Renal Function in Hypothyroidism

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وظائف الكلى في مرضى قصورالدرقية

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Abstract

Background Hypothyroidism induces significant changes in the function of organ systems such as the heart, muscles and brain. Renal function is also influenced by thyroid status. Physiological effects include changes in water and electrolyte metabolism, notably hyponatremia, and reliable alterations of renal hemodynamics, including decrements in renal blood flow, renal plasma flow, glomerular filtration rate (GFR).

Objective Renal function is profoundly influenced by thyroid status; the purpose of the present study was to determine the relationship between renal function and thyroid status of patients with hypothyroidism.

Design and Patients In 5 patients with primary hypothyroidism and control group renal functions are measured by serum creatinine and glomerular filtration rate (GFR) using modified in diet renal disease (MDRD) formula.

Result In hypothyroidism, mean serum creatinine increased and mean estimated GFR decreased, compared to the control group mean serum creatinine decreased and mean estimated GFR Increased. The hypothyroid patients showed elevated serum creatinine levels (> 1.1mg/dl) compared to control group (p value = .000). In patients mean estimated GFR decreased, compared to mean estimated GFR increased in the control group (p value= .002).

Conclusion Thus the kidney, in addition to the brain, heart and muscle, is an important target of the action of thyroid hormones.

خلاصة

تهدف هذه الدراسة لمعرفة وظائف الكلى لدى نساء بالغات مصابات بقصور الدرقية الأولي(Primary Hypothyroidism). أجريت هذه الدراسة على نساء مصابات بقصور

الدرقية الأولي. تم في البداية تحليل الدم لعدد 300 من المرضي لمعرفة وظائف الغدة الدرقية وللتأكد من وجود قصور الدرقية الأولي ومن ثم تم اختيار خمسة من النساء (Age: 44.2 ± 16 years) وذلك بعد قياس مستوى الهرمون المحرض للدرقية(TSH) والذي كان مرتفعا عن المستوى الطبيعي {(0.4- 4.0) 27.1 ± 79·0} وكذلك تم قياس هرمون الثايروكسين(T4) وكان منخفضا عن المستوى الطبيعي{(50- 150) 11.0 ± 21.6}وذلك بأستخدام طرق المقايسة الأشعاعية(RIA, and IRMA).

بعد تحديد قصور الدرقية تم قياس مستوى كل من البولينا(Urea)، الكرياتنين(Creatinine)، وسرعة معدل الرشيح الكبيبي في الكلى(Glomerular filtration rate (GFR) في الدم وذلك لمعرفة وظائف الكلى. كما تم قياس وظائف الكلى المذكورة سابقا لدى خمسة من نساء صحيحات(Age: 33 ± 9 years).

خلصت هذه الدراسة الى وجود ارتفاع في مستوى الكرياتنين عن المستوى الطبيعي لدى النساء المصابات بقصور الدرقية ((0.6–1.1mg/dl) 0.102 ± 1.18) مقارنة بالنساء الصحيحات(0.094 ± 0.78) ووجد اختلاف معنوي ($P < 0·000$) بين المجموعتين. عند قياس سرعة معدل الرشيح الكبيبي في الكلى(GFR) لدى المريضات وجد انخفاضا في مستواه في الدم(9.33 ± 67.55) مقارنة بالنساء الصحيحات(8.49 ± 117.35) وكان الفرق معنوي($P < 0·002$.).

خلصت هذه الدراسة الى ان مرض قصور الدرقية يؤثر تأثيراً معنوياً على وظائف الكلى .

Introduction

Hypothyroidism induces significant changes in the function of organ systems such as the heart, muscles and brain.[1,2] renal function is also influenced by thyroid status. Physiological effects include changes in water and electrolyte metabolism, notably hyponatremia, and reliable alterations of renal hemodynamics,[3] including decrements in renal blood flow, renal plasma flow, glomerular filtration rate (GFR). The cause of the decreased renal plasma flow and GFR observed is believed to be principally due to the generalized hypodynamic state of the circulatory system in hypothyroidism.[4] Most studies on the effect of thyroid hormone on the kidney, however, have been performed in rats. Furthermore, the renal effects of thyroid hormones in humans can be subtle and therefore often escape clinical attention, as the changes in measured parameters of renal function are often within the normal range. Hypothyroid adults have mildly elevated serum creatinine

values and decreased glomerular filtration rates (GFR)[1,2]. Verhelst *et al.*[5] found increased creatinine levels in patients with (subclinical) hypothyroidism compared to controls group.

GFR can be estimated from serum creatinine levels and creatinine clearance or measured by the clearance of inulin. Levey *et al.*, in their modification of diet in renal disease (MDRD) study, [6] introduced an estimation of the GFR based on multiple regression analyses of a large database, which provided a more accurate evaluation of GFR than creatinine clearance or other calculations. The gold standard in these determinations was clearance measured using ^{125}I-iothalamate.

