Z Ernährungswiss 37: 363–367 (1998)

U. Jung
M. Helbich-Endermann
R. Bitsch
S. Schneider
G. Stein

Are patients with chronic renal failure (CRF) deficient in Biotin and is regular Biotin supplementation required?

Ist bei chronisch niereninsuffizienten Patienten eine Biotin supplementation erforderlich

Summary In 23 patients with chronic renal failure (CRF), 23 patients on chronic intermittent hemodialysis treatment (DP), 22 patients after renal transplantation (RT) and 40 normal persons (NP), Biotin plasma levels and the urinary excretion were analysed and compared to the dietary Biotin intake. Unsupplemented DP had lower intake of Biotin than the CRF, RT, NP and DP with supplementation. DP excreted only 1.6–6.3 % of the daily intake as compared to 39.7 % in NP, 27.6 % in CRF and 24.3 % in RT.

In unsupplemented DP patients, Biotin plasma levels were elevated by 4 times and in supplemented patients by 6 times compared to NP. During hemodialysis treatment, the Biotin plasma level dropped by about 30 % in DP with and by 33 % in DP without vitamine supplementation. However, after 44 hours, the initial concentration was reached again in those receiving vitamine supplementation (99 % of basal level) and in DP without substitution (97 % of basal level).

Only in male DP significantly higher Biotin plasma levels before HD were detected irrespective of the supplementation dose as compared to female patients (30 μg and 300 μg Biotin after each dialysis session).

Biotin plasma concentration did not vary with respect to the underlying renal disease, the serum creatinine concentration and the length and frequency of dialysis treatment, including the type of dialyzer (low- vs high flux) used and the blood flow rate (QB 180–260 vs 270–280 vs 300 ml/min).

There were no major effects of the age of the patients (< 60 years vs > 60 years), the BMI, nicotine abuse, or alcohol intake on Biotin blood concentration.

Our results showed normal Biotin plasma levels which reflect a normal functional status and exclude a functional deficit, therefore there is no reason for a regular Biotin supplementation in patients with chronic renal failure.

Received: 17 September 1998
Accepted: 8 October 1998

U. Jung (✉) · S. Schneider · G. Stein
Department of Internal Medicine IV
University of Jena
Erlanger Allee 101
D-07740 Jena
Germany

M. Helbich-Endermann · R. Bitsch
Institute of Nutrition and Environment
University of Jena
Dornburger Strasse 29
D-07743 Jena
Germany

Zusammenfassung Bei 23 Patienten mit chronischer Niereninsuffizienz (CRF), 23 Dialysepatienten (DP), 22 Patienten nach Nierentransplantation (RT) und 40 Normalpersonen (NP) wurden die Biotin-Plasmaspiegel und die renale Ausscheidung über 24 Stunden gemessen und in Beziehung zur täglichen Biotinaufnahme mit der Nahrung gesetzt. Unsupplementierte DP zeigten niedrigere tägliche Biotinaufnahmen, als Patienten mit CRF, nach RT und als NP. Von der täglichen Biotinaufnahme schieden DP nur 1,6 %–6,3 % im Vergleich zu 39,7 % bei den NP, 27,6 % bei Patienten mit CRF und 24,3 % bei RT mit dem Urin aus.

Biotinsupplementierte DP wiesen 6fach und DP ohne zusätzliche Biotinzufuhr 4fach erhöhte Biotin-Plasmakonzentrationen gegenüber den NP auf. Während der Hämodialyse fiel die Biotin-Plasmakonzentration unter Biotinsubstitution um 30 % und ohne Biotinsubstitution um 33 % ab, alle Probanden erreichten nach 44 Stunden wieder die Ausgangsbiotinkonzentration.

Männliche DP zeigten unabhängig von der Höhe der Supplementierung (30 μg oder 300 μg Biotin)

vor der HD höhere Biotinkonzentrationen im Plasma.

Zwischen der Biotinkonzentration und der renalen Grunderkrankung, dem Serumkreatinin sowie der Dauer, Frequenz der Dialysebehandlung, den verwendeten Dialysatoren (low-, high flux) und der Blutflußrate (QB 180–260 vs 270–280 vs 300 ml/min) während der HD ließ sich kein Zusammenhang darstellen. Ebenso hatte das Alter der Patienten, der BMI und Nikotinabusus sowie die Alkoholaufnahme keinen Einfluß auf die Höhe der Biotin-Plasmakonzentration.

