Relationships between muscle K, Mg and Na content and acute hypophosphatemia (AH) with and without phosphate depletion in man*)

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Zusammenfassung

Die Gehalte der Skelettmuskulatur an Na, K, Mg, Cl und H_2O wurden bei Patienten mit AH nach Phosphat-armer parenteraler Ernährung mit und ohne Verarmung des Muskel-P gemessen. Es fanden sich Anstiege von extrazellulärem H_2O und Cl, ein Anstieg von extrazellulärem Na und eine Abnahme von intrazellulärem K und Mg. Diese Veränderungen fanden sich signifikant verstärkt ausgeprägt bei Patienten mit Muskel-P-Verarmung nach vorangegangener Malnutrition, obwohl sie auch nachweisbar bei gut ernährten Patienten mit AH, aber normalem Muskel-P-Gehalt waren. Die möglicherweise zugrunde liegenden Mechanismen werden diskutiert.

Summary

Muscle Na, K, Mg, Cl and H_2O composition was measured in patients with AH due to P-deficient total parenteral nutrition both with and without muscle P depletion. Increase of muscle extracellular H_2O and Cl and intracellular Na and decrease of K and Mg were found; these changes were significantly more pronounced in subject with muscle P depletion due to previous malnutrition, even if they were present also in wellnourished subjects with AH but normal muscle P content. Possible mechanisms are discussed.

Résumé

La composition du muscle en Na, K, Mg et Cl a été déterminée chez des patients avec une hypophosphatémie aiguë due à une nutrition parentérale totale déficitaire en Mg, à la fois avec et sans déplétion du P musculaire. Il a été trouvé un accroissement de H_2O et de Cl extracellulaires et du Na intracellulaire dans le muscle, et une réduction du K et du Mg, ces modifications ont été significativement plus marquées chez le sujet avec une déplétion du P musculaire due à une malnutrition antérieure, même si elles sont présentes aussi chez des sujets bien nourris avec une hypophosphatémie, mais avec une teneur normale du P musculaire. Discussion des mécanismes possibles.

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The appearance of acute hypophosphatemia (AH), with fall of serum inorganic phosphorus (Pi) below 1.0—1.2 mg% (0.3—0.4 mM/l), is not a rare finding in clinical medicine [2]. AH may develop during renutrition of chronic alcoholics or malnourished subjects, recovery from diabetic ketoacidosis and total parenteral nutrition, mainly in previously underfed and/or P depleted patients [5]. The influx of Pi into the cells, with or without true P depletion, is thought to be a common mechanism of all these causes of AH [5]. AH-associated cellular dysfunctions were recognized in red and white cells, platelets and brain [5, 12] and attributed to impaired resynthesis of ATP and other high-energy compounds; this should be due to reduced availability of small fraction of "free" cell Pi in equilibrium with extracellular Pi [12]. Moreover, experimental evidence of profound changes of skeletal muscle composition was obtained in experimental AH [6]; finally, a clinical pattern of muscle dysfunction, rhabdomyolysis, high muscle H_2O, Na, Cl and low K, associated to AH was described in chronic alcoholics, suggesting a central role of AH in human alcoholic myopathy [5, 7]. However, in alcoholism it is difficult to distinguish the effects of AH on muscle composition from those possibly related to other metabolic disturbances as hypomagnesemia, K depletion, ketoacidosis etc. [7].

In our previous work [11], we have studied muscle composition in a "pure" human model of AH, i.e. in subjects with AH due to P — deficient total parenteral nutrition (TPN). Our TPN — fed, acutely hypophosphatemic patients showed changes of muscle H_2O and electrolytes similar to those found in alcoholic myopathy. These findings, obtained in subjects without any apparent electrolyte inbalance other than AH, gave further evidence of an effect of AH "per se" on muscle cell composition in man [11]. The aim of the present work is to further investigate if these alterations are related to AH (i.e. the reduction of extracellular Pi) "per se" or, at least in part, to malnutrition and/or to muscle P depletion or, finally, to other metabolic effects of TPN.

