Kidney International, Vol. 66 (2004), pp. 591–596

Impairment of phenylalanine conversion to tyrosine in end-stage renal disease causing tyrosine deficiency

YVES BOIRIE, ROBERT ALBRIGHT, MAUREEN BIGELOW, and K. SREEKUMARAN NAIR

Endocrine Research Unit, Division of Endocrinology and Metabolism, and Nephrology Department, Mayo Clinic and Foundation, Rochester, Minnesota

Impairment of phenylalanine conversion to tyrosine in end-stage renal disease causing tyrosine deficiency.

Background. Tyrosine is not considered an indispensable amino acid because in humans phenylalanine is converted to tyrosine. Recent human studies demonstrated that tyrosine production from phenylalanine occurs not only in liver but also in kidney.

Methods. Here we report results from studies, performed in end-stage renal disease (ESRD) patients and in healthy controls using [^{15}N] phenylalanine and [$^{2}H_4$] tyrosine as tracers demonstrating the mechanism of tyrosine deficiency in patients with renal failure.

Results. Phenylalanine flux (an index of protein breakdown) was identical in both groups either before or during an infusion of amino acid mixture. In contrast, tyrosine flux (representing protein breakdown and tyrosine appearance from phenylalanine) and conversion of phenylalanine to tyrosine were lower in ESRD patients [2.05 $\pm$ 0.30 μmol/kg fat-free mass (FFM)/hour and 2.59 $\pm$ 0.52 μmol/kg FFM/hour, before and during amino acid infusion, respectively] than in the control subjects (4.07 $\pm$ 0.54 μmol/kg FFM/hour and 5.53 $\pm$ 0.86 μmol/kg FFM/hour, $P <$ 0.02, ESRD vs. controls, respectively). Plasma tyrosine concentrations in ESRD patients remained 40% lower than the controls during the postabsorptive state and following amino acid replacement.

Conclusion. We conclude that reduced conversion of phenylalanine to tyrosine causes tyrosine deficiency in patients with ESRD prompting to propose that tyrosine replacement is potentially required in patients with ESRD.

Tyrosine is not considered an essential amino acid in humans because unlike other essential amino acids such as branched chain amino acids and phenylalanine, tyrosine can be produced in the body by the hydroxylation on phenylalanine by phenylalanine hydroxylase. Phenylalanine hydroxylase was, until recently, thought to be exclusively located in liver in human subjects. Studies based on stable isotopes of phenylalanine and tyrosine, and measurements of these amino acids and their isotopic abundance in artery and renal vein clearly demonstrated that tyrosine is produced in kidney at least as much as in liver [1, 2]. Moreover, most of the tyrosine in liver is catabolized (a common catabolic pathway for phenylalanine and tyrosine) [1, 2]. Kidneys produce and release tyrosine to the systemic circulation, providing the main source (other than tyrosine appearing from protein breakdown) of tyrosine in the systemic circulation [1, 2]. Most of the commercially available amino acid mixtures have only low concentrations of tyrosine based on an assumption that normally phenylalanine is converted to tyrosine and because of the low solubility of tyrosine. It is possible that phenylalanine is not converted efficiently to tyrosine in end-stage renal disease (ESRD). The report that kidney is a key source of circulating tyrosine in healthy people prompted us to determine whether reduced phenylalanine conversion to tyrosine may explain the intriguing observations of altered phenylalanine and tyrosine levels in ESRD patients [3–6]. Elevated phenylalanine concentrations in the plasma of chronic renal failure patients have been observed, but it was constantly attributed to liver dysfunction and generalized phenylalanine hydroxylase activity. We hypothesized that tyrosine may be considered as an essential amino acid in patients with ESRD because tyrosine production from phenylalanine is impaired in these patients. A reduced supply of an amino acid in the fasted state may contribute to the muscle wasting in ESRD patients [7]. It is also possible that when parenteral nutrition—based on commercially available amino acid mixture—is administered to ESRD patients, a decreased tyrosine availability could be a limiting factor for the stimulation of protein synthesis and may contribute to protein wasting.

Therefore, to determine whether phenylalanine conversion to tyrosine is reduced in ESRD patients, we assessed phenylalanine and tyrosine fluxes, and conversion rate of phenylalanine to tyrosine in ESRD patients and in control subjects, matched for age, gender, and body mass index (BMI). We then assessed the response of

Key words: phenylalanine, tyrosine, renal failure, hemodialysis, muscle.