Aus diesen Ergebnissen ist zu schlußfolgern, daß eine regelmäßige Biotinsubstitution bei Patienten mit chronischer Niereninsuffizienz nicht notwendig ist.

Key words Biotin – chronic renal failure – hemodialysis – Biotin supplementation – Biotin concentration in plasma and urine

Schlüsselwörter Biotin – chronische Niereninsuffizienz – Hämodialyse – Biotinsubstitution – Biotinkonzentration im Plasma und im Urin

Introduction

In patients with chronic renal failure (CRF) and patients undergoing regular dialysis treatment (DP), a deficiency of water-soluble vitamins may occur (17) due to the following reasons:

1. The intake of fresh fruits and vegetables should be restricted due to the high potassium content (17, 20, 21).
2. During dialysis treatment, there are varying losses of vitamins according to the dialysis membrane used, the length of dialysis period and dietary habits of the patients.
3. Furthermore, the uremic dysfunction may affect the intestinal tract and result in a reduced gastrointestinal vitamin absorption.

The knowledge on metabolic alternations of the water-soluble vitamin Biotin by uremia itself and dialysis treatment is rather limited.

So far, there are controversial findings on the Biotin status in patients with CRF. De Bari et al. (5) and Descombes et al. (6) reported high Biotin plasma levels in patients on chronic hemodialysis for more than 5 years. On the other hand, Murray et al. (14) recommended Biotin supplementation for dialysis in order to avoid a suboptimal status. These controversial information promoted us to the following study.

Patients

In the present study, 23 patients with chronic renal failure (CRF), 23 patients on chronic intermittent hemodialysis treatment (DP), 22 patients after renal transplantation (RT) and 40 normal persons were included.

Chronic renal failure was defined with a creatinine serum level above 300 µmol/l. DP patients were treated with high-flux (n = 9, QB 250 ml/min, QD 500 ml/min) or with low flux dialyzer (n = 14, QB 250 ml/min, QD 500 ml/min). Blood- (QB) and dialysate flow (QD) are indepentent of dialyzer (low- vs high-flux). There are only differences in membrane cut off between the dialyzer (low- vs high-flux).

8 of the DP were supplemented with Dreisavit® (30 µg Biotin) and 15 patients with Ren-O-Vit® (300 µg Biotin) three times a week after dialysis session.

The basic anthropometric data of the patient groups are listed in Table 1.

Methods

In DP patients Biotin plasma concentrations were measured before and after dialysis session and again 44 hours later – before starting the next dialysis. Biotin dosis administered one hour before dialysis session started. IN CRF-, RT patients and in normal persons fasting Biotin levels were determined. The plasma levels and 24 hours urinary excretion rates were analysed during a vitamine supplementation period and 2 weeks after withdrawal. Aliquots of plasma and 24 hours urine samples were stored until analysis at -80 °C.

The Biotin concentration was determined by an enzyme linked immuno sorbent assay (ELISA Ridascreen® Biotin, r-Biopharm®). The principle of the test is based on the high affinity between Avidin and Biotin.

Peroxidase labelled Biotin competes with free Biotin of the sample for the Streptavidin binding followed by

Table 1 Basic data of patient groups (Mean ± SD)

	CRF	DP	RT	NP
n	23	23	22	40
Male/Female	17/6	13/10	17/5	20/20
Age (y)	58.5 ± 12.8	48.4 ± 14.0	46.9 ± 12.8	45.7 ± 10.9
Creatinine µmol/l	494 ± 203	862 ± 140	141 ± 80	84 ± 12

(CRF = chronic renal failure, DP = dialysis patients, RT = renal transplantation, NP = normal persons)

Table 2 Biotin intake, Biotin plasma concentration, and urine excretion, of the patient groups (Mean ± SD)

