Kidney International, Vol. 43 (1993), pp. 1319–1328

Water soluble vitamins in chronic hemodialysis patients and need for supplementation

ERIC DESCOMBES, ALFRED B. HANCK, and GILBERT FELLAY

Dialysis Unit, Department of Medicine, Hôpital Cantonal, Fribourg, and Vitamin Research Laboratories, Hoffmann-La-Roche, Basel, Switzerland

Water soluble vitamins in chronic hemodialysis patients and need for supplementation. Forty-three patients on chronic hemodialysis who before the present study had only received a low-dose supplement of folic and ascorbic acid were studied prospectively for one year. After baseline values were obtained in month one, increasing doses of postdialysis vitamin supplements were prescribed for the vitamins which were found to be insufficient in order to determine the minimal amount of oral postdialysis supplement necessary to normalize vitamin levels. According to our results no systematic supplement was indicated for biotin, riboflavin or vitamin B12. For folic acid and vitamin C, supplementation with lower doses than those prescribed in many dialysis units allowed optimal vitamin levels in the majority of patients; 2 to 3 mg/week (300 to 400 μg/day) of folic acid and of 1000 to 1500 mg/week (150 to 200 mg/day) of vitamin C was considered sufficient. A severe pyridoxine deficiency was present in most (> 80%) unsupplemented patients, either as judged by pyridoxal-5-phosphate determinations in plasma or determination of specific enzyme activation in erythrocytes (EGOTo and α-EGOT); a postdialysis supplement of at least 100 to 150 mg/week of pyridoxine hydrochloride (> 15 to 20 mg/day) corrects this deficiency. The activity of the thiamine-dependent enzyme transketolase in erythrocytes (ETKo) was insufficient in 35% and marginal in 21% of the patients, while whole blood thiamine determined simultaneously in 10 of the ETKo-deficient patients was within the normal range. These results suggest that in uremia insufficient transketolase activity may be related to inhibition of the enzymatic system rather than to true vitamin deficiency. On a long-term basis a supplement of 200 to 300 mg/week of thiamine hydrochloride (30 to 45 mg/day) restored ETKo to satisfactory levels in most patients; whether this supplement is to be recommended warrants further studies.

The prescription of water-soluble vitamin supplements is routine practice in many dialysis units. Recently Allman et al reported that among ten major dialysis centers in Australia a supplement of thiamine, riboflavin, pyridoxine, ascorbic acid and nicotinamide was given in all and of folic acid in eight of the ten centers [1].

While fat soluble vitamins are known to accumulate in uremia [2, 3], deficiencies of different water soluble vitamins have been reported [3–16]. However, recent reports questioned the need for vitamin supplementation, based on the fact that nowadays hemodialysis (HD) patients are no longer on severely restricted diets, that dialysate losses may be lower than previously considered, and that recent studies in patients receiving systematic supplementation showed excessively high vitamin levels [17–25]. Literature data are therefore somewhat controversial. A review of literature data reveals two points which may lead to difficulties regarding a satisfactory comparison of the reported results. The first is related to the differences in analytical methods used to assess the vitamin status—either by microbiological, chemical or enzymatic assays in serum, plasma or erythrocytes—as these differences could explain some of the apparently contradictory conclusions reported in the literature. The second point is that in different studies the patients differ considerably with respect to whether or not supplementation had been previously prescribed, which may unquestionably influence the status of vitamin body stores.

As the patients treated at our center had previously received only a low-dose supplement of folic acid (< 420 μg/day) and ascorbic acid (< 85 mg/day), we decided to investigate them prospectively in order to: (a) study the status of water soluble vitamins in all the chronic HD patients attending the center and (b) determine the minimal amount of oral postdialysis supplement giving satisfactory vitamin levels in most of them.

Methods

Patients

All 43 HD patients attending our center at the beginning of the study were included. Informed consent was obtained from all. Their mean age was 59 ± 13 years (range 18 to 79) and 25 were male; they had been dialyzed for a mean of 38 months (range 1 to 171). The etiologies of CRF were glomerulonephritis ($N = 12$), polycystic kidney disease ($N = 8$), hypertensive ($N = 5$), diabetic ($N = 4$) and analgesics nephropathy ($N = 3$), chronic pyelonephritis ($N = 2$), obstructive nephropathy ($N = 2$) and miscellaneous ($N = 7$). Twenty-one patients were anuric, the remainder had a residual diuresis of 200 to 1600 ml/day. They were on a diet corresponding to a daily protein intake of 0.8 to 1.2 g/kg with individual recommendations concerning salt, potassium and water intake. Most patients were receiving a phosphate binder and about a third a supplement of 1-25-dihydroxy-cholecalciferol (Rocaltrol®). During the study period erythropoietin therapy was progressively introduced for the majority of patients. Only a few patients were taking drugs known to interact with absorption or metabolism of either of the studied vitamins.

Received for publication June 10, 1992
and in revised form January 19, 1993
Accepted for publication January 21, 1993

Table 1. Schedule of vitamin prescription

	Before	Month 1	2	3	4	5–8	9–12
Biotin	—	—	—	—	—	—	—
Folic acid	1	1	1	1	1	1	1
Vitamin B1	—	—	100	200	300	100	100
Vitamin B2	—	—	—	—	—	—	—
Vitamin B6	—	—	40	80	150	40	40
Vitamin B12	—	—	—	—	—	—	—
Vitamin C	200	200	200	200	200	200	500

Vitamin doses in mg were given orally after each dialysis session (2 or 3 times a week).

Dialysis therapy

The patients were dialyzed at our center either two ($N = 20$) or three ($N = 23$) times a week with short dialysis sessions; the mean weekly dialysis time was eight hours and 45 minutes (range 6 to 12 hours). All patients were dialyzed with a single-pass monitor using hollow fiber dialyzers, either cellulose acetate CA 210 ($N = 17$) and CF 23.08 ($N = 10$) or polyacrylonitrile Filtral 12 ($N = 3$) and Filtral 16 ($N = 13$). Non-recirculating dialysate flow was 500 ml/min, the mean blood flow 345 ± 30 ml/min and the mean ultrafiltration 2.10 ± 0.93 liters per session.

Vitamin prescription

Until the time of this study the patients attending our center had only been systematically receiving an oral postdialysis supplement of 1 mg of folic acid (Folvite®) and 200 mg of ascorbic acid (Redoxon®). As the patients were dialyzed two or three times per week, the weekly doses were therefore 2 to 3 mg (280 to 420 μg/day) and 400 to 600 mg (55 to 85 mg/day) respectively. No other vitamin supplements had ever been given regularly. Questioning all our patients prior to the study showed that five (12%) had taken irregular supplements of one or more of the studied vitamins during the months preceding the study.

During the first month of the study no changes were made in supplements; all but six of the patients had three determinations of each studied vitamin and the mean was used as the baseline value. As preliminary data had shown thiamine and pyridoxine deficiencies, a postdialysis supplement of these two vitamins was then given in progressive doses of 100, 200 and 300 mg of thiamine hydrochloride (Benerva®) and 40, 80 and 150 mg of pyridoxine hydrochloride (Benadon®; Table 1). The increase was made on a monthly basis and before each change a new vitamin determination was obtained at the end of months 2, 3 and 4. Six patients dropped out of the study in this period owing to transplantation (1), death (1), switching to peritoneal dialysis (1), refusal to continue the study (1) and transfer to another center (2).

After the four-month first part of the study, all the patients received the following doses of oral postdialysis supplement (Table 1): 1 mg of folic acid, 100 mg of thiamine hydrochloride, 40 mg of pyridoxine hydrochloride and 200 mg of ascorbic acid. At month 9, as our results had shown insufficient vitamin C plasma levels in many patients, the postdialysis vitamin C supplement was increased from 200 to 500 mg. Twelve months after the initial assessment a new control was performed. For vitamins B1, B2, B6 and C, two vitamin determinations were performed at a week's interval and the mean was considered. For folic acid and vitamin B12 a single determination was performed. Thirty-eight patients were attending our center at the end of the twelfth month: 27 belonged to the initial cohort and the remainders had entered our chronic dialysis program in the previous eight months.