Received for publication April 3, 2003
and in revised form November 25, 2003
Accepted for publication March 9, 2004

Table 1. Amino acid composition of aminosyn

Ingredient	Concentration
Arginine	980 mg/100 mL
Glycine	1.28 g/100 mL
Histidine	300 mg/100 mL
Isoleucine	720 mg/100 mL
L-Alanine	1.28 g/100 mL
L-Methionine	400 mg/100 mL
Leucine	940 mg/100 mL
Lysine acetate	720 mg/100 mL
Phenylalanine	440 mg/100 mL
Proline	860 mg/100 mL
Serine	420 mg/100 mL
Threonine	520 mg/100 mL
Tryptophan	160 mg/100 mL
Tyrosine	44 mg/100 mL
Valine	800 mg/100 mL

phenylalanine and tyrosine metabolism to an intravenous infusion of a commonly used amino acid mixture just as parenteral nutrition is administered.

METHODS

Materials

[15N] Phenylalanine (98 mol% excess) (MPE), and [^{2}H4] tyrosine (91 MPE) were supplied by Cambridge Isotope Laboratories (Andover, MA, USA). Isotopic purity of tracers was checked by gas chromatography-mass spectrometry (GCMS). Solutions of tracer were prepared by the pharmacy department and tested for sterility and pyrogens.

Subjects

Six ESRD patients, aged 37 to 66 years, on regular maintenance in-center hemodialysis were selected for the study. They were compared to age, gender, and BMI matched control subjects. All subjects had end stage renal disease due to hypertensive nephrosclerosis ($N = 3$), polycystic kidney disease ($N = 1$), focal segmental glomerulosclerosis ($N = 1$), and antibiotic-induced nephrotoxicity ($N = 1$). All ESRD patients had been treated with hemodialysis exclusively for at least 6 months with Cobe Centry3^{TM} dialysis machines and polysulfone high-flux reusable dialyzers. Standard measurements of dialysis adequacy and management of ESRD-associated anemia are provided. All clinical and anthropometric characteristics of the subjects are presented in Table 1. None had any infectious disease or was treated with glucocorticoids before or during the study period. The Institutional Review Board of the Mayo Clinic and Foundation approved the experimental protocol, and the purpose of the study was explained to the patients before they gave their written informed consent.

Protocol design

Prior to the study, protein and energy intakes were assessed by a dietician on a 1-week diet history. All tests were performed the day following a dialysis session in the postabsorptive state, implying that the last meal was taken between 6:30 p.m. and 7:00 p.m. in the evening preceding the study day. A saline line was inserted in an antecubital vein opposite to the fistula arm at 8:00 p.m. Tracers' infusions began the next day at 3:00 a.m. until 11:00 a.m. A priming dose of [^{15}N] phenylalanine [1 mg/kg fat-free mass (FFM)], [^{15}N] tyrosine (0.3 mg/kg FFM) and [$^2H_4$] tyrosine (0.6 mg/kg FFM) injection was followed by a continuous infusion of [^{15}N] phenylalanine (1 mg/kg FFM/hour) and [$^2H_4$] tyrosine (0.6 mg/kg FFM/hour). At 7:00 a.m. (T240 minutes) tracers' infusion rates were increased for [^{15}N] phenylalanine at 1.5 mg/kg FFM/hour and [$^2H_4$] tyrosine at 0.65 mg/kg FFM/hour and saline solution was replaced by an amino acid mixture (aminosyn 10%) (Table 1) (Abbott Laboratories, Chicago, IL, USA) which was infused at a rate of 1.6 mL/kg FFM/hour. The phenylalanine and tyrosine infusion by the aminosyn were, respectively, 44 μmol/kg FFM/hour for phenylalanine and 4 μmol/kg FFM/hour for tyrosine in the two groups. Blood samples were drawn at 3:00 a.m. then at 6:45 a.m., 6:50 a.m., 6:55 a.m., 7:00 a.m., and at 10:45 a.m., 10:50 a.m., 10:55 a.m., and 11:00 a.m. for plasma isotopic enrichments of phenylalanine and tyrosine, amino acids concentrations, glucose, and hormonal analysis.

Body composition analysis

Fat mass and FFM were measured using dual x-ray absorptiometry analysis. In addition, muscle mass was estimated from appendicular FFM data as previously described [8]

Analytic methods and kinetics calculations

[^{15}N] phenylalanine, [^{15}N] tyrosine and [$^2H_4$] tyrosine enrichments were measured as previously described [9] using GCMS after derivatizing them as previously reported [10].