Patient groups	kcal/day	Biotin intake µg/1000 kcal	Biotin intake µg/day	Biotin plasma concentration ng/l	Urine volume l/day	Biotin urine excretion µg/day	(Percentage of) Biotin urine excretion in % of Biotin intake
	x ± SD	x ± SD	x ± SD	x ± SD	x ± SD	x ± SD	(%)
CRF	2035 ± 371	15 ± 4.8	30 ± 9.3	964 ± 343	2.3 ± 0.5	8.3 ± 5.3	27.7
DP without suppl.	1761 ± 418	11 ± 3.2	19 ± 5.3	1749 ± 541	0.6 ± 0.5	1.2 ± 0.8	6.3
DP with suppl.	1799 ± 434	63 ± 3.7	114 ± 57.4	2361 ± 689	0.5 ± 0.5	1.9 ± 2.3	1.7
RT	2386 ± 550	16 ± 6.5	37 ± 12.8	788 ± 375	2.4 ± 0.8	9.0 ± 6.3	24.3
NP	2212 ± 553	17 ± 2.9	37 ± 11.3	418 ± 368	1.0 ± 0.5	14.7 ± 12.1	39.7

(CRF = chronic renal failure, DP without suppl. = dialysis patients without supplementation, DP with suppl. = dialysis patients with supplementation, RT = renal transplantation, NP = normal persons)

oxidation of a simultaneously added organic dye in equimolar amounts by the activated enzyme and the absorption is measured at 450 nm. The oxidation is inversely proportional to the concentration of free Biotin in the sample. The detection limit of the ELISA was 60 ppt (60 ng/l plasma).

The dietary Biotin intake of all patients was carefully calculated on the basis of a 7 day record of food intake using a computer-based software (EBIS version 1.1).

Routine autoanalyzer methods were used to determine serum protein, albumin, urea and creatinine levels.

Statistics

The statistical procedures were performed using SPSS for Windows® V. 6.02. The statistical difference between values of two independent groups were calculated with Man-Whitney U Wilcoxon Rank Sum W Test. We used the t-Test for paired samples to describe the influence of vitamin supplementation on the plasma Biotin level. To describe the dependence of Biotin plasma levels on the Biotin intake and urine excretion we used the Spearman Rank Correlation. The level of significance was 0.05.

Results

In unsupplemented DP, a slightly reduced caloric intake but a significantly lowered supply of Biotin was observed compared to CRF, RT, NP and DP with supplementation (Table 2). Due to the low urine volume, DP showed a significant lower Biotin excretion as compared with CRF ($p = 0.045$), RT ($p = 0.02$) and NP ($p < 0.0001$). DP showed a urinary excretion of only 1.6 %–6.3 % of the daily intake as compared to 39.7 % in NP, 27.6 % in CRF and 24.3 % in RT (Table 2). The Biotin plasma levels in DP were elevated by 4 fold without and 6 fold with supplementation compared to NP.

Plasma levels of CRF and RT were 2 times higher than in NP (Table 2). RT had identical Biotin intake as NP but the Biotin plasma levels were twice as high (Table) 2).

There were significant differences between the Biotin plasma concentrations before and at the end of HD. During hemodialysis treatment, the Biotin plasma level decreased by about 30 % in DP with and 33 % in DP without vitamine supplementation. After 44 hours, the initial concentration was reached again in those receiving vitamine supplementation (99 % of basal level) and in DP without vitamine substitution (97 % of basal level).

The Biotin plasma level before HD without vitamine supplementation was 26 % lower than in patients with supplementation.

Only male DP showed significantly higher Biotin plasma levels before HD irrespective of supplementation with Ren-O-Vit® (300 µg) or Dreisavit® as compared to female (Table 3). This was the only significant difference between male and female patients. Supplementation with Ren-O-Vit® resulted in significantly higher Biotin plasma levels before HD, at the end of HD and 44 hours later as compared to patients without any supplementation and those treated with Dreisavit® (Table 4). No sex specific differences were found, too.

