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HOW TO EVALUATE THE CARBOHYDRATE INTOLERANCE IN URAEMIA. IS SERUM REVERSE T_3 CLINICALLY USEFUL?

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Summary

This study investigates the possibility that serum 3,3′5′tri-iodothyronine (rT_3) may have clinical value as an indicator of carbohydrate metabolic control in uraemia. Thyroxine (T_4), T_3, rT_3, thyroid stimulating hormone (TSH), insulin and glucose were measured in 44 uraemic patients receiving dialysis, 30 patients on haemodialysis (group 1) and 14 on peritoneal dialysis (group 2). An oral glucose tolerance test was done in all patients. Twelve patients in group 1 and three in group 2 had an impaired glucose tolerance while two patients in group 1 and three in group 2 had an overt diabetes mellitus. Serum rT_3, rT_3: T_4 and rT_3: T_3 molar ratios were significantly increased in uraemic patients with overt diabetes mellitus and in those with impaired glucose tolerance. Furthermore serum rT_3 showed positive correlations with fasting blood glucose and insulin, blood glucose and insulin areas and peaks during glucose tolerance test and glucose/insulin coefficient. In both groups of uraemic patients there was no significant difference in serum T_3 between patients with impaired glucose tolerance and those with normal glucose tolerance. We conclude that serum rT_3 assay provides information about the degree of carbohydrate intolerance in end-stage renal failure and that it might be proposed as a clinically useful index of blood glucose control instead of glycosylated haemoglobins.

Introduction

In end-stage renal failure glycosylated haemoglobins are not useful indices of long-term carbohydrate metabolic control. Indeed either total glycosylated haemoglobin (HbA1) or its most abundant fraction A1c(HbA1c) have been reported to be elevated despite the shortened life span of erythrocytes. De Boer et al [1] did not find any correlation between HbA1c and glucose intolerance in uraemic patients and concluded that renal failure itself causes an increase in HbA1c. Kovarick et al [2] reported a positive relationship between HbA1 and the degree of renal failure. The causes of such increase in HbA1 and HbA1c

are still controversial and largely unknown. In previous studies [3–5] we concluded that it is probably the final result of a variety of mechanisms involving, at least in part, hyperazotaemia and uraemic acidosis. It has been known for several years that thyroid dysfunction may exist in uncontrolled diabetes mellitus. Recently Kabadi et al [6] reported a low serum tri-iodothyronine (T_3) and a raised 3,3'5' tri-iodothyronine (reverse T_3) (rT_3) which returned to normal on improvement in hyperglycaemia. In chronic renal failure thyroid status has been extensively investigated but little is known about rT_3 whose serum values have been found either normal, low or increased [7,8]. The aim of this study is to further elucidate these apparently controversial reports on rT_3 in chronic renal failure by attempting to assess the relation between glucose tolerance and thyroid hormone concentration and to investigate the possibility that serum rT_3 assay may have clinical value as indicator of carbohydrate metabolic control in uraemia.

Materials and methods

We studied 44 patients with end-stage renal failure (23 women and 21 men, mean age 47 years, range 22–66 years) on dialysis of variable duration (8 months to 12 years). Thirty patients received haemodialysis and 14 were on peritoneal dialysis. Serum levels of thyroxine (T_4), T_3, rT_3, thyroid stimulating hormone (TSH), insulin and glucose were measured before dialysis after an overnight fast. Thyroid hormones and insulin were determined by radioimmunoassay methods. An oral glucose tolerance test was done and interpreted according to the National Diabetes Data Group's criteria. Blood glucose was measured by the glucose-oxidase method. The control group consisted of 60 healthy subjects well matched for age and sex.

Linear regression analysis and Student's 't' test for unpaired data were used for statistical analysis.

Results

In patients with end-stage renal failure serum T_4 and T_3 was significantly reduced when compared with those of the control group (T_4: 5.5±1.2μg/dl vs 8.3±1.7; $p<0.001$; T_3: 1.0±0.3ng/ml vs 1.4±0.2; $p<0.01$) while we could find no difference in serum rT_3 (0.175±0.05ng/ml vs 0.185±0.03) and TSH (1.6±1.3μU/ml vs 2.6±1.4). Table I summarizes data regarding thyroid hormones in patients receiving haemodialysis (group 1) and peritoneal dialysis (group 2) respectively. Twelve patients in group 1 and three in group 2 had an impaired glucose tolerance while two patients in group 1 and three in group 2 had an overt diabetes mellitus. In both groups of uraemics there was no difference in serum T_3 between patients with impaired and those with normal glucose tolerance but diabetic patients on peritoneal dialysis showed lower values of T_3. Serum rT_3, rT_3: T_4 and rT_3: T_3 molar ratios were significantly increased in uraemic patients with overt diabetes mellitus and in those with impaired glucose tolerance of both groups. Furthermore serum rT_3 showed positive correlations