Free amino acid concentrations in plasma were measured by high-performance liquid chromatography (HPLC) system as previously described [11]. Plasma insulin and other hormones [glucagon, cortisol, insulin-like growth factor (IGF), IGF-BP1, and IGF-BP3) were measured by chemiluminescent sandwich assay (Sanofi Diagnostics, Chaska, MN, USA). Plasma glucose concentrations were measured enzymatically with an autoanalyzer (Beckman Instruments, Fullerton, CA, USA).

The calculations of phenylalanine and tyrosine flux were performed based on the equation previously described [12].

$$\text{Phenylalanine flux or Qp (mmol/kg/hour)} = \text{iPh} \times ([^{15}\text{NPhp/phenylalanine}_I) - 1)$$

Table 2. Anthropometric, clinical, and biologic data of the population

	Controls	End-stage renal disease
Age *years*	53.83 ± 5.16	53.50 ± 4.88
Weight *kg*	83.17 ± 6.99	79.37 ± 6.77
Body mass index kg/m^2	25.93 ± 1.73	26.26 ± 2.14
Fat-free mass *kg*	59.73 ± 3.43	53.87 ± 3.00
Muscle mass *kg*	36.67 ± 2.63	30.36 ± 2.02[a]
Fat mass *%*	22.14 ± 2.64	24.45 ± 4.21
Duration of hemodialysis *years*	—	4.25 ± 1.49
Glucose *mg/dL*	98.08 ± 1.55	93.25 ± 4.46
Bicarbonate *mEq/L*	26.33 ± 0.99	26.00 ± 0.65
Blood urea nitrogen *mg/dL*	17.33 ± 1.41	33.00 ± 3.92[a]
Creatinine *mg/dL*	1.18 ± 0.03	7.52 ± 0.33[a]
Serum albumin level *g/dL*	4.5 ± 0.13	3.9 ± 0.13
Length of dialysis session *minutes*	—	240 ± 15
Urea reduction ratio *%*	—	72 ± 2.62
Hemoglobin *g/dL*	14.6 ± 0.32	11.7 ± 0.43[a]

Mean ± SD.
[a] $P < 0.05$ end stage renal disease vs. control subjects.

Table 3. Baseline and amino acid–induced changes in plasma hormones

	Controls		End-stage renal disease (ESRD)	
	Saline	Amino acid	Saline	Amino acid
Insulin	5.9 ± 1.4	7.7 ± 1.3	5.9 ± 1.0	10.0 ± 1.8
Glucagon	60.8 ± 6.1	87.2 ± 12.6	114.1 ± 27.7[a]	181.3 ± 49.2[a]
Cortisol	18.8 ± 2.2	14.0 ± 2.3	21.9 ± 2.4	16.4 ± 2.0
Growth hormone	0.19 ± 0.11	1.22 ± 0.50	0.75 ± 0.28[a]	1.23 ± 0.74
IGF free	0.73 ± 0.20	0.67 ± 0.15	1.29 ± 0.46	1.07 ± 0.30
IGF total	127 ± 12	129 ± 16	153 ± 33	144 ± 29
IGF-BP1	67.4 ± 15.5	48.1 ± 16.7	35.2 ± 5.2[a]	19.0 ± 7.6
IGF-BP3	2753 ± 157	2757 ± 185	4169 ± 208[b]	4036 ± 136[b]

IGF is insulin-like growth factor. Mean ± SEM.
[a] $P < 0.10$ ESRD vs. control subjects.
[b] $P < 0.01$ ESRD vs. control subjects.

in which iPh is the rate of infusion of [^{15}N] phenylalanine, ^{15}NPhp is the arterial plasma isotopic enrichment of [^{15}N] phenylalanine at plateau and phenylalanine$_i$ is the isotopic enrichment of [^{15}N] phenylalanine infused. Tyrosine flux (Qt) is calculated in a similar way as phenylalanine using [$^2H_4$] tyrosine as tracer.

The conversion rate of phenylalanine to tyrosine (Q_{PT}) is calculated as follows:

$$Q_{PT} = Q_T \times \frac{^{15}NT_P \times QP}{^{15}NPh_P \times iPh + QP}$$

in which QT and Q_P represents the fluxes of phenylalanine and tyrosine, $^{15}NT_P$ and at $^{15}NPh_P$ represent [^{15}N] tyrosine and [^{15}N] phenylalanine enrichment in plasma at plateau, and iPH represents infusion rate (μmol/kg/hour) of [^{15}N] phenylalanine.