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Methods

H_2O, Cl, Na, K, Mg and total P were measured in muscle tissue (needle biopsy) [8] of 17 healthy controls and 23 subjects with AH (serum Pi below 1.2 mg%) which had appeared after 3—18 days of TPN treatment; TPN had been performed with 35—40 KCal (50 % dextrose), 1.5—2.0 mM Na, 1.2—1.8 mM K, 0.15—0.20 mM Ca, 0.16—0.20 mM Mg, no more than 0.08 mM P, 0.15—0.20 gr N (aminoacid solution) (amounts per Kg body weight per day). Muscle biopsy was made into 12—24 hours after the onset of AH. Subjects were divided into 2 groups. *Group I:* 11 subjects were malnourished and underweight; their deviation from ideal body weight was -13 ± 6 %. Clinical diagnosis was: gastrointestinal cancer (n = 8), chronic alcoholism (n = 2), protracted meningitidis (n = 1). *Group II:* 12 previously well-nourished, acutely ill patients were considered. Clinical diagnosis was: head injury (n = 9), surgery for aorto-coronary by-pass (n = 2) and for gastric perforation (n = 1).

Balance studies

13 external balance studies for Na, K, Mg, Pi were performed in 12 subjects submitted to TPN and suffering from head injury; 9 of them were submitted to muscle biopsy before and after a 5—11 days' study period in which they were fed with a TPN formula identical to that reported above but with 10—15 mM of P/day. 4 of them (group A) developed AH (serum Pi 0.7—1.2 mg%), while 5 subjects (group B) did not (serum Pi 2.9—4.5 mg%). The other 4 subjects (group C) had AH at the beginning of the study period (serum Pi 0.8—1.2 mg%) and P supplementation of 60—100 mM/day was given during study period, to correct AH up to serum Pi 3.4—4.0 mg% at the time of second biopsy. Only 2 subjects from group C were malnourished. In subjects submitted to balance studies and in 21 controls, muscle Alkali Soluble Protein Nitrogen (ASPN) was also measured.

Muscle biopsy and analysis techniques as well as the calculations for extra and intracellular water by means of muscle Cl space were described elsewhere [8, 9, 11].

Results

Table 1 shows muscle findings ($\pm$ S.D.) and P-values in groups I and II and in all AH subjects, compared to controls. In both groups, muscle K and Mg were significantly reduced and Cl and Na increased in reference to both FFS and ICW; both K and Na changes in group I were greater than those found in group II; intra/extracellular ratio for K was also reduced. ICW was normal, ECW increased in both groups, showing an expansion of EC space, with preservation of cell volume. Total muscle P was only slightly depressed in group II, while severely low levels of Pm were found in group I; therefore mean value for all AH subjects was reduced. It is of interest that identical levels of extracellular Pi are compatible with both normal and depleted muscle cell P content. Except serum Pi, extracellular electrolyte and acid base parameters (not reported in table) neither did show significant alterations in both groups nor were different between group I and II.

Balance studies

ASPN content measured in 12 subjects was 101 $\pm$ 14 gr/Kg FFS, not different from normal values (106 $\pm$ 8).

Figures 1—2 and 2B summarize the changes of muscle composition and external balance values in the 3 groups of patients submitted to balance studies.

Group A: AH developed into 5—11 days; muscle H_2O, electrolytes and P were normal at the beginning of the study and the changes of TW, ECW, Na_m, Cl_m (increase) and K_m, Mg_m, K_i and K_i/K_e (decrease) were clearly apparent at the end, when TW (3.65 $\pm$ 0.34), ECW (1.08 $\pm$ 0.13), Cl_m (154 $\pm$ 36), Na_m (191 $\pm$ 41) were increased with statistical significance and K_m (357 $\pm$ 51), Mg_m (32 $\pm$ 7), K_i (139 $\pm$ 22), K_i/K_e ratio (36 $\pm$ 6) were reduced in comparison with control values reported in table 1 (see also for symbols).

Muscle P showed only a slight reduction. External balance values of Na and K were in agreement with the muscle findings, while for Mg and P only marginal variations were found.