Blood sampling and laboratory determinations

Vitamin B1 status was determined by the transketolase test (ETK) [26], vitamin B2 status by glutathion-reductase test (EGR) [27], and vitamin B6 by the glutamate-oxaloacetate transaminase test (EGOT) [28]. These tests are based on the estimation of vitamin-dependent red cell enzymes activity before and after *in vitro* vitamin supplement. For these determinations vitamin-dependent enzyme activity in erythrocytes was measured before (ETKo, EGRo and EGOTo) and after addition of the active form of the respective vitamin. The ratio of enzyme activity after/before vitamin addition was given as alpha-ratio (α-ETK, α-EGR and α-EGOT ratios) which is a measure of the coenzyme-free apoenzyme. If the patient has adequate stores of the vitamin, then most of the enzyme will have vitamin bound to it as a cofactor, and the increase in the activity on the addition of exogenous vitamin will be small, with an alpha-ratio value near to one. With low vitamin stores, however, there will be a large increase in the enzyme activity after exogenous vitamin addition and the alpha-ratio will be much higher than one. It should be noted that enzyme activity tests in erythrocytes measure needs for a vitamin in the form of the coenzyme of specific enzymes at the point of action, so they reflect the actual intracellular needs. Measuring concentrations in blood or other tissue stores are more indirect hints correlating to the real needs only if none of the factors influencing bioavailability at the point of action are compromised, correct apoenzyme and coenzyme-binding potency included.

Plasma biotin was determined by the method of Frigg and Brubacher [29], and plasma vitamin C by the method of Deutsch and Weeks [30] modified by Brubacher and Vuilleumier [31]. Pyridoxal-5-phosphate was determined in plasma by the method of Reinken [32]. Whole blood thiamine was determined according to Vuilleumier et al [33]. Plasma folic acid and vitamin B12 were determined by radioassay with the [^{125}I] folate/[^{57}C] vitamin B12 radioassay kit from Baxter Healthcare Corporation (which uses a purified intrinsic factor as binding protein for vitamin B12 determinations). Each determination was the mean of a duplicated run. Blood for vitamin determinations was always drawn before dialysis. For biotin, folic acid, vitamin B12 and vitamin C determinations the blood was placed into dry heparinized tubes, and for vitamins B1, B2, B6 and pyridoxal-5-phosphate determinations in ACD tubes. For vitamin C determinations the plasma was stabilized within an hour after drawing in a 5% metaphosphoric acid solution. Blood and plasma samples which were not analyzed rapidly were stored at −70°.

Statistical analysis

Group comparisons were made with the one way analysis of variance (ANOVA) and significance was considered for $P <$

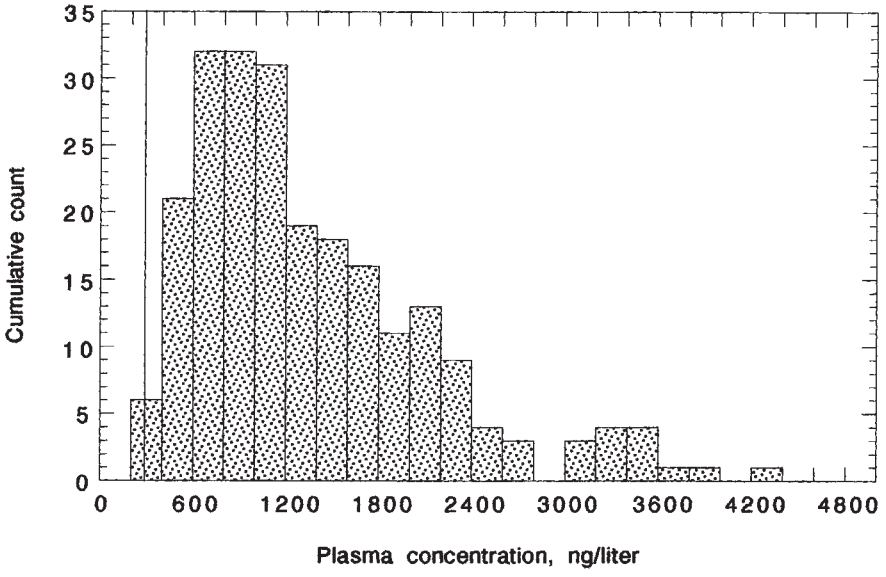

Fig. 1. *Distribution of plasma biotin determinations* (N = *229*). Normal value > 342 ng/liter.

0.05. Correlation coefficients were determined with the Pearson-Product Moment correlation method. The results are reported as mean ± standard deviation unless otherwise stated. A systematic analysis was made to statistically compare vitamin levels with respect to different parameters, namely: age, sex and weight of the patients, the etiology of renal failure, time on dialysis and dialysis duration, number of dialyses per week, type of filter used, the presence or not of residual diuresis and mean predialysis urea and creatinine values. Sometimes significant differences were found to be not easily interpretable due to several possible biases; only the results considered to be clearly not influenced by such bias are reported.

Results

Biotin

The mean value of all plasma biotin determinations performed during four months was 1340 ± 577 ng/liter (normal > 342 ng/liter). Figure 1 shows their distribution and that almost all determinations were either in the normal or high range. Subnormal values were found four times (1.7%). On the other hand, more than 70% of the patients had mean values higher than 1000 ng/liter, the highest values found in the general population. The patients on HD for more than five years had significantly higher levels than those having been dialyzed for shorter periods (1642 ± 873 vs. 1274 ± 740 ng/liter, $P < 0.01$) and anuric patients had significantly higher values than those with residual diuresis (1581 ± 620 vs. 1116 ± 857 ng/liter, $P < 0.01$).

Vitamin B12

The mean value of the vitamin B12 plasma concentrations during the study period was 551 ± 235 pg/liter (normal > 200 pg/liter, $N = 282$). Almost all individual values were in the normal range. Low values were observed seven times (2.5%), but no patient had a long-standing deficiency state, and three patients had mean values higher than 1000 pg/liter. Females had significantly higher values than males (636 ± 410 vs. 528 ± 280 pg/liter, $P < 0.05$).

Folic acid

During the study period the mean folic acid (FA) concentration was 10.41 ± 3.22 ng/liter in patients receiving 1 mg of FA twice a week and 12.09 ± 3.93 ng/liter in patients treated three times a week ($P < 0.05$; normal > 3 ng/liter). Figure 2 shows that most plasma values were in the optimal range between 5 and 15 ng/liter. Low values were observed in four samples (1.5%), but no patient had a long-standing deficiency state. Similarly, occasional values higher than 20 ng/liter were found, but no patient had mean values higher than 20 ng/liter. These data suggest that the supplement given was enough to maintain plasma levels within the optimal range in most patients.

Vitamin C

During the first four months of the study the mean plasma values were 5.68 ± 2.04 mg/liter in patients receiving 400 mg/week of vitamin C and 7.76 ± 3.87 mg/liter in patients receiving 600 mg/week ($P < 0.05$). The patients dialyzed for more than five years had significantly lower plasma concentrations than those having been dialyzed for shorter periods (5.63 ± 3.25 vs. 7.12 ± 4.08 mg/liter, $P < 0.05$); 12 patients (27%) were in the deficient range (< 4 mg/liter) whereas 11 others (25%) were in the low-normal range (4 to 6.2 mg/liter). In view of these results the postdialysis vitamin C supplement was increased from 200 to 500 mg in the second part of the study. Figure 3 compares the results obtained in month 1 and in month 12 and shows that the higher supplement led to a significant increase of the mean plasma levels ($P < 0.01$).

Independently of the dose of vitamin C, elderly patients (> 60 years) had lower plasma concentrations than the younger ($P < 0.01$). When the 500 mg supplement was introduced patients dialyzed with polyacrilonytrile filters had significantly lower plasma levels than those dialyzed with cellulose acetate filters (6.93 ± 3.61 vs. 11.09 ± 4.90 mg/liter, $P < 0.01$).