Statistical analysis

All data are presented as means ± SEM. Factorial analysis of variance (ANOVA) was used to calculate the differences in body composition, hormonal concentrations, plasma amino acids levels, and phenylalanine and tyrosine kinetics between the two groups. Paired *t* tests were used in each group to compare baseline and the response to the amino acid mixture infusion. Results are considered as significant with $P < 0.05$.

RESULTS

Anthropometric and clinical data

Patients and control subjects were matched for age, gender and BMI, so that no statistical significant difference was detected for these parameters between the two groups (Table 2). However, when muscle mass was estimated from appendicular FFM, it was found to be significantly lower in the ESRD patients and close to ~6 kg difference was observed ($P < 0.05$) (Table 2). Blood urea and creatinine were much higher in the patients than in the control subjects ($P < 0.001$) as expected. However, bicarbonate concentration was similar in both groups indicating that ESRD patients were not in a state of acidosis. Patients with the ESRD had adequate dialysis delivery, anemia therapy, and there was a statistically no significant differences in albumin levels between the groups. The ESRD patients have albumin levels within the range of a healthy population.

Plasma hormonal concentrations

Insulin, cortisol, free- and total IGF-1 were not statistically different between the two groups in the basal state or during amino acid infusion (Table 3). However, there was a tendency of a non-statistically significant higher baseline and amino acid–induced plasma glucagon ($P = 0.09$), a higher basal growth hormone ($P = 0.08$), a lower basal IGF-BP1 ($P = 0.08$). Finally, IGF-BP3 concentrations were found markedly elevated in the patients both at baseline and during amino acid infusion in comparison with the control subjects ($P < 0.001$).

Plasma amino acids concentration

As depicted in Table 4, different amino acid profiles were found between ESRD and control groups. Plasma tyrosine, valine, leucine, and lysine concentrations were significantly lower in the ESRD patients than in the matched control subjects (34 ± 12 vs. 58 ± 11 for plasma tyrosine, ESRD vs. control subjects, $P < 0.05$). After amino acid infusion, there was a global increase for all amino acids, except for glutamate, glutamine, and tyrosine concentrations (30 ± 9 vs. 52 ± 13 for plasma tyrosine, ESRD vs. control subjects, $P < 0.05$). The infused amino acid mixture is deficient in these three amino acids but tyrosine was expected to be produced from conversion

Table 4. Plasma amino acid concentrations during saline and during amino acid infusion

	Saline		Amino acid	
	Controls	ESRD	Controls	ESRD
Glutamic acid	43 ± 11	51 ± 10	44 ± 11	55 ± 16
Serinle	69 ± 16	49 ± 15	147 ± 43[a]	112 ± 21
Glutamine	465 ± 73	427 ± 137	465 ± 81	406 ± 103
Histidine	56 ± 8	51 ± 15	78 ± 9[a]	72 ± 17
Glycine	209 ± 65	356 ± 193	674 ± 162[a]	825 ± 235
Threonine	87 ± 18	80 ± 33	180 ± 53[a]	174 ± 55
Alanine	237 ± 65	189 ± 52	497 ± 87[a]	418 ± 79
Arginine	103 ± 30	92 ± 18	252 ± 59[a]	222 ± 38
Tyrosine	58 ± 11	34 ± 12[b]	52 ± 13	30 ± 9[b]
Valine	183 ± 46	104 ± 26[b]	417 ± 105[a]	327 ± 54
Methionine	30 ± 8	24 ± 10	95 ± 12[a]	75 ± 7
Phenylalanine	63 ± 15	53 ± 12	131 ± 29[a]	126 ± 10
Isoleucine	54 ± 10	41 ± 12	177 ± 31[a]	162 ± 15
Leucine	116 ± 22	70 ± 21[b]	289 ± 44[a]	236 ± 21
Lysine	189 ± 26	133 ± 34[b]	370 ± 36[a]	282 ± 49

ESRD is end-stage renal disease. Mean ± SD.
[a]Indicates that both controls and ESRD increased ($P < 0.05$) during amino acid infusion in comparision with saline.
[b]$P < 0.05$ ESRD vs. control subjects.

from phenylalanine. Plasma concentrations of glutamine and glutamate were similar in both control and ESRD patients, although tyrosine concentrations remained lower in ESRD patients during both baseline state and during amino acid infusion.

