperthyroidism may mask a reduction in kidney function when kidney function is monitored by plasma creatinine concentration is of concern and warrants further investigations. To elucidate the mechanism behind this relation is beyond the scope of the current study. However, it would be in the interest of good patient care to know if the plasma creatinine alterations seen in thyroid disorders truly represent alterations in GFR, if they are influenced by other confounding factors or if kidney function affects thyroid hormone levels.

Conclusion

In thyroid disorders, renal function can be affected to different degrees. This study investigates the relation between thyroid function and plasma creatinine concentration in a large patient material and the amount of patient results used carries high statistical power. There was a significant difference in plasma creatinine concentration between hypothyroid patients when compared to controls, as well as for hyperthyroid patients when compared to controls. Hypothyroidism was associated with approximately 20% higher plasma creatinine concentration and hyperthyroidism with approximately 20% lower plasma creatinine concentration. There was

a significant negative correlation between FT3 and plasma creatinine concentration. Thyroid hormone screening and potential correction of thyroid dysfunction should be considered in patients with plasma creatinine abnormalities without identifiable cause. Kidney function may be of concern in patient's with thyroid dysfunction and GFR results in these patient groups should be interpreted with caution.

Acknowledgement

Much needed statistics support was given by biostatistician Salmir Nasic and research coordinator Anna-Lena E-son Loft.

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