Thiamine (B1)

Figure 4 reports the results of erythrocyte transketolase determinations according to the different vitamin supplementation levels. Without supplementation the ETKo value was in

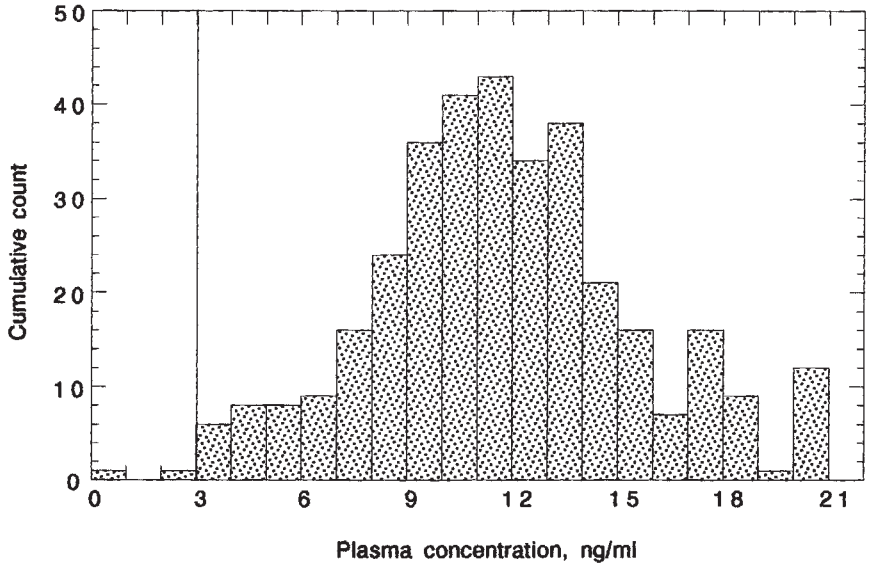

Fig. 2. *Distribution of plasma folic acid in patients receiving a supplement of 1 mg of folic acid twice or three times a week* (N = 269). Normal value > 3 ng/liter.

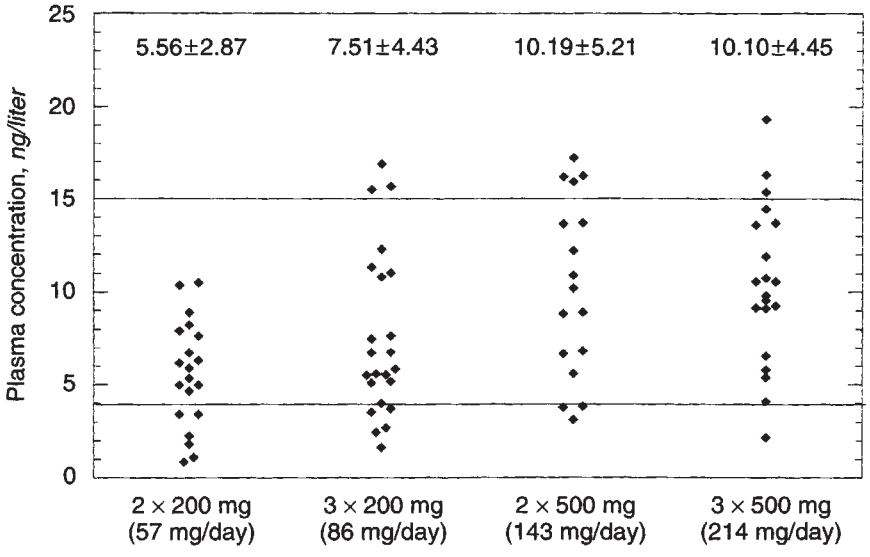

Fig. 3. *Vitamin C plasma levels in patients receiving 200 mg or 500 mg of ascorbic acid two or three times a week.* Mean values (± SD) are given at the top of each group. The area between the solid lines is the normal range.

the insufficient range in 15 patients (35%) and in the marginal range in nine (21%); the α-ETK was insufficient in two (5%) and marginal in seven (16%) patients. Thiamine supplementation rapidly normalized the α-ETK values in almost all patients, nevertheless, it took longer and higher vitamin doses to normalize ETKo values in the majority of patients. The patients dialyzed with polyacrilonytrile filters had significantly lower ETKo levels than those treated with acetate cellulose filters both without (72.6 ± 9.0 vs. 78.2 ± 12.7 U/liter, $P < 0.05$) and with vitamin supplementation (80.7 ± 11.2 vs. 84.4 ± 11.5 U/liter, $P < 0.05$).

Total whole blood thiamine was simultaneously measured in 10 patients who before supplementation had insufficient ($N = 8$) or marginal ($N = 2$) ETKo values. In these patients the mean thiamine concentration was normal (84.6 ± 15.7 nmol/liter, normal range = 60 to 112 nmol/liter) and only one patient, who was known for concomitant alcohol abuse, had insufficient levels. After supplementation the whole blood thiamine levels were higher than normal either with a supplement of 200 to 300 mg/week (145.9 ± 34.3 nmol/liter) or of 600 to 900 mg/week (156.1 ± 36.5 nmol/liter).

Riboflavin (B2)

The α-EGR index was normal in all patients during the whole study period. By contrast approximately 10% of the patients had insufficient and 25% marginal EGRo values. Females had significantly lower α-EGR and higher EGRo values compared to males ($P < 0.05$) and the same was found for older (> 60 years) compared to younger patients ($P < 0.01$). Patients on dialysis for more than five years had higher EGRo values ($P < 0.05$).

Pyridoxine (B6)

Figures 5 and 6 report the results of erythrocyte transaminase and pyridoxal-5-phosphate (PLP) determinations. These data

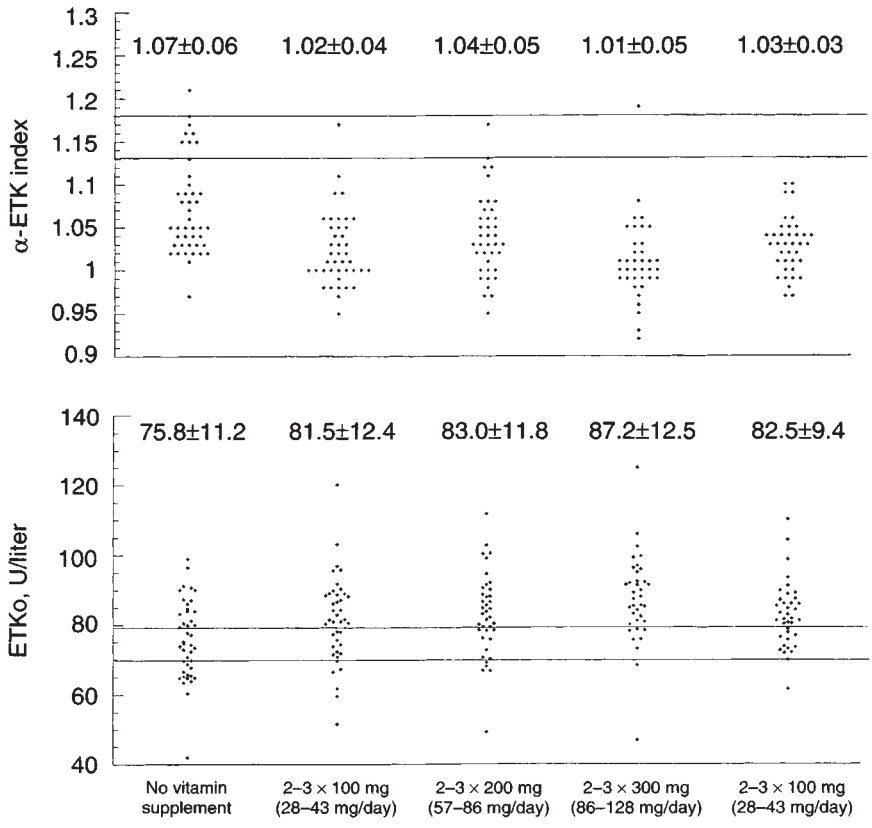

Fig. 4. *For vitamin B1, ETKo and alpha-ETK values are according to the weekly vitamin supplement.* Mean values (± SD) are given at the top of each group. The area between the solid lines represents the marginal zone.

show a severe vitamin B6 deficiency in the majority of unsupplemented patients. EGOTo was in the insufficient range in 33 patients (77%) and in the marginal range in five (12%); the α-EGOT index was insufficient in 28 (65%) and marginal in four (9%) patients, and PLP respectively in 35 (87%) and two (5%) patients. Females had significantly higher α-EGOT, lower EGOTo and lower PLP values than males ($P < 0.05$). The same pattern was found for anuric patients dialyzed three times a week compared to patients with a residual diuresis dialyzed twice a week ($P < 0.01$). Patients dialyzed for less than five years had higher PLP levels than those dialyzed for longer periods (1.62 ± 1.43 vs. 1.03 ± 0.72 μg/liter, $P < 0.05$).

