

Evaluation of Thyroid function Status in Hemodialysis Patients

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Abstract

Background The interactions between kidney and thyroid functions are known for years. Thyroid hormones (TH) are necessary for growth and development of the kidney and for the maintenance of water and electrolytes homeostasis. On the other hand, kidney is involved in the metabolism and elimination of TH. Chronic renal failure (CRF) affects thyroid function in many ways, including low circulating thyroid hormone levels, altered peripheral hormone metabolism, insufficient binding to carrier proteins, possible reduction in tissue hormone content and altered iodide storage in the thyroid gland. Thus, patients with renal failure may have various abnormalities of thyroid function; nevertheless, they are typically clinically euthyroid.

Objectives: the aim of the present study is to evaluate thyroid function status in patients with hemodialysis in Karbala province, and to determine the benefit of thyroid function test as a routine test requested in hemodialysed patients.

Methods: Forty-two hemodialysed patients who attend hemodialysis unit in Al_Hussien teaching hospital in Karbala province with mean age of (44.4±15.9), another 32 apparently healthy subjects with mean age (41.4±12.5) took part in the current study as a control group. An early morning fasting sample of venous blood from each, total triiodothyronine (TT3), total thyroxine (TT4) and thyroid stimulating hormone TSH were estimated by Enzyme Linked ImmuoSorbent Assay(ELISA).

Result: The (TT3) level in haemodialysed patients was significantly lower than the level TT3 in control group ($P < 0.001$). T-student test reveals no significant difference in the total thyroxine (TT4) level between haemodialysed patients and control group. Also There was no significant difference in the mean level of TSH between hemodialysis and control group. About 41% of haemodialysed patients have TT3 level in the lower tertile of the reference range another 26% have TT3 level below the reference value. There was no correlation between TT3 level in hemodialysis group and duration of hemodialysis (in months).

Conclusion: Abnormalities in thyroid function test in hemodialysis patient are more common than that in general population, and low T3 syndrome is considered the main disorder that affect the thyroid function test in hemodialysis patients. So this disorder should be investigated in those patients routinely as, its presence in hemodialysis patients indicates a bad prognosis for them .

الخلاصة

موظنة: التداخل بين وظائف الكلى والغدة الدرقية معروف لسنوات مضت حيث تعتبر هرمونات الغدة الدرقية ضرورية لنمو وتطور الكلية وكذلك لحفظ التوازن المائي والايوني. من ناحية اخرى فالكلية تدخل في العمليات الايضية التي تحدث للهرمونات الدرقية وكذلك طرحها خارج الجسم . يؤثر عجز

الكلية المزمن على وظائف الغدة الدرقية بطرق متعددة تتضمن انخفاض مستوى هرمونات الدرق، تغيير الايض الهرموني السطحي، عدم كفاية الارتباط بالبروتينات الحاملة، احتمالية تقليل هرمونات النسيج وكذلك تغيير خزن اليود في الغدة الدرقية. لذلك فمرضى العجز الكلوي قد يكون لديهم مختلف الاختلالات في عمل الغدة الدرقية على الرغم من كونهم طبيعيين الغدة الدرقية من الناحية السريرية.

الهدف: تهدف هذه الدراسة لتقييم حالة وظيفة الغدة الدرقية لمرضى ديلزة الدم في محافظة كربلاء، وكذلك لتحديد فوائد فحص وظيفة الغدة الدرقية كفحص روتيني يطلب لهؤلاء المرضى.

طريقة العمل: لقد شارك في هذه الدراسة 42 مريضاً معدل اعمارهم (44.4 ± 15.9) من مرضى ديلزة الدم والذين يراجعون وحدة الديليزة في مستشفى الحسين التعليمي في محافظة كربلاء اضافة الى 32 شخصاً من الأصحاء معدل اعمارهم (41.4 ± 12.5) والذين شكلوا مجموعة السيطرة. تم اخذ العينات في الصباح الباكر من المشاركين في الدراسة من خلال الدم الوريدي وهم في حالة صيام ثم تم قياس T3, T4, TSH بواسطة طريقة الانزيم المرتبط بالمناعية.

النتائج: لوحظ ان مستوى T3 عند مرضى ديلزة الدم هو اقل بشكل مهم مما هو عليه عند مجموعة السيطرة ($P < 0.001$). ولا يوجد هناك فرق مهم في مستوى T4 و TSH بين مرضى ديلزة الدم ومجموعة السيطرة. وقد لوحظ ان 41% من مرضى ديلزة الدم كان لهم مستوى T3 في الثلث الأوسط من الحد الطبيعي هذا بالإضافة 26% لهم مستوى T3 اقل من الحد الطبيعي. كما ان ليس هناك ارتباط او علاقة بين مستوى T3 والمدة التي يتعالج به المرضى بواسطة ديلزة الدم.

