Plasma and Urine Amino Acid Imbalance in Chronic Renal Failure

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Previous investigations upon patients undergoing long-term regular dialysis treatment have demonstrated an imbalance in the plasma amino acids in which the levels of essential amino acids and tyrosine were low and the levels of non-essential amino acids were high compared with normal values (Young & Parsons, 1970). The most severe imbalance was observed in patients undergoing peritoneal dialysis, who lost appreciable amounts of protein and amino acids and were maintained on low protein diets. Their imbalance showed similarities to that found in protein deficiency disease (Holt et al, 1963) and in normal individuals maintained on low protein diets (Swendsweid et al, 1966). Patients on haemodialysis who were on higher protein intakes with no protein loss into the dialysis fluid had a less severe imbalance. In all these patients, however, the imbalance showed a significant correlation with the degree of uraemia. The percentage of essential amino acid nitrogen in the plasma was lowest when the creatinine was high. We have carried out further investigations on the level of plasma amino acids in non-dialysed patients with varying degrees of renal failure and have considered the extent and effect of urinary excretion of amino acids.

PATIENTS AND METHODS

Amino acids and creatinine were measured in the plasma and 24 hour urines of fourteen patients, male and female, with varying degrees of renal failure. The techniques used have been described previously (Young & Parsons, 1970). The estimations of amino acids in urine were slightly elevated by small amounts of other ninhydrin positive compounds which were present (Hamilton, 1967) and were not completely separated by the 19 hour chromatographic technique used in these investigations.

RESULTS

PLASMA AMINO ACIDS

The mean levels of amino acids in the plasma for two groups of patients are compared with normal values in Table I.

Table I. Mean concentrations of plasma amino acids in two groups of patients with renal failure as compared with normal values

Plasma amino acids mg/100 ml	Normals Mean [24]	Patients	
		Cr. Cl. 32-88 ml/min. Mean [4]	Cr. Cl. 0.03-16 ml/min. Mean [10]
Essential			
Threonine	1.70 (0.17)	1.96 (0.18)	1.22 (0.66)+
Valine	2.53 (0.42)	3.07 (0.75) < 0.05	1.32 (0.36)++
Methionine	0.30 (0.07)	0.33 (0.09)	0.31 (0.18)
Isoleucine	1.04 (0.25)	1.12 (0.38)	0.51 (0.17)++
Phenylalanine	0.95 (0.13)	1.23 (0.27) *	0.91 (0.39)
Lysine	2.50 (0.41)	3.50 (1.32) *	2.20 (0.91)
Leucine	1.71 (0.35)	2.04 (0.77)	0.82 (0.30)++
Non-essential			
Tyrosine	1.15 (0.18)	1.26 (0.19)	0.59 (0.20)++
Arginine	2.22 (0.53)	1.94 (1.05)	1.56 (0.45)+
Proline	2.10 (0.46)	2.77 (0.30) *	1.86 (0.90)
Serine	1.45 (0.40)	1.38 (0.51)	1.56 (0.83)
Aspartic acid	0.13 (0.05)	0.20 (0.15) **	0.15 (0.11)
Glutamic acid	1.18 (0.35)	1.50 (0.71) < 0.02	1.29 (0.62)
Glycine	1.25 (0.30)	1.74 (0.49) *	2.36 (1.33)**
Alanine	2.60 (0.50)	3.96 (1.09) **	3.51 (1.52)*
Ornithine	0.90 (0.11)	1.30 (0.03) **	1.03 (0.19)*
Histidine	1.30 (0.27)	1.37 (0.63)	1.30 (0.61)
Citrulline	0.66 (0.15)	0.90 (0.49) **	1.12 (0.43)**

Mean values significantly lower than normal + $p < 0.01$ ++ $p < 0.001$
Mean values significantly higher than normal * $p < 0.01$ ** $p < 0.001$
( ) Standard deviation

Group I (Creatinine clearances 32-88 ml/min)

Most amino acid levels in plasma were elevated above the normal but there was no imbalance between the essential amino acids and the non-essential amino acids.

Group II (Creatinine clearances 0.03-16 ml/min)

All these patients exhibited an amino acid imbalance in which the plasma levels of most essential amino acids, and in addition tyrosine and arginine, were significantly low, but the non-essential amino acids were higher than normal. The mean value for methionine was not representative of all the

patients. Three of the patients were on a Giovannetti diet containing 12 g of protein/day supplemented with methionine and the plasma levels were greater than normal. In three patients who received protein intakes of 40 g/day and in four patients who were allowed unrestricted protein the plasma methionine level was below normal.

In Group II the decrease in essential amino acid nitrogen expressed as a percentage of the total amino acid nitrogen ($\frac{E}{T}\%$) correlated closely with the creatinine clearance (Figure 1). Thus with increasing severity of renal impairment there was a reduction in the percentage of essential amino acid in the blood.