When a vitamin supplement was given α-EGOT and PLP values rapidly normalized in a majority of patients with a vitamin supplement of 80 to 120 mg/week of pyridoxine hydrochloride, but a higher supplement was necessary to normalize EGOTo (up to 300 to 450 mg/week). With vitamin supplementation females still had significantly lower PLP levels than males (8.73 ± 0.4.69 vs. 11.42 ± 4.57 μg/liter, $P < 0.01$).

Clinical and laboratory data

Table 2 reports the development of some clinical, hematologic and laboratory data from the 27 patients who participated during the entire study period. There was a progressive increase of hemoglobin and erythrocyte concentrations due to the introduction of erythropoietin therapy. Significant findings concerning factors influencing vitamin levels have already been reported under each vitamin. It has to be noted that no significant correlation was found between the vitamin levels and the patients' weight, the etiology of the renal failure, the number and duration of the dialysis sessions or the mean predialysis urea concentrations.

Discussion

The prescription of a supplement of water soluble vitamins to HD patients is a routine procedure in many centers [1]. This practice is based on the results of several reports having shown low levels of various water soluble vitamins in chronic HD patients, and on the hypothesis that normal vitamin levels and normal vitamin function are a goal to be achieved [3–16]. The vitamin supplement is generally given orally, either on a daily basis or post-dialysis (only once after each dialysis). At our center it was prescribed on a postdialysis basis as this type of prescription is associated with good compliance and allows limiting the number of tablets given to patients who already have a high number of oral medications.

Rare cases of overt vitamin deficiency, such as scurvy, beriberi or Wernicke's encephalopathy, have been reported in HD patients [34–41]. However, vitamin deficiency should be considered a progressive process that begins long before the apparition of overt clinical manifestations, which are preceded by a depletion of body stores and biochemical alterations of cell metabolism [42, 43]. Not surprisingly therefore, deficiencies of water soluble vitamins in HD patients have been associated with several abnormalities such as depression of the immune response [44, 45], neuropathy [46–49], and impaired amino acid and lipid metabolism [50, 51], leukocyte hypersegmentation [52], and bone marrow megaloblastosis [53] or mild scurvy [54]. Nevertheless, there has been recent criticism concerning the need and/or the doses for supplementation [17–25]. This was

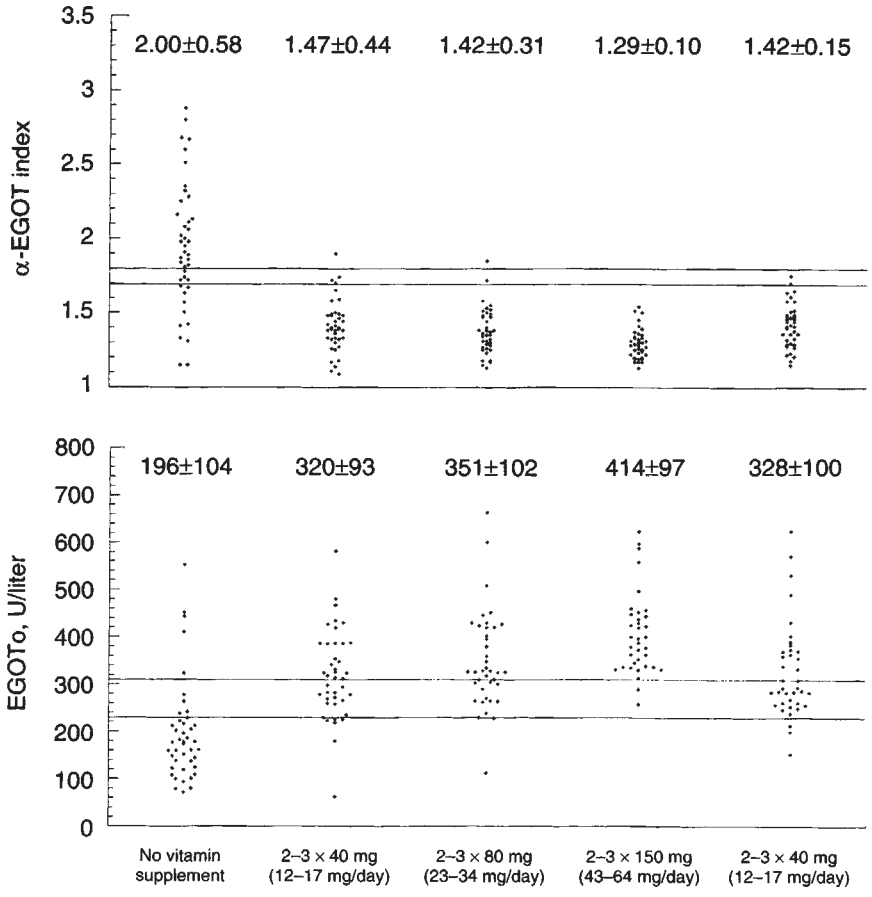

Fig. 5. *For vitamin B6, EGOTo and alpha-EGOT values are according to the weekly vitamin supplement.* Mean values (± SD) are given at the top of each group. The area between the solid lines represents the marginal zone.

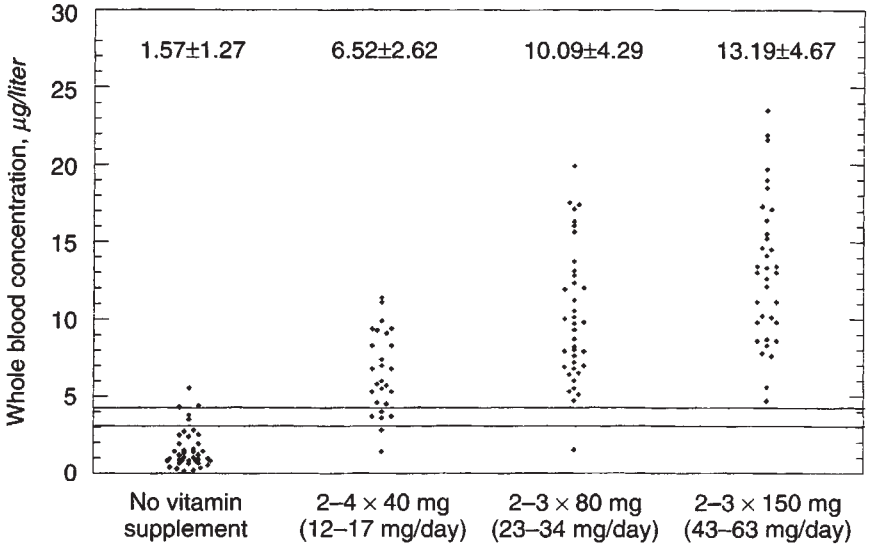

Fig. 6. *Pyridoxal-5-phosphate levels according to the weekly vitamin supplement.* Mean values (± SD) are given at the top of each group. The area between the solid lines represents the marginal zone.

related to the results of studies showing very high vitamin concentrations in supplemented patients, levels which would never be observed in patients with normal renal function [17, 19–25]. It was suggested that the assumption that water soluble vitamins are non-toxic is based on the fact that in normal persons the excess is excreted by the kidney [25] and that these supraphysiological vitamin levels could be associated with side effects, such as worsening of the uremia-associated secondary hyperoxalemia by ascorbic acid prescription [19–22].