Phenylalanine and tyrosine fluxes and phenylalanine conversion to tyrosine

Phenylalanine fluxes during saline and amino acid infusion (Figs. 1 and 2) were similar in ESRD and the control subjects (see Fig. 1). The amino acid–induced elevation of phenylalanine flux was mostly explained by the rate of appearance of phenylalanine from infused amino acids. The endogenous flux (appearance rate) of phenylalanine was reduced by amino acid infusion in both ESRD patients and controls [51 ± 2 vs. 43 ± 3 ($P < 0.05$) in controls and 49 ± 2 vs. 42 ± 2 ($P < 0.05$) in ESRD]. Although phenylalanine flux (representing body protein breakdown) was similar in ESRD and control groups, the ESRD group had a lower tyrosine flux during both baseline and during amino acid infusion (27.8 ± 1.3 μmol/kg FFM/hour^{-1} and 26.3 ± 1.3 vs. 32.3 ± 1.2 μmol/kg FFM/hour^{-1} and 31.5 ± 1.5 μmol/kg FFM/hour^{-1} for ESRD vs. control at baseline and after amino acid infusion). The conversion rate of phenylalanine to tyrosine was ~ twofold higher in the control subjects (4.07 ± 0.54 μmol/kg FFM/hour and 5.53 ± 0.86 μmol/kg FFM/hour before and during amino acid infusion, respectively) than the ESRD patients (2.05 ± 0.30 μmol/kg FFM/hour and 2.59 ± 0.52 μmol/kg FFM/hour, $P < 0.02$, ESRD vs. controls). After amino acid infusion, there was a significant increase in phenylalanine conversion rate in the control subjects ($P < 0.055$ using two-tailed t test and <0.03 using one-tailed test). Since the hypothesis was that phenylalanine infusion results in increased conversion of phenylalanine to tyrosine, it was considered to be significant (one-tailed t test). A similar increase was not found in the ESRD patients (P = NS).

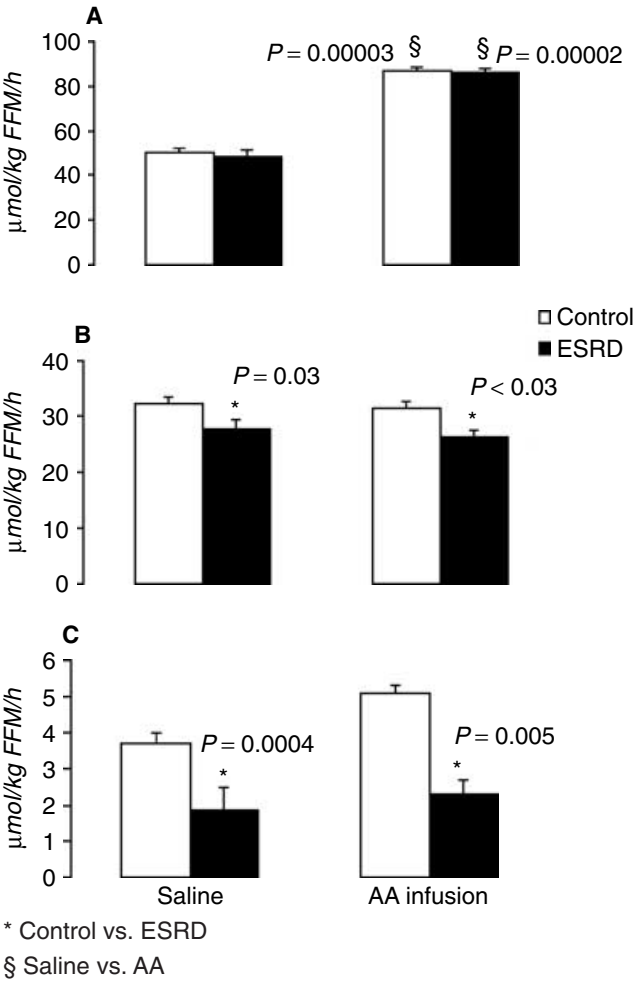

Fig. 1. Comparison of phenylalanine flux, tyrosine flux, and phenylalanine conversion to tyrosine (phenylalanine to tyrosine) during saline infusion and amino acid (AA) infusion. (*A*) Phenylalanine flux were not statistical significantly different between control and end-stage renal disease (ESRD) subjects and in both cases increase occurred with amino acid infusion. (*B*) Tyrosine flux was lower in ESRD patients than controls during saline and amino acid infusion. (*C*) Phenylalanine conversion to tyrosine was lower in ESRD patients than controls during saline and during amino acid infusion.