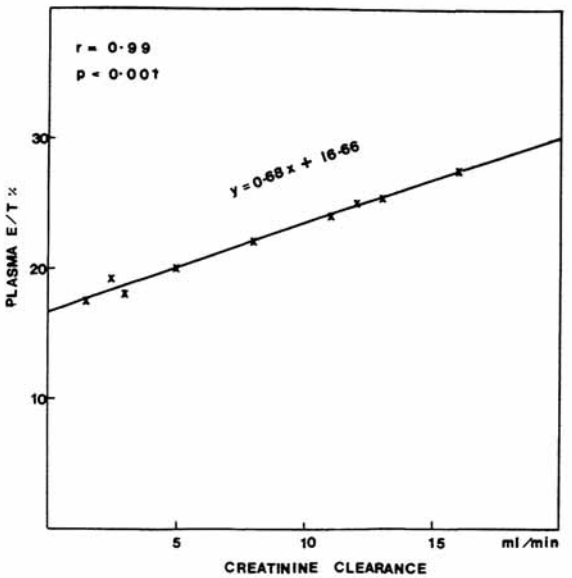

Figure 1. Correlation between $\frac{E}{T}\%$ and creatinine clearance in non-dialysed patients with severe renal failure

The two groups of non-dialysed patients are compared with normal individuals, haemodialysis and peritoneal dialysis patients in Table II. The results are tabulated in order of increasing plasma creatinine along with the protein intake. Values for the dialysed patients were the mean of pre-dialysis determinations.

URINARY EXCRETION OF AMINO ACIDS

The relationship between the plasma levels and the urinary excretion of amino acids for each group of patients is shown in Figures 2 and 3. The concentration of each amino acid in plasma and the quantity excreted in 24 hours

Table II. Relationship between E/T%, plasma creatinine and protein intake in patients with renal failure as compared with normal individuals

	Non-dialysed			Dialysed	
	Normal (24)	Cr. Cl. 32-88 (4)	Cr. Cl. 0.03-16 (10)	Haemodialysis (9)	Peritoneal Dialysis (30)
Protein intake g (approx)	Unrestricted	Unrestricted	12 → Unrestricted	60 → Unrestricted	40
Creatinine mg/100 ml	1.1 (0.2)	1.3 (0.5)	10.7 (6.0)	11.3 (3.1)	20.2 (2.6)
E/T%	32.9 (2.0)	33.3 (1.9)	22.4* (3.9)	26.9* (2.0)	19.8* (2.3)

$$\frac{E_{\%}}{T_{\%}} = \frac{\text{Tyrosine + essential amino N}}{\text{Total amino N}} \times 100$$

* Mean values significantly lower than normal $p < 0.001$

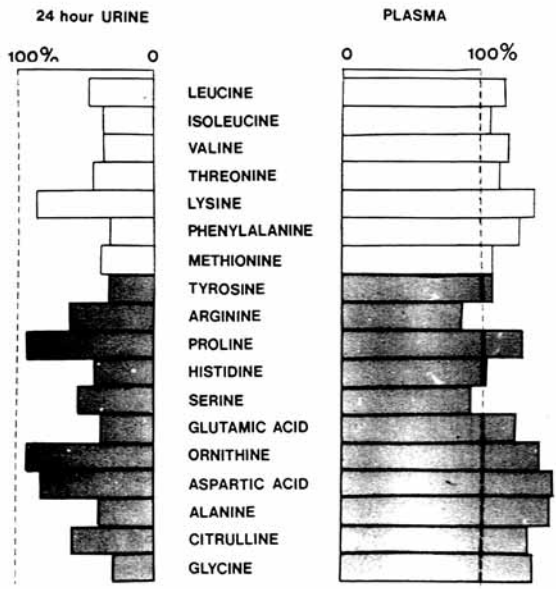

Figure 2. Relationship between the plasma levels and the urinary excretion of amino acids in patients with creatinine clearances 32-88 ml/minute.
Essential amino acids (white) Non-essential amino acids (grey)

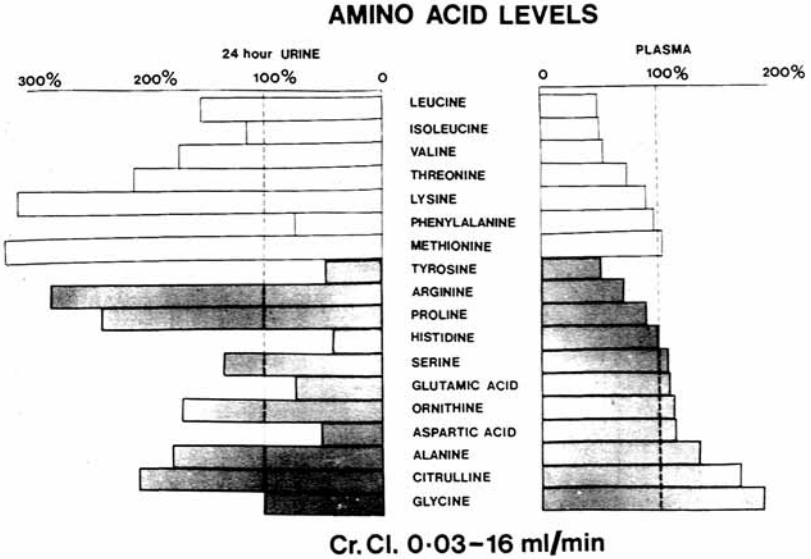

Figure 3. Relationship between the plasma levels and the urinary excretion of amino acids in patients with creatinine clearances 0.03-16 ml/minute.
Essential amino acids (white) Non-essential amino acids (grey)

is expressed as a percentage of the mean values found in normal individuals. The normal 100% values are shown by dotted lines.