TABLE I. Circulating thyroid hormones concentrations in patients with end-stage renal failure enrolled in a chronic dialysis programme

Patients (n=44)	rT_3 ng/ml	$rT_3 : T_3$	$rT_3 : T_4$	T_3 ng/ml	T_4 μg/dl	TSH μU/ml
Haemodialysis (n=30)						
Patients with normal glucose tolerance (n=16)	0.14 ±0.03	0.141 ±0.02	0.027 ±0.007	1.05 ±0.23	5.6 ±1.1	1.6 ±1.1
Patients with impaired glucose tolerance (n=12)	0.24 ±0.03	0.223 ±0.08	0.038 ±0.004	1.20 ±0.35	6.2 ±0.9	1.5 ±1.0
Patients with overt diabetes mellitus (n=2)	0.30 ±0.03	0.271 ±0.03	0.042 ±0.001	1.05 ±0.35	5.1 ±0.3	1.6 ±1.0
Peritoneal Dialysis (n=14)						
Patients with normal glucose tolerance (n=8)	0.127 ±0.05	0.109 ±0.06	0.024 ±0.01	1.14 ±0.24	5.1 ±1.1	1.4 ±1.0
Patients with impaired glucose tolerance (n=3)	0.203 ±0.01	0.242 ±0.13	0.037 ±0.01	1.07 ±0.65	5.4 ±1.6	2.26 ±1.4
Patients with overt diabetes mellitus (n=3)	0.258 ±0.04	0.289 ±0.03	0.046 ±0.01	0.74 ±0.19	5.7 ±1.9	2.23 ±1.5

Results are expressed as Mean±SD

with pre-dialysis blood glucose and insulin, blood glucose and insulin areas and peaks during glucose tolerance test and glucose/insulin coefficient (Table II). These indices of carbohydrate metabolic control did not correlate with serum T_3. Finally no correlation was found between thyroid hormones and dialysis duration.

TABLE II. Linear regression analysis between serum rT_3 and some indices of carbohydrate metabolic control

x	y	Regression coefficient r =	Significance p<
rT_3	pre-dialysis glycaemia	0.509	0.001
rT_3	pre-dialysis insulinaemia	0.545	0.001
rT_3	glycaemic area during oral glucose tolerance test	0.486	0.005
rT_3	insulinaemic area during oral glucose tolerance test	0.780	0.001
rT_3	glycaemic peak during oral glucose tolerance test	0.502	0.001
rT_3	insulinaemic peak during oral glucose tolerance test	0.762	0.0001
rT_3	glucose/insulin coefficient	0.758	0.0001

Units used: rT_3 =ng/ml; glycaemia=mg/dl; insulinaemia=μU/ml

Glucose/insulin coefficient = $\frac{\text{glycaemia} - 30}{\text{insulinaemia} \times 100}$

Discussion

There are conflicting reports in the literature regarding serum rT_3 in chronic renal failure [7–9]. Some of the confusion may have arisen due to the types of patients studied. Some studies have included only patients on haemodialysis while others included patients treated conservatively or mixed populations of patients on one or other form of treatment. The alterations in serum hormones in chronic renal failure could be due to the state of chronic non-thyroidal illness, the coexistent catabolism, the metabolic consequences of uraemia and the type of dialysis therapy. Kaptein et al [9] demonstrated multiple alterations in the peripheral metabolism and distribution of rT_3 in patients with chronic renal failure suggesting that one or more of the abnormal metabolic consequences of the uraemic state are the most likely causative factors responsible for the alterations in rT_3 metabolism. Recently we suggested [10] that glucose intolerance may influence, at least in part, rT_3 metabolism in uraemic patients on haemodialysis. The present study confirms that serum rT_3 is greater in uraemic patients with impaired glucose tolerance and overt diabetes mellitus. The close correlations between rT_3 and the degree of carbohydrate metabolic control, as assessed by glucose and insulin measurements, suggest a causal relationship between glucose intolerance and increased rT_3. The mechanism leading to the increase of rT_3 is more difficult to define. It is possible that the glucose intolerance, due to a decreased utilization of glucose by tissues, may lead to a state of cellular starvation in which the peripheral tissue conversion of T_4 to rT_3 is increased. Alternatively the higher rT_3 may be due to a decreased hormone clearance resulting from an inhibition of rT_3 degradation and/or entrance into tissues.

Finally, our data contribute to clarify, at least in part, the controversial reports on rT_3 in chronic renal failure. Serum rT_3 is strongly influenced by the degree of carbohydrate intolerance and its assay might be proposed as a clinically useful index of blood glucose control in end-stage renal failure.

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