Group B: In this group, in which even after 5—10 days of low — P TPN no significant fall of serum Pi occurred, H_2O and electrolytes in muscle were normal at the beginning as well as at the end of the study period, with only marginal changes. Muscle P showed a slight fall as well as in group A. Variations of external balances were unsignificant.

Tab. 1:

Muscle values	AHPP			Controls		P values			
	I (N = 11)	II (N = 12)	I + II (N = 23)	N	C	I + II vs C	I vs C	II vs C	I vs II
TW M ± SD	3.771 0.354	3.598 0.283	3.681 0.324	27	3.278 0.194	0.001	0.001	0.001	NS
ECW	1.138 0.304	0.946 0.239	1.038 0.284	17	0.782 0.197	0.005	0.001	NS	NS
ICW	2.631 0.443	2.651 0.263	2.642 0.352	17	2.516 0.252	NS	NS	NS	NS
Cl_m	146.2 32.3	120.4 41.9	136.9 40.0	17	99.3 21.9	0.001	0.001	0.02	NS
Na_m	255.1 62.6	202.3 44.6	227.3 59.1	27	133.7 23.8	0.001	0.001	0.001	0.05
K_m	348.9 38.5	406.0 48.9	378.7 50.5	48	458.3 33.1	0.001	0.001	0.001	0.005
Mg_m	31.9 4.4	35.7 6.8	33.9 6.0	38	40.2 3.8	0.001	0.001	0.01	NS
P_m	176.7 26.7	252.0 32.5	215.9 48.2	17	280.6 36.8	0.001	0.001	0.05	0.001
Na_i	34.6 24.9	25.6 18.7	30.1 21.9	17	8.4 6.7	0.001	0.001	0.005	NS
K_i	133.9 18.8	153.2 19.5	143.7 21.3	17	182.5 24.0	0.001	0.001	0.005	0.025
Mg_i	12.2 2.1	13.3 2.6	12.8 2.4	17	15.6 1.8	0.001	0.001	0.02	NS
K_i/K_e	33.8 6.0	34.9 5.0	34.4 5.4	17	42.1 4.9	0.001	0.001	0.005	NS

I = AHPP with malnutrition
II = AHPP without malnutrition
FFS = muscle fat free solids;
TW, ECW, ICW = total, extracellular and intracellular water, Kg/KgFFS
Cl_m, Na_m, K_m, Mg_m, P_m = mM/KgFFS;
Na_i, K_i, Mg_i = mM/Kg ICW

Fig. 1

CHANGES IN MUSCLE COMPOSITION DURING TPN WITH AND WITHOUT ACUTE HYPOPHOSPHATEMIA

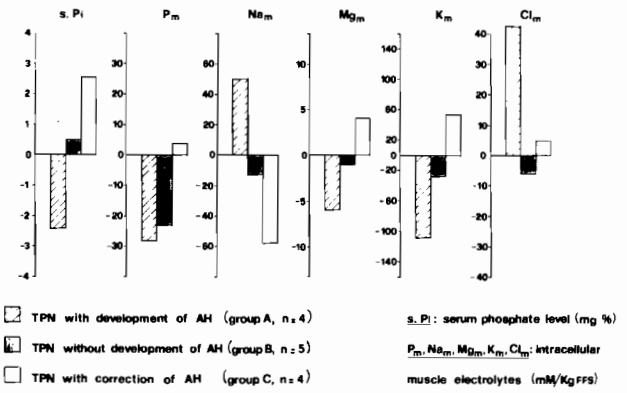
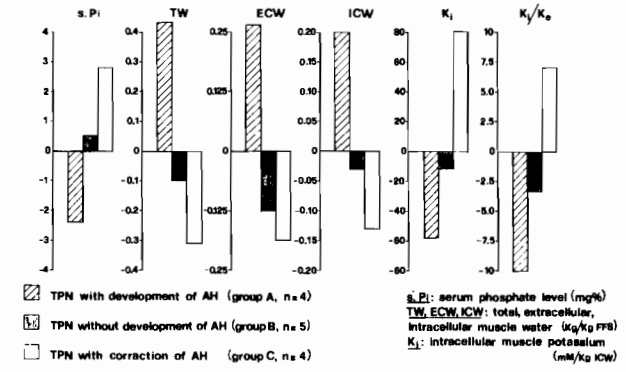