The ratios of phenylalanine conversion to tyrosine to phenylalanine flux and concentration and tyrosine/phenylalanine were significantly higher during the baseline and during amino acid infusion in the control subjects than in ESRD patients.

DISCUSSION

The current study was performed to test a hypothesis that there is an impairment of phenylalanine conversion to tyrosine, in patients with ESRD. The results

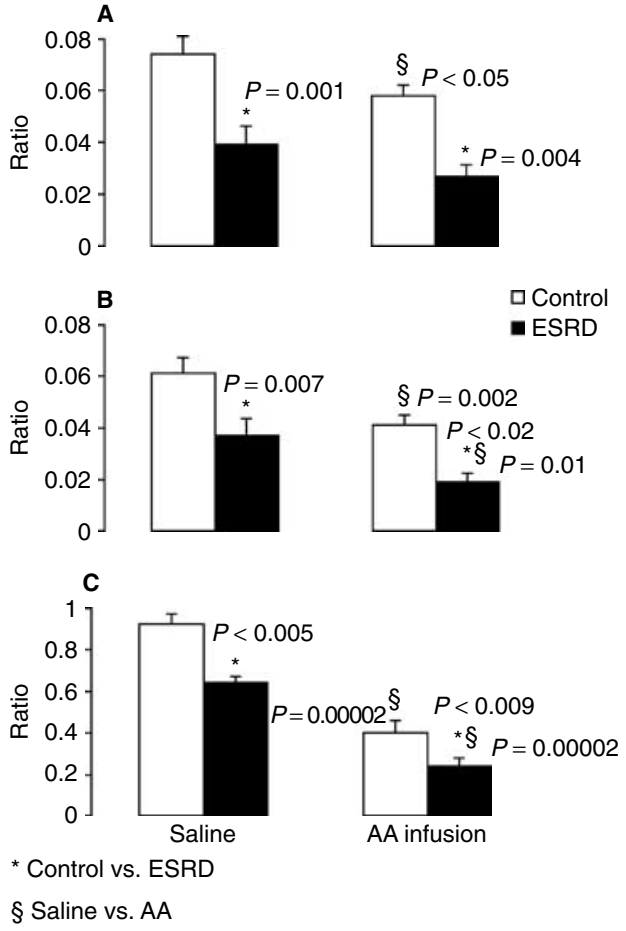

Fig. 2. Comparison of phenylalanine conversion to tyrosine as a function of phenylalanine flux and phenylalanine concentration and tyrosine/phenylalanine ration in control and end-stage renal disease (ESRD) subjects. (*A*) Phenylalanine to tyrosine/phenylalanine flux. (*B*) Phenylalanine to tyrosine/phenylalanine concentration. (*C*) Tyrosine/phenylalanine. All these parameters were lower in ESRD patients than in the control subjects.

demonstrated a substantial reduction in tyrosine production from phenylalanine despite a similarity of phenylalanine fluxes (representing protein breakdown) between the ESRD patients and the control subjects. When the conversion rate of phenylalanine to tyrosine is expressed as a function of phenylalanine flux or concentration, the ESRD patients were noted to have substantially lower ratios at the baseline and during the infusion of amino acid mixture. These results together support that ESRD patients are less efficient in hydroxylating phenylalanine to tyrosine.