The purpose of the present study was to prospectively evaluate changes in renal function in patients with primary hypothyroidism. We used an estimation of the GFR based on a mathematical equation using serum urea, albumin and creatinine. [6]

Patients and Methods

Patients

The study group comprised 5 patients (females) with primary hypothyroidism and 5 healthy females as control group. All patients gave their written informed consent, and the local ethics committee approved the studies.

The patients were studied at diagnosis; that is TT4 or TSH being between the reference values for hypothyroid patients. The target levels for thyroid hormone and TSH were between the reference ranges (see below). Blood samples were drawn in the fasting state for determination of TSH, total T3 (TT3), thyroxine concentration (TT4), serum creatinine, blood urea nitrogen (BUN), and albumin.

Methods

TSH levels were measured by an Immunoradiometriassay (IRMA) with a detection limit of 0·01 mU/l (normal range 0·4–4·0 mU/l). Serum TT3 levels (normal range 0.8–3.0 nmol/l) and TT4 (range 50–150 nmol/l) were assayed by radioimmunoassay (RIA). Serum creatinine levels (normal range females 0. 6–1.1mg/dl) were assayed using a BioSystems reagents (Creatinine alkaline picrate) and instruments (Spectrophotometer). BUN concentration (range 7.0-18mg/dl) was determined by measuring urea using urease/salycilate which is an enzymatic colorimetric method and convert the urea mass units to those urea nitrogen apply: mg/dl x 0.467. Albumin

concentration was measured (normal range 3.81–4.65g/dl) using the Bromocresol green (BCG) reaction.

Equation for GFR determination (The MDRD formula is):[6]

GFR (ml/min/1·73 m^2) = 170 × $(P_{cr})^{-0·999}$ × $(age)^{-0·176}$ × (0·762 if patient is female) × (1·180 if patient is black) × $(BUN)^{-0·170}$ × (Alb)+0.318

Where Pcr is the serum creatinine concentration (mg/dl), BUN the blood urea nitrogen concentration (mg/dl) and Alb the serum albumin concentration (g/dl)].

Statistical analysis

Statistical analysis of the data was performed by means of paired t-test using SPSS software. A P-value < 0·05 (two-tailed) was considered significant.

Results

Table1 gives detailed data, thyroid function, creatinine and estimated GFR. In hypothyroidism, mean serum creatinine increased and mean estimated GFR decreased, compared to the control group mean serum creatinine decreased and mean estimated GFR Increased. Four out of five hypothyroid patients showed elevated serum creatinine levels (> 1.1mg/dl). One of those patients with normal ranges, although all patients showed an increase in creatinine level Compared to control group (p value = .000), (Fig.1). In the hypothyroid patients, there was no evidence for other causes of elevated serum creatinine levels such as glomerulonephritis. Mean serum urea nitrogen (BUN) increased and mean serum BUN of control group decreased (p value= .030), (Fig.2). In hypothyroid patients mean estimated GFR decreased, compared to mean estimated GFR increased in the control group (p value= .002) (Fig. 3).

Discussion

This study encompassing patients with hypothyroidism which is shows significant changes in renal function. These changes are similar whether renal function is expressed as creatinine levels or as estimated GFR. Although our study lacks the use of a gold standard for the measurement of renal function, the findings are in accordance with earlier studies on changes in serum creatinine, estimated GFR values based on serum creatinine, and GFR measured by methods applying radioactively labelled markers (gold standards).[3] The measurement of creatinine levels, BUN, and the estimated GFR shows significant

changes compared to control group (with p value 0.000, 0.03, and 0.03 respectively). This result similar to that done by Verhelst *et al.*[5], and Stuart H. etal. Again An increased serum creatinine and decreased glomerular filtration rate and renal blood flow have been described[2,7,8].

The decreases in renal plasma flow and glomerular filtration rate (GFR) that accompany hypothyroidism are believed to be related to the generalized hypodynamic state of the circulatory system in hypothyroidism. Elevation of serum creatinine levels is not generally mentioned as an abnormality that occurs in association with hypothyroidism, although reports of such an association exist.

The rise in creatinine levels during hypothyroidism was not associated with abnormal creatine kinase levels or other evidence of hypothyroid myopathy or intrinsic renal disease. The findings demonstrated that very little time is required for the development of elevated serum creatinine levels during the hypothyroid state. The results argue against the previously held notion of a net unchanged creatinine value because of a balance between the decrease in renal clearance and a decrease in creatinine generation.

The hypothyroid state is associated with a consistent elevation in the serum creatinine level, presumably related to a decrease in the GFR. The changes in serum creatinine levels develop rapidly and appear to be reversible. It may be clinically relevant to know of this association in that it could account for creatinine elevation in a patient with hypothyroidism. It should also alert the clinician to consider evaluation of thyroid function in a patient who has a modest serum creatinine elevation but whose thyroid status is unknown.

How can our findings be explained? First, circulating volume, which is dependent on cardiac function, influences GFR. In hypothyroidism, cardiac output is decreased and circulating volume is diminished, resulting in a decreased renal blood flow or 'pre-renal insufficiency'. Triiodothyronine has a direct effect on systemic vascular resistance, which influences cardiac output,[9] but could also influence renal blood flow.