Group I (Creatinine clearances 32-88 ml/min) [Figure 2]

In this group of patients the excretion of all amino acids were lower than normal whilst the plasma levels were raised.

Group II (Creatinine clearances 0.03-16 ml/min) [Figure 3]

These patients showed considerable alterations in the excretion of many amino acids. The excretion of some of the non-essential amino acids remained lower than normal whilst the plasma levels were normal or slightly elevated. However the excretion of essential amino acids and arginine were greatly increased even though the corresponding levels in the plasma were lower than normal. Tyrosine was lower than normal in both plasma and urine of all patients.

The plasma levels of threonine and the corresponding clearances for each

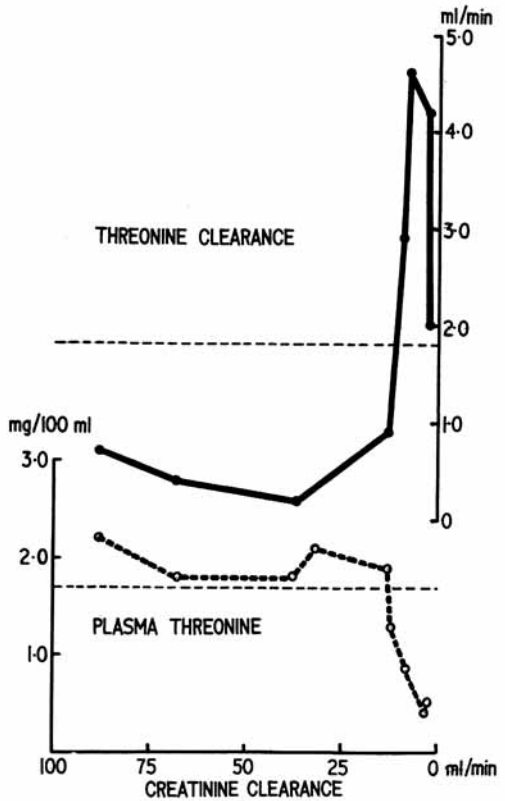

Figure 4. Plasma level and clearances of threonine for each of the patients

patient are shown in Figure 4. In the presence of a moderate degree of renal impairment a reduced clearance and a slightly elevated plasma level were observed. At very low creatinine clearances, low plasma levels occurred in the presence of increased urinary excretion.

DISCUSSION

It is apparent from our data that non-dialysed patients with progressive renal failure develop an amino acid imbalance in which most essential amino acids and tyrosine and arginine are low and the non-essential amino acids are higher than normal. Such an imbalance indicates that these patients have an overall impairment of nutritional state in which they have less essential amino acid available for protein synthesis. The addition to the diet of essential amino acids either singly as in a Giovannetti diet, or as a mixture (Young & Parsons, 1970) results in an increase in their plasma levels; however, a complete correction of the imbalance may not be possible in the presence of severe uraemia. Whilst protein intake is a fundamental factor in the levels of essential amino acids found in the plasma the overall imbalance in these patients is also related to the degree of renal impairment. The percentage of essential amino nitrogen in the second group of non-dialysed patients (22.4%) was lower than might be expected, as compared with dialysed patients if dietary protein and degree of uraemia were the only factors involved. This may be explained by the wide range of protein intakes within this group, but it is also possible that the significant changes in the urinary losses of amino acids with progressive renal failure may be contributory.

In the patients with severe renal failure the calculated clearances of some amino acids particularly essential amino acids and arginine were noted to be up to three times the normal values, despite the obvious decreased glomerular filtration rate, thus indicating a gross impairment in tubular reabsorption mechanism. The total excretion of free amino acids in these patients was approximately the same as in normal individuals, but the proportion of essential amino acids was doubled. It is not possible to say with certainty whether such disproportionate losses of amino acids are coincidental secondary effects of severe renal impairment or if they contribute to or initiate the amino acid imbalance in blood.

CONCLUSIONS

1. Non-dialysed patients with progressive renal failure develop an amino acid imbalance.
2. The decrease in plasma essential amino acids indicates a deterioration in nutritional state.
3. The imbalance is related to the degree of renal impairment and an increased urinary loss of essential amino acids.

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REFERENCES

Hamilton, P. B. (1967) Technicon Symposia, 1, 317
Holt, L. E., Snyderman, S. E., Norton, P. M., Roitman, E. and Finch, J. (1963) Lancet, ii, 1343
Swendseid, M. E., Tuttle, S. G., Figuoroa, W. S., Mulcare, D., Clark, A. J. and Massey, F. (1966) Journal of Nutrition, 88, 239
Young, G. A. and Parsons, F. M . (1970) Clinica Chimica Acta, 27, 491