Previous reports suggested that uremic patients have lower tyrosine levels and tyrosine phenylalanine ratio [3–6]. The demonstration in the current study that the conversion rate of phenylalanine to tyrosine is approximately 50% lower among patients with ESRD in comparison with healthy control subjects will explain the underlying mechanism for this reduced tyrosine levels in ESRD patients. There are three separate sources of tyrosine appearance in people—from diet, appearance of tyrosine from protein breakdown and conversion from phenylalanine. A similar level of phenylalanine flux in the fasted state indicates that the endogenous rates of appearance of amino acids from protein breakdown are similar in both controls. Therefore the low tyrosine levels in these patients should have other cause than a reduced appearance from protein breakdown. The phenylalanine conversion is the only other source of tyrosine. Previous studies demonstrated that kidney plays a pivotal role in maintaining the circulating tyrosine levels in humans [1] and that kidney contributes at least 50% to whole body phenylalanine conversion to tyrosine [1]. Even when exogenous amino acid infusions with high levels of phenylalanine were similar, the conversion of phenylalanine to tyrosine was increased only in control subjects but not in patients with ESRD. The reduced phenylalanine conversion to tyrosine is therefore likely the cause of low plasma concentrations of tyrosine in patients with ESRD, both at baseline and during infusion of an amino acid mixture. This observation is consistent with the previous report that kidney not only converts phenylalanine to tyrosine like liver, but unlike liver do not catabolize tyrosine [1]. Kidney, therefore, is a net contributor of tyrosine to the systemic circulation and this contribution of kidney did not appear to occur in ESRD patients. As a result, the contribution of tyrosine appearing from the conversion from phenylalanine is crucial to maintain normal plasma levels of tyrosine.

Plasma tyrosine concentrations were consistently lower in the ESRD patients, indicating that a chronically lower tyrosine production may reduce tyrosine pool. Hence, exogenous higher tyrosine requirement may be needed to maintain the proper amino acid compositions. Indeed, the relevance of this observation must be considered in the setting of high amino acids requirement in clinical conditions which are associated with possible higher tyrosine requirement (such as critical illness. Of note, tyrosine is the precursor for all catecholamines). The current data make a strong case for tyrosine replacement in people with ESRD. However, the tyrosine requirement has to be defined based on various levels of tyrosine needed to maintain normal tyrosine levels in the ESRD patients. This has been shown for example in premature children with low phenylalanine hydroxylase action [13] or during sepsis in children where tyrosine could be considered as an essential amino acid since production was not sufficient to cover tyrosine requirement [14]. Tyrosine's poor solubility may limit its availability in the traditional parenteral solutions and the current study suggests that the ESRD patients may require parenteral amino acid mixture with higher tyrosine concentration than people with normal kidney function.

Another important aspect on our observation is the ongoing losses of amino acids which occur with hemodialysis [15–19]. This may explain why phenylalanine did not accumulate as expected by a limited conversion to tyrosine. Indeed, among predialysis patients, it is quite usual to find elevated phenylalanine concentrations [6], which is consistent with a reduced conversion of this amino acid to tyrosine. It remains to be investigated whether many or any of the symptoms related to chronic renal failure is due to altered phenylalanine to tyrosine ratio. Phenylalanine toxicity may exist among patients with advanced chronic renal failure who have not yet initiated hemodialysis. The impact of reduced tyrosine levels in ESRD remains to be defined. Current estimation of amino acid requirements is based on studies performed in people with normal kidney function. Tyrosine balance was studied in healthy people with various doses of phenylalanine requirement [20]. Such studies can not be translated directly to people with ESRD to determine the requirement of tyrosine in their diet. The reduced muscle protein synthesis, especially of mitochondrial protein and myosin heavy chain in people with ESRD [7], resulting in muscle wasting and weakness may result from lack of compliment of all plasma amino acids in the free amino acid pool. [7]. This possibility is supported by recent report showing that insulin in combination with amino acids enhance muscle mitochondrial protein synthesis [21]. The present study raises several questions. Is tyrosine an essential amino acid in ESRD patients? Do we have to consider these patients similar to phenylketonuric patients from a diet end point? Finally, does renal transplant correct these abnormalities?

CONCLUSION

Phenylalanine conversion to tyrosine is substantially reduced in patients with ESRD, both in the basal state and after an amino acid mixture infusion. As a result, the end stage renal failure patients appear to be deficient of tyrosine during the postabsorptive state and during exogenous infusion of commercially available amino acid solutions. This metabolic impairment is subtle at the whole body level, but it may be rate limiting for protein synthesis or other functions in the body when amino acid requirements increase. In addition, an accumulation of phenylalanine in predialysis patients may be the consequence of a lower conversion of phenylalanine to tyrosine in these patients. Based on the current study, it is proposed that serious consideration should be given for tyrosine replacement for patients with end stage renal failure.

ACKNOWLEDGMENTS

We gratefully acknowledge the nursing and dietetics staff of the General Clinical Research Center (GCRC), Mayo Clinic Rochester, skillful technical assistance of Dawn Morse, Chan Boyer, and Mai Persson, staff of integrated physiology core (GCRC) and Immunochemistry Core Laboratory, and Melissa Aakre for secretarial help. The study was supported by grants from the National Institute of Health R01DK41973 and RR00585.