الاستنتاج: ان التغيرات الغير طبيعية في فحص وظيفة الغدة الدرقية هي أكثر شيوعاً مما هو عليه عند عامة المجتمع. وتعتبر متلازمة T3 الواطئ هي الإختلال الأبرز الذي يؤثر على فحص وظيفة الغدة الدرقية عند مرضى ديلزة الدم. وان هذا الإختلال يجب ان يتحرى عنه وبشكل روتيني باعتبار وجوده عندهم يمثل مؤشراً خطيراً لمستقبل حالة المرض.

Introduction

The interactions between kidney and thyroid functions are known for years⁽¹⁻⁴⁾. Thyroid hormones (TH) are necessary for growth and development of the kidney and for the maintenance of water and electrolyte homeostasis. On the other hand, kidney is involved in the metabolism and elimination of TH. From a clinical practice viewpoint, it should be mentioned that both hypothyroidism and hyperthyroidism are accompanied by remarkable alterations in the metabolism of water and electrolyte, as well as in cardiovascular function. All these effects generate changes in water and electrolyte kidney management^(5, 6). Moreover, the decline of kidney function is accompanied by changes in the synthesis, secretion, metabolism, and elimination of TH. Thyroid dysfunction acquires special characteristics in those patients with advanced kidney disease⁽⁷⁾. Chronic

renal failure (CRF) affects thyroid function in many ways, including low circulating thyroid hormone levels, altered peripheral hormone metabolism, insufficient binding to carrier proteins, possible reduction in tissue hormone content and altered iodide storage in the thyroid gland⁽⁸⁾. Thus, patients with renal failure may have various abnormalities of thyroid function; nevertheless, they are typically clinically euthyroid⁽⁹⁾.

Chronic kidney disease affects both hypothalamus-pituitary-thyroid axis and TH peripheral metabolism⁽¹⁰⁻¹³⁾. Uremia influences the function and size of the thyroid^(7, 12, 14-18).

Uraemic patients have an increased thyroid volume compared with subjects with normal renal function and a higher prevalence of goiter, mainly in women^(7, 15, 18). Also, thyroid nodules and thyroid carcinoma are more common in uraemic patients than in the general population⁽¹⁹⁾.

Serum thyroid stimulating hormone (TSH) concentrations are

usually normal or elevated in chronic kidney disease (CKD), but its response to its releasing hormone thyroid releasing hormone (TRH) is generally low^(12, 13, 16, 21, 22). These findings suggest the presence of intrathyroidal and pituitary disturbances associated with uremia⁽²¹⁾. Also, both TSH circadian rhythm and TSH glycosylation are altered in CKD. The latter may compromise TSH bioactivity. Free and total triiodothyronin (T3) and thyroxine (T4) concentrations are usually normal or low in patients with CKD^(7, 12, 13, 15, 16, 20, 23).

Most hemodialysis patients are euthyroid. Hypothyroidism is not infrequent in these patients. However, a diagnosis of hypothyroidism in hemodialysis patients should not be made solely on the basis of reduced T₄ and T₃ levels but requires documentation of substantial TSH elevation (TSH >5 mU/l but <20 mU/l may occur in 20% of uraemic patients and are more indicative of non-thyroidal illness than hypothyroidism). Hemodialysis is associated with alterations in the concentration of circulating TH, usually to a reduction in serum total and free T₃ concentrations.⁽²⁴⁾

The aim of the present study is to evaluate thyroid function status in patients with hemodialysis in Karbala province, and to determine the benefit of thyroid function test as a routine test requested in hemodialysed patients.

Methods

Patients

Forty-two hemodialysed patients were selected from a larger group of hemodialysed patients who attend hemodialysis unit in Al_Hussien teaching hospital in Karbala province during August and September 2009. Informed consent was obtained from

each subject, and the local committees of ethics approved the studies. Patients with evidence of thyroid disease or on medication known to alter the thyroid function were excluded.

Control Group

Thirty two apparently healthy subjects, similar to the patients' gender distribution, and age, took part in the current study as a control group.

From each patient and control group's subject, an early morning fasting sample of venous blood was collected in a plain tube, before hemodialysis session started. And the sample of blood left in the plain tube for more than 30 minutes until complete coagulation of the sample ensured, then the sample was centrifuged and clear serum separated and stored in a deep freezer (-20°C to -40 °C) until assay.

Hormonal Assay

Total thyroxin (TT4) and total triiodothyronine (TT3) and thyroid stimulating hormone (TSH) were estimated by using commercially available kit.