Deficiency of water soluble vitamins in HD patients has been mainly attributed to either insufficient intake, excessive losses in dialysate, or impaired vitamin metabolism [3, 5]. Table 3

Table 2. Clinical, hematologic and laboratory data in 27 patients during the study year (predialysis values, except for body wt)

	Units and normal values	Month 1	Month 5	Month 12
Post-HD body wt	kg	61.7 ± 11.9	61.2 ± 12.4	61.9 ± 12.5
Systolic TA	mm/Hg	147 ± 15	147 ± 17	147 ± 16
Diastolic TA	mm/Hg	82 ± 6.9	83 ± 7.1	82 ± 7.6
Glucose	3.6–6.1 mmol/liter	6.1 ± 1.4	5.7 ± 1.5	5.7 ± 1.1
Urea	<7.8 mmol/liter	25.4 ± 3.8	26.7 ± 4.5	24.8 ± 3.6
Creatinine	<115 μmol/liter	842 ± 220	892 ± 225	862 ± 182
Uric acid	180–340 μmol/liter	288 ± 71	285 ± 86	256 ± 62[a,b]
Total proteins	65–80 g/liter	73.2 ± 5.1	73.2 ± 4.9	68.1 ± 5.2[a,b]
Cholesterol	2.5–6.2 mmol/liter	5.37 ± 1.03	4.96 ± 1.06[a]	5.52 ± 1.14[b]
HDL cholesterol	1.1–2.2 mmol/liter	1.16 ± 0.36	1.15 ± 0.40	1.21 ± 0.37
Triglycerides (N = 11)	1.1–2.3 mmol/liter	1.83 ± 0.56	1.56 ± 0.82	1.84 ± 0.45
Hemoglobin	>120 g/liter	92 ± 19	96 ± 17	105 ± 10[a]
Hematocrit	%	29 ± 4.8	30 ± 6.0	31 ± 3.2[a]
Erythrocytes	4.5–5.5 T/liter	2.97 ± 0.58	3.10 ± 0.64	3.30 ± 0.43[a]
MCV	78–96	93.1 ± 4.4	92.6 ± 5.8	92.7 ± 5.2
Thrombocytes	150–300 G/liter	216 ± 53	206 ± 66	232 ± 64
Leukocytes	4.0–10.0 G/liter	5870 ± 2060	5298 ± 1640	6167 ± 1892
% Segmented	%	61.6 ± 10.8	62.9 ± 10.9	59.1 ± 9.9[b]
Total lymphocytes	1.0–4.0 G/liter	1139 ± 462	1163 ± 574	1434 ± 672[a,b]

[a] $P < 0.05$ compared to initial values
[b] $P < 0.05$ compared to month 5

Table 3. Recommended dietary allowance for normal persons and calculated vitamin content of diets with different protein intake[a]

Vitamin	Units	Recommended dietary allowance	Daily protein intake *g/day* 40	60	80
Biotin	μg	100–200	13.40	17.80	15.80
Folic acid	μg	400	260	290	320
Vitamin B1	mg	1.2–1.6	0.60	1.00	1.10
Vitamin B2	mg	1.2–1.8	0.80	1.20	1.80
Vitamin B6	mg	1.6–2.2	1.00	1.20	1.50
Vitamin B12	μg	3	2.30	3.20	5.10
Vitamin C	mg	40–60	86	87	88

[a] Adapted from references [3, 5].

Table 4. Vitamin stores in humans[a]

Vitamin B12	3–5 years
Folic acid	1–1.5 years
Vitamin B2	3–4 months
Vitamin B6	3–4 months
Vitamin C	3–4 months
Vitamin B1	4–10 days

[a] Adapted from Schaeffer et al [6].

reports the vitamin content of different diets compared to the recommended dietary allowance. This table shows that for diets containing less than 40 grams of protein/day the vitamin intake can be quite below the recommended amounts, but that this difference is much less for diets containing 60 to 80 grams of protein/day. Limited data are available concerning vitamin losses during HD. Concerning vitamin C, Sullivan and Eisenstein reported that 80 to 280 mg are lost per procedure, which exceeds either daily intake and normal losses in urine [54, 55]. Gäng et al recovered only 70 to 135 μg of pyridoxal-5-phosphate in dialysate per procedure (7 hr HD), which corresponds to the urinary daily losses in normal persons [56]. Estimated folic acid losses range from 10 to 250 μg per procedure [52, 57–59], whereas Kesse-Elias et al were unable to detect vitamin B12 in dialysate [60].

According to these data, it appears that the intake of some vitamins may not be so low and losses in dialysate not so important as was previously considered. However, vitamin intake and dialysate losses *per se* do not give comprehensive information concerning the vitamin status at a given time, which also depends on the status of body stores. The amount of body stores varies greatly according to the vitamin, as shown in Table 4, and of course directly depends on the vitamin intake during the previous weeks or months. This point is important in the evaluation of some recent longitudinal studies performed in patients previously supplemented and in which the vitamin supplement was withdrawn—a situation quite different to the one of patients who have never received any vitamin supplement and who may present long-standing depleted stores. For example, in two studies in which vitamin C supplement was withdrawn the plasma levels fell from supraphysiological to normal or lower-normal values in a period of 12 to 24 months [61, 62], a finding in sharp contrast with the data of several papers concerning patients who had never been supplemented showing a severe vitamin C deficiency in most patients [7–10, 54, 55, 63–67]. Similar discrepancies also exist for folic acid when comparing the results from studies performed on never supplemented patients [4, 15, 16, 53, 57] to those in which the vitamin supplement was withdrawn [17, 58, 61, 68, 69]. Therefore, we consider that the question concerning the need for vitamin supplementation can more satisfactorily be answered by studies performed in patients who never received any extra supplement.

Another point that may contribute to vitamin deficiency is impaired metabolism [3, 5]. Some reports have shown evidence of abnormal metabolism of certain water soluble vitamins, particularly pyridoxine and thiamine. Ross et al showed in

CAPD patients that while total pyridoxine (including non-active metabolites of the vitamin) determined by microbiological methods was normal in all patients, pyridoxal-phosphate (PLP), the principal active form of the vitamin, was severely deficient in 63% [70]. This discrepancy suggested that in spite of normal vitamin levels the vitamin metabolism is impaired in uremia [70, 71]. Concerning thiamine, Sterzel et al showed *in vitro* that the thiamine-dependent enzyme transketolase is inhibited by dialyzable low-molecular-weight substance(s) [72]. The results obtained for thiamine in the present study in the patients with low ETKo activity in which whole body thiamine was simultaneously determined (and was normal) also suggest that an impaired metabolism (of the apoenzyme) rather than true vitamin (coenzyme) deficiency accounts for the abnormal transketolase activity.

According to previous discussion, it appears that the comparison of the results reported in the literature may be influenced by several factors, and has to be made cautiously considering, if possible, all the different elements influencing the vitamin status as well as its assessment. Furthermore, our data analysis shows that among the points discussed above, the status of each individual vitamin may depend on several elements as different as sex (riboflavin, pyridoxine, vitamin B12), age (riboflavin, vitamin C), residual diuresis (biotin, pyridoxine), time on dialysis (biotin, riboflavin, pyridoxine, vitamin C), or the type of filter used (thiamine, vitamin C), which makes data comparison even more complex.

Our results concerning biotin, riboflavin and vitamin B12 which show normal to high values in most of unsupplemented patients are in agreement with most reports in literature. For biotin previous investigators reported normal or high values [4, 63, 73]. Our data also show normal to supranormal levels, and the progressive increase of biotin levels with time on dialysis and the higher levels in anuric patients suggest that the epuration of this vitamin by the artificial kidney is less than that by the natural one. Normal to high total riboflavin levels were reported in plasma and blood cells [63, 74, 75]. Low EGRo activity was found in only 10% of our patients, a similar figure to that reported by Myldeck et al; this author reported that EGR values normalized with a daily supplement of 2 mg/day [76]. For vitamin B12 all investigators except two [47, 77] reported normal or high plasma levels compared to controls [4, 15, 16, 53, 61, 63, 69, 74, 78].