Reprint requests to K. Sreekumaran Nair, Endocrine Research Unit, Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905. E-mail: nair.sree@mayo.edu

REFERENCES

1. Moller N, Meek S, Bigelow M, *et al*: The kidney is an important site for *in vivo* phenylalanine-to-tyrosine conversion in adult humans: A metabolic role of the kidney. *Proc Natl Acad Sci USA* 97:1242–1246, 2000
2. Tessari P, Deferrari G, Robaudo C, *et al*: Phenylalanine hydroxylation across the kidney in humans. *Kidney Int* 56:2168–2172, 1999
3. Letteri JM, Scipione RA: Phenylalanine metabolism in chronic renal failure. *Nephron* 13:365–371, 1974
4. Pickford JC, McGale EH, Aber GM: Studies on the metabolism of phenylalanine and tyrosine in patients with renal disease. *Clin Chim Acta* 48:77–83, 1973
5. Young GA, Parsons FM: Impairment of phenylalanine hydroxylation in chronic renal insufficiency. *Clin Sci* 45:89–97, 1973
6. Jones MR, Kopple JD, Swendseid ME: Phenylalanine metabolism in uremic and normal man. *Kidney Int* 14:169–179, 1978
7. Adey D, Kumar R, McCarthy JT, Nair KS: Reduced synthesis of muscle proteins in chronic renal failure. *Am J Physiol* 278:E219–E225, 2000
8. Heymsfield SB, Smith R, Aulet M, *et al*: Appendicular skeletal muscle mass: Measurement by dual-photon absorptiometry. *Am J Clin Nutr* 52:214–218, 1990
9. Nair KS, Ford GC, Ekberg K, *et al*: Protein dynamics in whole body and in splachnic and leg tissues in type I diabetic patients. *J Clin Invest* 95:2926–2937, 1995
10. Meek SE, Persson M, Ford GC, Nair KS: Differential regulation of amino acid exchange and protein dynamics across splanchnic and skeletal muscle beds by insulin in healthy human subjects. *Diabetes* 47:1824–1835, 1998
11. Hill DW, Walter FH, Wilson TD, Stuart JD: High performance liquid chromatographic determination of amino acids in the picomole range. *Ann Chem* 51:1338–1341, 1979
12. Thompson GN, Pacy PJ, Merritt H, *et al*: Rapid measurement of whole body and forearm protein turnover using a [$^2H_5$] phenylalanine model. *Am J Physiol* 256:E631–E639, 1989
13. Kilani RA, Cole FS, Bier DM: Phenylalanine hydroxylase activity in preterm infants: Is tyrosine a conditionally essential amino acid. *Am J Clin Nutr* 61:1218–1223, 1995
14. Castillo L, Yu YM, Marchini JS, *et al*: Phenylalanine and tyrosine kinetics in critically ill children with sepsis. *Pediatr Res* 35:580–588, 1994
15. Lim VS, Kopple JD: Protein metabolism in patients with chronic renal failure: Role of uremia and dialysis. *Kidney Int* 58:1–10, 2000
16. Mitch WE: Malnutrition: A frequent misdiagnosis for hemodialysis patients. *J Clin Invest* 110:437–439, 2002
17. Pupim LB, Flakoll PJ, Brouillette JR, *et al*: Intradialytic parenteral nutrition improves protein and energy homeostasis in chronic hemodialysis patients. *J Clin Invest* 110:483–492, 2002
18. Mitch WE: Insights into the abnormalities of chronic renal disease attributed to malnutrition. *J Am Soc Nephrol* 13:S22–S27, 2002
19. Boirie Y, Broyer M, Gagnadoux MF, *et al*: Alterations of protein metabolism by metabolic acidosis in children with chronic renal failure. *Kidney Int* 58:236–241, 2000
20. Basile-Filho A, Beaumier L, El-Khoury AE, *et al*: Twenty-four-hour L-[1-^{13}C] tyrosine and L-[3,3-$^2H_2$] phenylalanine oral tracer studies at generous, intermediate, and low phenylalanine intakes to estimate aromatic amino acid requirements in adults. *Am J Clin Nutr* 67:640–659, 1998
21. Stump CS, Short KR, Bigelow ML, *et al*: Effect of insulin on human skeletal muscle mitochondrial ATP production, protein synthesis, and mRNA transcripts. *Proc Natl Acad Sci* 100:7996–8001, 2003