TSH: TSH estimated by using the ultra sensitive TSH enzymed linked immunosorbent assay (ELISA), which based on principle of solid phase enzyme linked immunosorbent assay⁽²⁵⁾. The assay system utilizes a unique monoclonal antibody directed against a distinct antigenic determinant on the intact. Mouse monoclonal anti-TSH antibody is used for solid phase immobilization (on the microtiter wells). A goat anti-TSH antibody is in the antibody- enzyme (horseradish peroxidase) conjugate solution. The test sample is allowed to react simultaneously with two antibodies. After 1-2-hour incubation at room temperature, the wells are washed with water to remove unbound antibodies. A solution of TMB reagent (substrate) is added and incubated for 20 minutes,

resulting in the development of a blue color. The color development is stopped with addition of Stop Solution changing the color to yellow. The concentration of TSH is directly proportional to the color intensity of the test sample. Absorbance is measured by ELISA reader at 450 nm.

T3 and T4: T3 or T4 (Thyroid hormones TH) also estimated by Enzyme Immunoassay, in which certain amount of anti-TH antibody is coated on microtiter well. A measured amount of patient serum, and constant amount of TH conjugated with horseradish peroxidase are added to the microtiter wells. During incubation, TH and conjugated TH compete for the limited binding sites on the anti-TH antibody. After 60 minutes incubation at room temperature, the wells are washed several times with water to remove unbound TH conjugate. A solution of TMB Reagent is then added and incubated for 20 minutes, resulting in the development of blue color. The color development is stopped with addition of Stop Solution, and the absorbance is measured spectrophotometrically at 450 nm. The intensity of color formed is proportional to the amount of enzyme

present and is inversely related to the amount of TH in the sample⁽²⁶⁾.

Biostatistical analysis

The results were expressed as (mean \pm standard deviation). Pooled t-test was used for the comparison of significant difference between the healthy and control groups in the measured parameters. Correlation coefficient (r) was also used for searching about any correlation between the parameters.

Result

From the forty two hemodialysed patients there were 16 females with 26 males a ratio of (1:1.6), their ages range from 18 to 73 years (mean 44.4 ± 15.9), and their period of treatment by hemodialysis ranges from 1 to 60 months (mean 19.4 ± 17.4).

Another 32 subjects who represent the control group, 12 of them were female and 20 were male with ratio (1:1.7), and their ages range from 18 to 65 years (mean 41.4 ± 12.5).

The mean level of TT3, TT4, and TSH for both hemodialysis and control groups are illustrated in the table 1.

Table 1. The mean level of thyroid function test in hemodialysis patients and control group.

Parameter	Control group	Hemodialysis group	P Value
T3	1.27 \pm 0.41	0.77 \pm 0.3	P< 0.001 (Significant)
T4	8.05 \pm 1.66	8.95 \pm 2.23	Not significant
TSH	2.1 \pm 1.19	2.04 \pm 2.27	Not significant

The total triiodothyronine (TT3) level in haemodialysed patients was significantly lower than that in control group (P< 0.001). T-student test reveals no significant difference in the total thyroxine (TT4) level between haemodialysed patients and control groups. Also There was no significant difference in the mean level of TSH

between hemodialysis and control groups.

Twenty eight of 42 (67%) of haemodialysed patients have TT3 level below 0.85 nmol/L, and 11 (26%) have TT3 level below the reference value. So about 41% of haemodialysed patients have TT3 level in the lower tertile of the reference range.

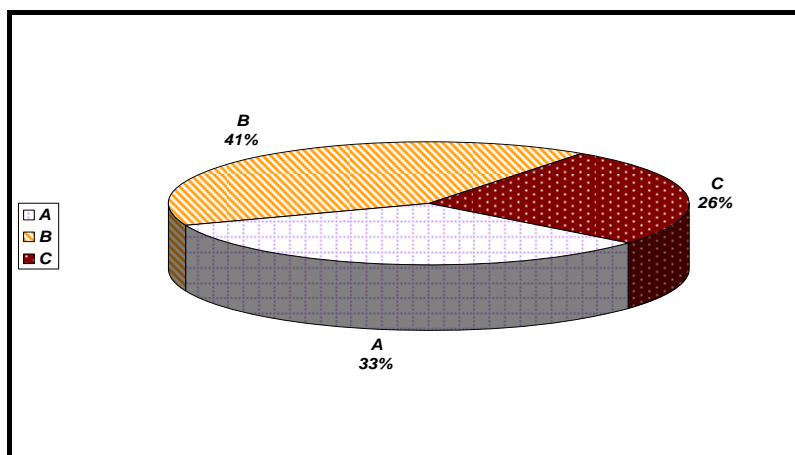


Figure 1. Reveals the TT3 level in hemodialysis patients, where (A) represents the percent of patients with TT3 level in the upper two tertile of the reference range, (B) represents TT3 level in the lower tertile, and (C) represent TT3 level below the reference range.