Second, it is well known that creatinine clearance is an overestimation of the GFR because of its dependence on muscle mass and active tubular secretion. It is conceivable that the tubular secretion of creatinine is under the influence of thyroid hormones. Indeed, T4

regulates transcription in the sarcoplasmatic reticulum, affecting the Na^+/Ca^{2+} exchanger and the Na^+/K^+-ATPase activity in the kidneys.[10] These processes could be of importance for the active tubular secretion of creatinine. Third, creatinine production in muscle is dependent on the thyroid status. In hypothyroid patients, myopathy and even rhabdomyolysis may occur. This results in an enhanced release of creatinine from muscles[11].

In conclusion, renal function expressed as serum creatinine or estimated GFR (MDRD formula) changes significantly in patients with hypothyroidism. Effects of thyroid hormones on muscle function, influences on effective circulating volume and cardiac function, and also a direct effect of thyroid hormones on the kidney can explain this. Thus the kidney, in addition to the brain, heart and muscle, is an important target of the action of thyroid hormones.

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Table 1: Values thyroid function tests, serum creatinine and estimated GFR in patients with hypothyroidism and control group

	Hypothyroidism (n = 5, age: 44.2 ± 16 years)	**Control group (n = 5, age: 33 ± 9 years)**
TSH (mU/l)	79·0 ± 27.1 (0.4- 4.0)	1.62± 0.63(0.4- 4.0)
TT3 (nmol/l)	0.44 ± 0.26 (0.8- 3.0)	1.76 ± 0.56 (0.8- 3.0)
TT4 (nmol/l)	21.6 ± 11.0 (50- 150)	96.4 ± 3.7 (50- 150)
Creatinine mg/dl)	1.18 ± 0.102(0.06–1.1mg/dl)	0.78 ± 0.094
Estimated GFR (MDRD, ml/min)	67.55 ± 9.33	117.35 ± 8.49
Values are mean ± SD, range in parentheses.		
P Cr hypo-Cr c < 0·000; *P GFR- GFR C* < 0·002.		

Fig.1 Serum Creatinine in Hypothyroid patients and Control group.

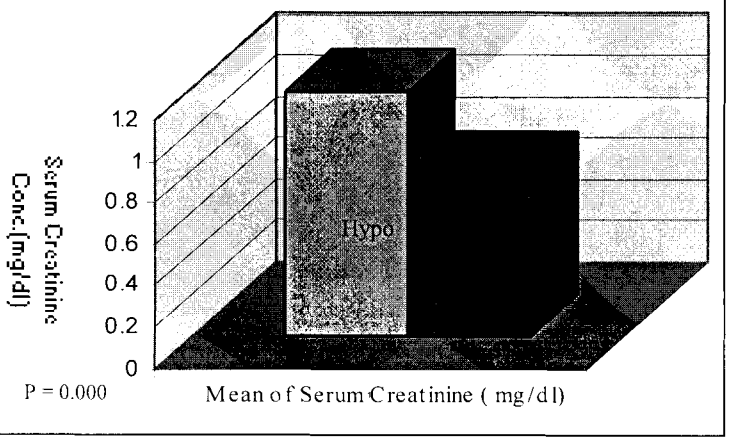
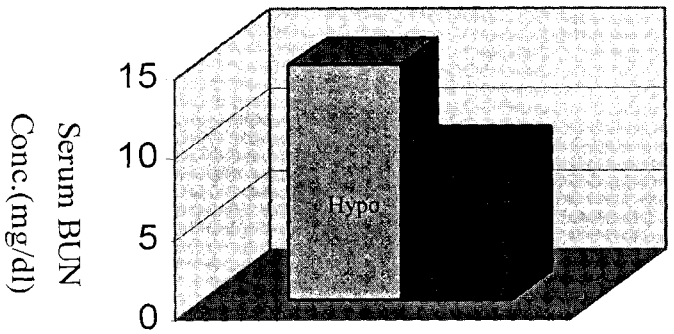


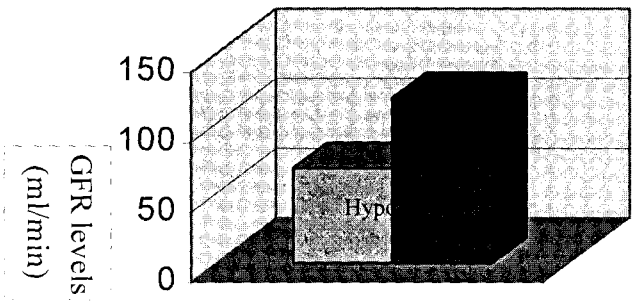
Fig.2 Serum BUN in Hypothyroid patients and Control group.



P= 0.030

Mean Serum BUN(mg/dl)

Fig.3 Estimated GFR in Hypothyroid patients and Control group.



P = 0.002

Mean GFR (ml/min)