Folic and ascorbic acids have been classically supplemented in HD patients at doses up to 1 to 5 mg/day and 200 to 1000 mg/day, respectively [3, 5, 22, 79, 80]. These supplement doses were found to be associated with very high vitamin levels in several studies [17–24]. Our data agree with recent reports suggesting that lower doses than those previously prescribed are sufficient. In our study a postdialysis supplement of 2 to 3 mg/week (300 to 400 μg/day) of folic acid and of 1000 to 1500 mg/week (150 to 200 mg/day) of vitamin C allowed normal vitamin levels in the great majority of patients. Folic acid doses we propose approximate the daily dietary allowance, whereas for vitamin C the proposed doses are about three times higher. Recent works have pointed out that excessive vitamin C supplementation can worsen uremia-related secondary hyperoxalemia [19–22]. In this respect it is worth noting that with the supplementation given few patients had supranormal plasma values, within levels that according to the study of Pru et al, should not be associated with significant hyperoxalemia [20]. Although oxalic acid was not measured in our patients, we believe that the supplementation we propose should be safe in this respect. However, it should be noted that the question of whether different modalities of vitamin prescription (daily or postdialysis prescription) may have different effect on oxalic acid metabolism has not be addressed by the present study, and is still unanswered.

Because of impaired metabolism the appreciation of pyridoxine status in HD patients will depend on the method used to assess the vitamin status. While authors who measured total pyridoxine [61, 63, 69, 74] report normal to high concentrations, all authors who measured either pyridoxal-5-phosphate (PLP), the main active form of the vitamin, [11, 13, 48, 56] or transaminase erythrocyte activity [11, 12, 44, 45, 50, 81] concluded that unsupplemented HD patients present severe pyridoxine deficiency. Both PLP and transaminase determinations were performed concurrently in our study and show a severe deficiency of the active form of this vitamin. This deficiency can be corrected by pharmacological doses of 100 to 150 mg/week (> 15 to 20 mg/day) of pyridoxine hydrochloride, a dose higher than the 10 mg/day proposed by Kopple et al [12]. The reason for this difference is not clear, but may be related to the different mode of prescription of the vitamin supplement (daily vs. postdialysis prescription).

For thiamine, as for pyridoxine, the appreciation of the status depends on which parameter is studied. All authors except one [74] who determined total thiamine reported normal or even high levels in plasma, blood or leukocytes [61, 63, 82, 83]. By contrast, authors who studied transketolase activity report normal [84, 85] to low levels [72, 86, 87]. Our results show that despite normal α-ETK values in most patients and normal thiamine levels (in the 10 patients in whom this parameter was also measured), ETKo levels were low or marginal in 56% of our patients. Sterzel et al and Lonergan et al reported that the inhibition of transketolase activity could be reversed by dialysis but not by vitamin supplementation [72, 86]. Contrary to their conclusions our results show that transketolase activity may be normalized by pharmacological doses of thiamine hydrochloride (> 200 to 300 mg/week, 35 to 40 mg/day); whether this supplement is to be recommended cannot be stated from our data alone.

In conclusion, our results and the above discussion suggest that the vitamin status in an individual dialyzed patient depends on several different interacting factors including sex, age, actual vitamin intake, previous supplementation, dialysate losses, residual kidney function, time on dialysis and the type of filter used. Impaired metabolism also plays an important role, and further studies in this field are needed to understand better vitamin nutrition and metabolism in the uremic population.

Ideally vitamin prescription should be based on individual monitoring. However, due to the number of patients on dialysis, this procedure is both time consuming and too expensive; therefore, from a practical point of view a population-based approach should be considered. According to our results no systematic supplement seems to be indicated for biotin, riboflavin and vitamin B12. Supplementation of folic acid and vitamin C with lower doses than those previously prescribed in many dialysis units allows optimal vitamin levels in the majority of patients. A postdialysis supplement of 2 to 3 mg/week (300 to

400 μg/day) of folic acid and of 1000 to 1500 mg/week (150 to 200 mg/day) of vitamin C can be considered sufficient and safe. To correct pyridoxine deficiency a postdialysis supplement of at least 100 to 150 mg/week of pyridoxine hydrochloride (> 15 to 20 mg/day) should be considered. The prescription of 200 to 300 mg/week of thiamine hydrochloride (30 to 45 mg/day) normalizes erythrocyte transketolase activity in most HD patients in which this parameter is insufficient. Whether this supplement is to be recommended warrants further studies.

Acknowledgments

The authors thank Miss Marianne Thalmann and the nursing staff of the dialysis unit, as well as Miss Violette Hasler and the technicians of our laboratory for their skillful collaboration.

Reprint requests to Dr. Eric Descombes, Division of Nephrology, Centre Hospitalier Universitaire Vaudois, CH-1011, Lausanne, Switzerland.