Furthermore, there were positive correlations between Biotin plasma levels before HD and Biotin intake ($r = 0.45$, $p = 0.033$) and between Biotin plasma concentration and Biotin excretion in the urine ($r = 0.62$, $p = 0.014$). No

Table 3 Biotin plasma concentrations of males and females before HD without and with supplementation of Ren-O-Vit® (300 µg Biotin) or Dreisavit® (30 µg Biotin) after each dialysis session

Sex	Biotin plasma concentration									
	n	Vitamin supplement Dreisavit (30 µg Biotin) x ± SD ng/l	n	Controls x ± SD ng/l		n	Vitamin supplement Ren-O-Vit (30 µg Biotin) x ± SD ng/l	n	Controls x ± SD ng/l	
Males	4	2532 ± 521	4	1553 ± 460	p = 0.02	9	2693 ± 588	9	1932 ±580	p = 0.018
Females	6	1587 ± 515	6	1381 ± 707	n.s.	4	2166 ± 705	4	1850 ± 342	n.s.

n.s. = no significant difference

correlation existed between Biotin intake and urinary excretion.

Biotin plasma concentrations did not vary with respect to the underlying renal disease, the serum creatinine concentration and the duration and frequency of dialysis treatment, including type of dialyzer (low- vs high-flux) used and the blood flow rate (QB 180–260 vs 270–280 vs 300 ml/min).

There were no major effects of the age of the patients (< 60 years vs > 60 years), the BMI, nicotine abuse, or alcohol intake on Biotin blood concentration.

Discussion

The discussion on the need of regular substitution of water-soluble vitamins in patients with CRF is controversial. An impaired metabolism as well as the loss of vitamins during hemodialysis is often associated with the limited intake of fresh fruits and vegetables and other dietary restrictions which could lead to a deficiency of water-soluble vitamins including Biotin (9, 13, 16, 18).

With special regard to Biotin, some authors do not recommend substitution (19), others advocate a supplementation, because Biotin seems to play an important role in the improvement and prevention of neurological disorders in DP (4, 14, 20, 21).

Our study shows that contrary to the caloric supply the Biotin intake of DP without any vitamine substitution is substantially reduced as compared to patients with CRF, RT and NP. The non-supplemented DP showed an intake which is lower than the estimated safe daily range of 30–100 µg (7, 15).

On the other hand, Biotin excretion is dependent on renal function. Therefore patients with normal renal function showed a high Biotin excretion rate in urine, whereas DP with residual urine volume had very low values independent of a vitamine supplementation.

Little is known about the Biotin loss during hemodialysis treatment. In our study, we observed a mean decrease of plasma levels by 30 % during hemodialysis. In patients receiving vitamine supplementation the decrease was about 30 % and in patients without vitamine substitution about 33 %, irrespective of the special mode of dialysis treatment (low- vs high-flux dialyzer) and blood flow rate.

In the DP, the plasma levels returned to their basic value 44 hours after dialysis session independent of vitamine supplementation. Whether a not well understood homoeostatic mechanism might be responsible for this restoration phenomenon of the Biotin plasma level remains to be elucidated.

A broad range of “normal” plasma Biotin levels in healthy adult persons of 0.2 up to 1.2 µg/l is reported by several authors (3). In patients with CRF, Allman et al.

Table 4 Biotin plasma concentrations before, at the end of hemodialysis (HD) and 44 hours later in patients without and with supplementation of Ren-O-Vit® and Dreisavit®

	n	Before HD x ± SD	End of HD x ± SD	44 h later x ± SD
Dreisavit® (30 µg Biotin)	8	2059 ± 696	1303 ± 493	2026 ± 757
Ren-O-Vit® (300 µg Biotin)	15	2482 ± 668	1807 ± 747	2450 ± 700
Without supplementation	23	1749 ± 542	1168 ± 489	1686 ± 588

reported on high plasma levels and an oversupplementation in DP. During vitamine supplementation, patients reached very high plasma levels which were not found in normal controls (1, 2).

In agreement with other studies, we found elevated Biotin plasma levels not only in patients with CRF and after RT, but also in DP with and without vitamine supplementation (5, 6, 10). The Biotin plasma concentration was neither dependent on the ethiology of renal disease nor on the time of dialysis treatment per week or the total duration of regular dialysis treatment. The patients age, the BMI, nicotine abuse or alcohol intake had also no influence on the Biotin plasma concentration of either of the patient groups.

We are not aware of a functional deficit despite normal plasma Biotin levels in DP.