The coefficient correlation was done between TT3 level in hemodialysis group and duration of hemodialysis (in months), and there was no correlation between the above two parameters. Also there was no correlation between the TT3 level and the age parameter in haemodialysed patients.

Discussion

Serum TSH concentrations are usually normal or elevated in chronic kidney disease but its response to its releasing hormone (TRH) is generally low^(27,28). These findings suggest the presence of intrathyroidal and pituitary disturbances associated with uremia⁽²⁹⁾. In our present study, TSH level in hemodialysed patient is only slightly lower than that of control group. And this findings are consistent with (Katsuhiko et al) study and many others⁽³⁰⁾. In recent study, performed in Iran the major abnormalities in TSH level found to be an elevation of its level⁽³¹⁾.

Also in another study performed in Turkey, a high incidence of hypothyroidism and nodular goiter in end stage renal failure, was observed⁽³²⁾.

In the present study there is no significant changes in serum concentration of TT4, while there is significant reduction in the serum concentration of TT3.

In end stage renal disease (ESRD), both plasma fT3 and T3 are often reduced, and this alteration is attributed to impaired extrathyroidal T4 to T3 conversion, whereas T4 and fT4 are much less frequently depressed in these patients⁽³³⁾.

The different behavior of fT4 and fT3 in ESRD may depend on the fact that the depression of T3 is much greater than that of T4 and/or that, T3 being less tightly bound to thyroid-binding globulin than T4, alterations in thyroid hormone binding in ESRD are more apt to disturb the interpretation of T4 assays than those of T3⁽³⁴⁾.

In (Sarookhani 2007), the most prevalent abnormality was related to T4 (all less than normal levels) and least one associated with FTI. While the majority of abnormal T3 and FTI were diminished type, it was an elevated type for the majority of abnormal T3RU and TSH⁽³¹⁾.

While in (Chih et al 1998) , they found that continuous ambulatory peritoneal dialysis (CAPD) patients

had a higher frequency of reduced TT4 while HD patients had a higher frequency of reduced TT3⁽³⁵⁾. This difference is probably because high amounts of T4 are lost (about 8-29µg/day) through peritoneal dialysate from ESRD patients receiving CAPD⁽³⁶⁾. On the other hand, HD patients would have a higher probability of reduced T3 than would CAPD patients, due to inhibition of liver 5'- deiodinase mRNA released by IL-1 & alpha; during hemodialysis membrane reaction^(37,38). The later study revealed a result which is close similar to our result specially regarding to the low level of T3 in patients with hemodialysis. This condition, which has been called "low-T3 syndrome", is characterized by decreased serum concentrations of free iodothyronine (fT3) and increased concentrations of reverse triiodothyronine (rT3), without a compensatory increase in thyroid stimulating hormone (TSH)^(39,40). The precise mechanisms responsible for the low-T3 syndrome are not well understood, however recent studies have documented that the low-T3 syndrome correlates with poor cardiac prognosis and that the low-T3 syndrome is a strong predictor of death in cardiac patients⁽⁴¹⁾, but the pathophysiological mechanisms of these relations remain unclear⁽⁴²⁾.

Approximately one fourth of patients with ESRD display low fT3, thyroid dysfunction being an emerging problem also in patients with moderate to severe chronic kidney diseases⁽⁴³⁾. Chronic renal failure apart, much interest has recently been focused on the reduced fT3 plasma concentration observed in various clinical conditions such as acute and chronic infections; diabetes; and cardiovascular (CV) diseases, including myocardial infarction and heart failure⁽⁴⁴⁾, and this finding is now perceived as an

alteration that is less innocent than previously thought⁽⁴⁵⁾.

In our study about 41% of hemodialysed patients have serum T3 level in lower tertile of the reference range. (Carminie et al 2005) study suggests that a healthy serum fT3 should be in the upper two tertiles (67%) of the reference range, and preferably in the upper tertile, in hemodialysis patients, otherwise in particular in case of serum T3 in the lower tertile, there may be higher risk of abnormal inflammatory markers⁽⁴⁶⁾.

A reduction in total T₃, but not in free T₃ concentrations was associated with an increased all-cause and cardiovascular mortality in euthyroid CKD patients (47). Total and free T₃ behave as survival markers in patients with CKD both in HD (48) and in PD⁽⁴⁹⁾. For these reasons, some authors have recommended measuring T₃ levels to assess the relationship between thyroid dysfunction and risk of mortality in this population. Finally, it has been recently reported that low levels of T₃ before renal transplantation are associated with decreased survival of the graft⁽⁵⁰⁾. So it is concluded that abnormalities in thyroid function test in hemodialysis patient are more common than that in general population, and low T₃ syndrome considered the main disorder affect the thyroid function test in hemodialysis patients. And this disorder should be investigated in those patients routinely as, its presence in hemodialysis patients indicates a bad prognosis for them .

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