References

1. ALLMAN MA, TRUSWELL AS, TILLER DJ, STEWART PM, YAU DF, HORVARTH JS, DUGGIN GG: Vitamin supplementation of patients receiving haemodialysis. *Med J Aust* 150:130–133, 1989
2. GENTILE MG, MANNA GM, D'AMICO G, TESTOLIN G, PORRINI M, SIMONETTI P: Vitamin nutrition in patients with chronic renal failure and dietary manipulation. *Contrib Nephrol* 65:43–50, 1988
3. STEIN G, SPERSCHNEIDER H, KOPPE S: Vitamin levels in chronic renal failure and need for supplementation. *Blood Purif* 3:52–62, 1985
4. LASKER N, HARVEY A, BAKER H: Vitamin levels in hemodialysis and intermittent peritoneal dialysis. *Trans Am Soc Artif Int Organs* 9:51–54, 1963
5. KOPPLE JD, SWENDSEID ME: Vitamin nutrition in patients undergoing maintenance hemodialysis. *Kidney Int* 7(Suppl 2):S79–84, 1975
6. SCHAEFFER G, QUIRIN H, KERN U, MIX A, NAKAYAMA T: Zur Frage der Vitaminzufuhr bei Dialysepatienten. *Akt Ernährung* 1:1–4, 1977
7. SULLIVAN JF, EISENSTEIN AB: Ascorbic acid depletion during hemodialysis. *JAMA* 220:1697–1699, 1972
8. SULLIVAN JF, EISENSTEIN AB, MOTTOLA OM, MITTAL AK: The effect of dialysis on plasma and tissue levels of vitamin C. *Trans Am Soc Artif Organs* 18:277–282, 1972
9. PÖNKÄ A, KUHLBÄCK B: Serum ascorbic acid in patients undergoing chronic hemodialysis. *Acta Med Scand* 213:305–307, 1983
10. PAPASTEPHANIDIS C, AGROYANNIS B, TZANATOS-EXARCHOU H, ORTHOPOULOS B, KOUTSICOS D, FRANGOS-PLEMENOS M, KALLITSIS M, YATZIDIS H: Re-evaluation of ascorbic acid deficiency in hemodialysed patients. *Int J Artif Organs* 10:163–165, 1987
11. STONE WJ, WARNOCK LG, WAGNER C: Vitamin B6 deficiency in uremia. *Am J Clin Nutr* 28:950–957, 1975
12. KOPPLE JD, MERCURIO K, BLUMENKRANTZ MJ, JONES MR, TALLOS J, ROBERTS C, CARD B, SALTZMAN R, CASCIATO DA, SWENDSEID ME: Daily requirement for pyridoxine supplements in chronic renal failure. *Kidney Int* 19:694–704, 1981
13. LACOUR B, PARRY C, DRÜEKE T, TOUAM M, KREIS H, BAILLY M, DURAND D: Pyridoxal-5'-phosphate deficiency in uremic undialyzed, hemodialyzed and non-uremic kidney transplant patients. *Clin Chim Acta* 127:205–215, 1983
14. GUZMAN FJ, GONZALEZ-BUITRAGO JM, VELA R, CAVA F, DE CASTRO S: Vitamin B6 status in uremia. *Klin Wschr* 68:183–186, 1990
15. FISCHER JT, PETERS W: Folic acid levels in patients with compensated renal failure and during long-term hemodialysis. *Dtsch Med Wschr* 102:1808–1813, 1977
16. MINAR E, ZAZGORNIK J, BAYER PM, LANSCHUTZER H, MENGELE K, MAROSI L: Hematologic changes in patients under long-term hemodialysis and hemofiltration treatment with special reference to serum concentrations of folic acid and vitamin B12. *Schweiz Med Wschr* 114:48–53, 1984
17. CUNNINGHAM J, SHARMAN VL, GOODWIN FJ, MARSH FP: Do patients receiving hemodialysis need folic acid supplement? *Br Med J* 282:1582, 1981
18. SWAISON CP, WINNEY RJ: Do dialysis patients need extra folate? *Lancet* 1(Jan 29):239, 1983
19. BALCKE P, SCHMIDT P, ZAZGORNIK J, KOPSA H, HAUBENSTOCK A: Ascorbic acid aggravates secondary hyperoxalemia in patients on chronic dialysis. *Ann Int Med* 101:344–345, 1984
20. PRU C, EATON J, KJELLSTRAND C: Vitamin C intoxication and hyperoxalemia in chronic hemodialysis patients. *Nephron* 39:112–116, 1985
21. ONO K: Secondary hyperoxalemia caused by vitamin C supplementation in regular hemodialysis patients. *Clin Nephrol* 26:239–243, 1986
22. ONO K, HISASUE Y, MORIMATSU M: Should vitamin C supplementation be restricted in regular hemodialysis patients? *Trans Am Soc Artif Organs* 32:111–113, 1986
23. LEUNG ACT, HENDERSON IS, MAHARAJ D, THOMSON G: Excessive accumulation of folic acid in uremic patients on dialysis. *Dial Transplant* 14:575–577, 1985
24. MANGIAROTTI G, CANAVESE C, SALOMONE M, THEA A, PACITTI A, GAIDO M, CALITRI V, PELIZZA D, CANAVERO W, VERCELLONE A: Hypervitaminosis B12 in maintenance hemodialysis patients receiving massive supplementation of vitamin B12. *Int J Artif Organs* 9:417–420, 1986
25. ALLMAN MA, TILLER D, TRUSWELL AS: Vitamin and dialysis. *Br Med J* 296:134, 1988
26. SCHOUTEN H, STATIUS VAN EPS LW, STRUYKER BOUDIER AM: Transketolase in blood. *Clin Chim Acta* 10:474–476, 1964
27. GLAZLE D, KÖRNER WF, CHRISTALLER S, WISS O: Method for the detection of a biochemical riboflavin deficiency. Stimulation of NADPH2-dependent glutathione reductase from human erythrocytes by FAD *in vitro*. Investigations on the vitamin B2 status in healthy people and geriatric patients. *Int J Vit Res* 40:166–183, 1970
28. KIRKLAND J, TRINDLER P: Serum glutamic-oxalacetic transaminase. *Proc Assoc Clin Biochem* 3:154, 1964
29. FRIGG M, BRUBACHER G: Biotin deficiency in chicks fed with a wheat-based diet. *Int J Vit Nutr Res* 46:314–321, 1976
30. DEUTSCH MJ, WEEKS CE: Microfluorometric assay for vitamin C. *J Assoc Anal Chem* 48:1248–1256, 1965
31. BRUBACHER G, VUILLEUMIER JP: Vitamin C, in *Clinical Biochemistry, Principles and Methods*, edited by CUTTINS HC, ROTH M, Berlin, W. de Gruyter, 1974, pp. 989–997
32. REINKEN L: Eine Mikromethode zur Bestimmung von Pyridoxal-5-Phosphat in serum mittls Decarboxylierung von L-Tyrosin-1-14C. *Int Z Vitam-Ernähr Forsch* 42:476–481, 1972
33. VUILLEUMIER JP, KELLER HE, RETTENMAIER R, HUNZIKER F: Clinical chemical methods for the routine assessement of the vitamin status in human populations. Part II: the water-soluble vitamins B1, B2 and B6. *Int J Vit Nutr Res* 53:359–371, 1983
34. IHLE BU, GILLIES M: Scurvy and thrombocytopathy in a chronic hemodialysis patient. *Austr N Z J Med* 13:523, 1983
35. GOTLOIB L, SERVADIO C: A possible case of beriberi heart failure in a chronic hemodialyzed patient. *Nephron* 14:293–298, 1975
36. LOPEZ RI, COLLINS GH: Wernicke's encephalopathy. A complication of chronic hemodialysis. *Arch Neurol* 18:248–259, 1968
37. FARIS AA: Wernicke's encephalopathy in uremia. *Neurology* 22: 1293–1297, 1972
38. EBELS EJ: Underlying illness in Wernicke's encephalopathy. Analysis of possible causes of under-diagnosis. *Eur Neurol* 12:226–228, 1974
39. JAGADHA V, DECK JH, SMYTH HS: Wernicke's encephalopathy in patients on peritoneal dialysis or hemodialysis. *Ann Neurol* 2:78–84, 1987
40. KIKUCHI H: The influence of hemodialysis on vitamin B1 levels. (abstract) *Proc Eur Dial Transplant Assoc* 27:143, 1990
41. DESCOMBES E, DESSIBOURG CA, FELLAY G: Acute encephalopathy due to thiamine deficiency (Wernicke's encephalopathy) in a chronic hemodialyzed patient: A case report. *Clin Nephrol* 35:171–175, 1991