The tissue pool in normal persons or any patient groups have so far not been determined. The influence of Biotin tissue pools is also corroborated by the observation, that plasma levels were in a normal range despite a suboptimal Biotin intake (15). Body pools, compartmentation, distribution between Biotin intake, excretion and loss during hemodialysis, possible enteropathic recirculation, and kinetics of distribution seem to affect the Biotin status in human.

According to our results, there is no reason for regular Biotin supplementation in patients with chronic renal failure.

Galley proofs as well as requests for reprints should be directed to Prof. Dr. R. Bitsch, Institute of Nutrition and Environment, Friedrich-Schiller-University Jena, Germany.

References

1. Allman MA, Tiller D, Truswell SA (1988) Vitamins and dialysis. Br Med J Clin Res Ed 296:134
2. Allman MA, Truswell SA, Tiller D, Stewart PM, Yau DF, Horvath JS, Duggin GG (1989) Vitamine supplementation of patients receiving hemodialysis. Med J Austra 150:130–134
3. Bitsch R, Bartel K (1994) Biotin wissenschaftliche Grundlagen, klinische Erfahrungen und therapeutische Einsatzmöglichkeiten. Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, p 11
4. Braguer D, Gallice P, Yatzidis H, Berland Y, Crevat A (1991) Restoration by Biotin of the *in vitro* microtuble formation inhibited by uremic toxins. Nephron 57:192–196
5. DeBari V, Frank O, Baker H, Needle M (1984) Water soluble vitamins in granulozytes, erythrozytes and plasma obtained from chronic hemodialysis patients. Am J Clin Nutr 39:410–415
6. Descombes E, Hanck AB, Fellay G (1993) Water soluble vitamins in chronic hemodialysis patients and need for supplementation. Kidney Int 43:1319–1328
7. Deutsche Gesellschaft für Ernährung (1991) Empfehlungen für Nährstoffzufuhr. Umschau-Verlag Frankfurt/Main, 5. Auflage, pp 132–134
8. Guilarte TR (1985) Measurement of Biotin levels in human plasma using radiometric-microbiological assay. Nutr Rep Int 31:1155–1163
9. Kopple JD, Swendseid ME (1975) Vitamin nutrition in patients undergoing maintenance hemodialysis. Kidney Int Suppl 7:79–84
10. Lasker N, Harvey A, Baker H (1963) Vitamin levels in hemodialysis and intermittent peritoneal dialysis. Trans Amer Soc Artif Int Organs, pp 51–56
11. Marumo F, Kamata K, Okubo M (1986) Deranged concentrations of water-soluble vitamins in the blood of undialysed and dialysed patients with chronic renal failure. Int J Artif Org 9:17–24
12. Mock DM, DuBoist DB (1986) A sequential, solid-phase assay for Biotin in physiologic fluids that correlates with expected Biotin status. Analytical Biochemestry 153:272–278
13. Mock DM, Malik MI (1992) Distribution of Biotin in human plasma: most of Biotin is not bound to protein. Am J Clin Nutr 56:427–432
14. Murray MA (1979) Vitamin and mineral needs of chronic hemodialysis patients. Dial Transplant 8:921–924
15. National Research Council (1989) Recommended Dietary Allowances, 10th edition. Nat Acad Press, Washington D.C., pp 165–169
16. Said HS, Redha R, Nylander W (1989) Biotin transport in human intestine: inhibition by anticonvulsant drugs. Am J Clin Nutr 49:127–131
17. Stein G, Sperschneider H, Koppe S (1985) Vitamin levels in chronic renal failure and need for supplementation. Blood Purif 3:52–62
18. Sweetman L, Nyhan W (1986) Inheritable Biotin-treatable disorders and associated phenomena. Ann Rev Nutr 6:317–343
19. Wolk R, Pharm D (1993) Mikronutrition in dialysis. Nutr Clin Pract 8:267–276
20. Yatzidis H, Koutsicos D, Agroyannis B, Papastephanidis C, Francos-Plemenos M, Delotala Z (1984) Biotin in the management of uremic neurologic disorders. Nephron 36:183–186
21. Yatzidis H, Koutsicos D, Alaveras AG, Papastephanidis C, Francos-Plemenos M (1981) Biotin for neurological disorders of uremia. N Engl J Med 305: 764