42. MARKS J: *The Vitamins. Their Role in Medical Practice*. Lancaster, MTP Press Limited, 1985
43. GABY SK, BENEDICH A, SINGH NV, MACHLIN LJ: *Vitamin Intake and Health. A Scientific Review*. New York, Marcel Dekker Inc, 1991
44. DOBBELSTEIN H, KÖRNER WF, MEMPEL W, GROSSE-HILDE H, EDEL H: Vitamin B6 deficiency in uremia and its implications for the depression of immune responses. *Kidney Int* 5:233–239, 1974
45. CASCIATO DA, MCADAM LP, KOPPLE JD, BLUESTONE R, GOLDBERG LS, CLEMENTS PJ, KNUTSON DW: Immunologic abnormalities in hemodialysis patients: Improvement after pyridoxine therapy. *Nephron* 38:9–16, 1984
46. RONSTAND SG: Vitamin B12 deficiency: A potential factor in the persistance of neuropathy during hemodialysis. (abstract) *Kidney Int* 6:90A, 1974
47. ROSTAND SG: Vitamin B12 levels and nerve conduction velocities in patients undergoing maintenance hemodialysis. *Am J Clin Nutr* 29:691–697, 1976
48. TEEHAN BP, SMITH LJ, SIGLER MH, GILGORE GS, SCHLEIFER CR: Plasma pyridoxal-5-phosphate levels and clinical correlations in chronic hemodialysis patients. *Am J Clin Nutr* 31:1932–1936, 1978
49. TANIGUCHI H, EJIRI K, BABA S: Improvement of autonomic neuropathy after mecobalamin treatment in uremic patients on hemodialysis. *Clin Ther* 9:607–614, 1987
50. KLEINER MJ, TATE SS, SULLIVAN JF, CHAMI J: Vitamin B6 deficiency in maintenance dialysis patients. Metabolic effect of repletion. *Am J Clin Nutr* 33:1612–1619, 1980
51. WOLFSON M, KOPPLE JD: The effects of vitamin B6 deficiency in chronically azotemic and sham-operated rats. *Kidney Int* 32(Suppl 22):S162–S166, 1987
52. SIDDIQUI J, FREEBURGER R, FREEMAN RM: Folic acid, hypersegmented polymorphonuclear leukocytes and the uremic syndrome. *Am J Clin Nutr* 23:11–16, 1970
53. HAMPERS CL, STREIFF R, NATHAN DG, SNYDER D, MERRILL JP: Megaloblastic hematopoiesis in uremia and patients on long-term hemodialysis. *N Engl J Med* 276:551–554, 1967
54. SULLIVAN JF, EISENSTEIN AB: Ascorbic acid depletion in patients undergoing dialysis. *Am J Clin Nutr* 23:1339–1346, 1970
55. SULLIVAN JF, EISENSTEIN AB: Ascorbic acid depletion in patients undergoing chronic hemodialysis. *J Lab Clin Med* 74:1017, 1969
56. GÄNG V, SCHULZ RJ, KULTZ J, HEILAND A: Vitamin B6 deficiency and substitution in chronic uremia. *Klin Wschr* 53:335–338, 1975
57. MACKENZIE JC, FORD JE, WATERS AH, HARDING N, CATTELL WR, ANDERSON BB: Erythropoiesis in patients undergoing regular dialysis treatment without transfusion. (abstract) *Proc Eur Dial Transplant Assoc* 5:172, 1968
58. ANDERSEN KEH: Folic acid status of patients with chronic renal failure maintained by dialysis. *Clin Nephrol* 8:510–513, 1977
59. MATESANZ R, VILA T, QUEREDA C, AVILA C, ONAINDIA JM, LOSADA M, NAVARRO JL, ORTUNO J: Folic acid supplements in hemodialysis patients. (abstract) *Proc Eur Dial Transplant Assoc* 18:72, 1981
60. KESSE-ELIAS M, ZIROYANNIS P, TJANETOU C, ALEVIZOU-TERZAKI V, GYFTAKI E: Estimation of vitamin B12 and its carrier proteins (transcobolamins) in dialysate and serum of patients on hemodialysis. (abstract) *Kidney Int* 26:613, 1984
61. RAMIREZ G, CHEN M, BOYCE HWJ, FULLER SM, GANGULY R: Longitudinal follow-up of chronic hemodialysis patients without vitamin supplementation. *Kidney Int* 30:99–106, 1986
62. ONO K: The effect of vitamin C supplementation and withdrawal on the mortality and morbidity of regular hemodialysis patients. *Clin Nephrol* 31:31–34, 1989
63. DEBARI VA, FRANK O, BAKER H, NEEDLE MA: Water soluble vitamins in granulocytes, erythrocytes, and plasma obtained from chronic hemodialysis patients. *Am J Clin Nutr* 39:410–415, 1984
64. KASPER H, MUSKAT E, MUELLER K: Untersuchungen zur Ascorbinsäurebedarfsdeckung bei chronischer Niereninsuffizienz und ihre Beeinflussung durh die extracorporale Hämodialyse. *Klin Wschr* 48:946–947, 1970
65. FROESE P, HERMEYER J, KESSEL M: Ascorbic acid content in plasma and in leukocytes in patients undergoing maintenance hemodialysis. *Klin Wschr* 55:1173–1174, 1977
66. KELLEHER J, MASCIE-TAYLOR BH, DAVISON AM, BRUCE G, LOSOWSKY MS: Vitamin status in patients on maintenance hemodialysis. *Int J Vit Nutr Res* 53:330–337, 1983
67. TOMSON CR, CHANNON SM, PARKINSON IS, MCARDLE P, QURESHI M: Correction of subclinical ascorbate deficiency in patients receiving dialysis: Effects on plasma oxalate, serum cholesterol, and capillary fragility. *Clin Chim Acta* 180:255–264, 1989
68. VANPELLICOM J, LINS RL, ELSEVIERS M, DEBROE ME: Influence of folic acid and vitamin B12 supplementation on anemia of hemodialysis patients. (abstract) *Kidney Int* 26:607, 1984
69. WANDEL E, MARX M, WAEBER M, MAYET M, DUMANN H, KOLBE H, EHRENTHAL W, KÖLHER H: Vitamin supplementation in hemodialysis patients: 6 months follow-up. (abstract) *Proc Eur Dial Transplant Assoc* 24:144, 1987
70. ROSS EA, SHAH GM, REYNOLDS RD, SABO A, PICHON M: Vitamin B6 requirements of patients on chronic peritoneal dialysis. *Kidney Int* 36:702–706, 1989
71. SPANNUTH CL, WARNOCK LG, WAGNER C, STONE WJ: Increased plasma clearance of pyridoxal-5′-phosphate in vitamin B6-deficient uremic man. *J Lab Clin Med* 90:632–637, 1977
72. STERZEL RB, SEMAR M, LONERGAN ET, TRESER G, LANGE K: Relationship of nervous tissue transketolase to the neuropathy in chronic uremia. *J Clin Invest* 50:2295–2304, 1971
73. LIVANIUO E, EVANGELATOS GP, ITHAKOSSIOS DS, YATZIDIS H, KOUTSICOS DC: Serum biotin in patients undergoing chronic hemodialysis. *Nephron* 46:331–332, 1987
74. MARUMO F, KAMATA K, OKUBO M: Deranged concentrations of water-soluble vitamins in the blood of undialyzed and dialyzed patients with chronic renal failure. *Int J Artif Organs* 9:17–24, 1986
75. ITO T, NIWA T, MATSUI E, OHISHI N, YAGI K: Plasma flavin levels of patients receiving long-term hemodialysis. *Clin Chim Acta* 39:125–129, 1972
76. MYDLÍK M, DERZSIOVÀ K, VÀLEK A, TAKÀC M: Vitamins B1, B2 and B6 status in chronic renal failure. (abstract) *Proc Eur Dial Transplant Assoc* 19:102, 1982
77. BASTOW MD, WOODS HF, WALLS J: Persistent anemia associated with reduced serum vitamin B12 levels in patients undergoing regular hemodialysis therapy. *Clin Nephrol* 11:133–135, 1979
78. HEILMANN E, POBLOZKI F, MÜLLER H, BUSCH G, LOEW H: Verhalten von Vitamin B12 in Serum bei Hämodialysepatienten. *Med Welt* 27:2280–2281, 1976
79. MURRAY MA: Vitamin and mineral needs of chronic hemodialysis patients. *Dial Transplant* 8:921–924, 1979
80. SKOUTAKIS VA, ACCHIARDO SR, MEYER MC, HATCH FE: Folic acid dosage for chronic hemodialysis patients. *Clin Pharm Ther* 18:200–204, 1975
81. BALCKE P, SCHMIDT P, ZAZGORNIK J, KOPSA H: Intraerythrocyte GOT-activity in uremia and influence of pyridoxine treatment. *Klin Wschr* 61:859–863, 1983
82. NIWA T, ITO T, MATSUI E: Plasma thiamine levels with hemodialysis. *JAMA* 218:885–886, 1971
83. NIWA T, ITO T, MATSUI E, ISHIGURO I, KUWATA S: Plasma level and transfer capacity of thiamine in patients undergoing long-term hemodialysis. *Am J Clin Nutr* 28:1105–1109, 1975
84. KOPPLE JD, DIRIGE OV, JACOB M, WANG M, SWENDSEID ME: Transketolase activity in red blood cells in chronic uremia. *Trans Am Soc Artif Organs* 18:250–256, 1972
85. WARNOCK LG, CULLUM UX, STOUDER DA, STONE WJ: Erythrocyte transketolase activity in dialysis patients with neuropathy. *Biochem Med* 10:351–359, 1974
86. LONERGAN ET, SEMAR M, STERZEL RB, TRESER G, NEEDLE MA, VOYLES L, LANGE K: Erythrocyte transketolase activity in dialyzed patients. A reversible metabolic lesion of uremia. *N Engl J Med* 284:1399–1403, 1971
87. KURIJAMA M, MIZUMA A, YOKOMINE R, IGATA A, OTUJI Y: Erythrocyte transketolase in uremia. *Clin Chim Acta* 108:167–177, 1980