Fig. 2

CHANGES IN MUSCLE COMPOSITION DURING TPN WITH AND WITHOUT ACUTE HYPOPHOSPHATEMIA (AH)



Group C: At the beginning of the study period a statistically significant increase of TW (3.71 ± 0.37), ECW (1.10 ± 0.17), Cl_m (143 ± 36) and Na_m (213 ± 30) was found with respect to normal values (table 1), while K_m (380 ± 50), Mg_m (32 ± 4), K_i (146 ± 26) and K_i/K_e (33 ± 8) were reduced. The correction of AH by P replacement was associated with a fall of TW, ECW, Na_m, Cl_m and a rise of K_m, Mg_m, K_i/K_e. Muscle P did not change significantly as mean value, but it increased in malnourished subjects with high positivity of external balance and it decreased in well-nourished patients despite positivity of balance. External balance of Na and K was in agreement with the correction of muscle values; Mg balance was slightly negative despite the increase of muscle Mg.

Figure 3: In this graph we have plotted the changes of muscle Mg against those of muscle K in the subjects submitted to balance studies; the linear relationship shows a reciprocal dependence between muscle Mg and K.

Fig. 2B

CHANGES OF SERUM Pi AND EXTERNAL BALANCES DURING TPN WITH AND WITHOUT AH

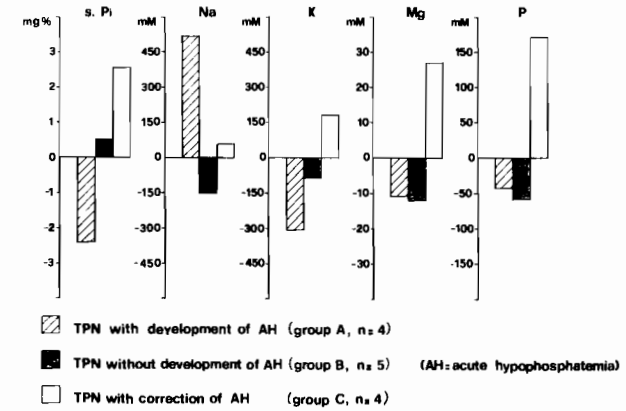
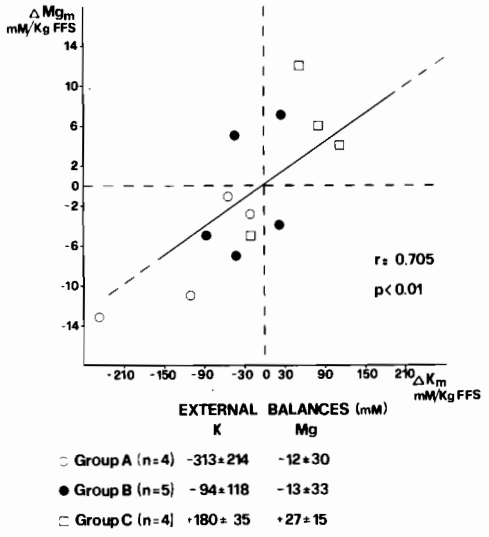


Fig. 3

RELATIONSHIP BETWEEN MUSCLE Mg AND K CHANGES DURING TPN



Discussion

The changes in muscle water and electrolyte composition we show in human AH are quite similar to those found by *Knochel* et al [6] in previously P-depleted, partially starved dogs with hyperalimentation — induced AH.

However, we observed significant alterations of cell K, Mg and Na even in subjects without previous malnutrition and with normal or only slightly depressed muscle P; in malnourished, muscle P-depleted subjects the changes are more profound. This may suggest that AH "per se" can alter cell electrolyte composition without true P depletion. Previous muscle P depletion due to malnutrition seems to be associated with greater alterations of cell composition when AH devel-

ops, indicating that AH may enhance previous subtle changes in cell composition due to malnutrition and/or to P depletion, as observed in both experimentally P-depleted dogs [3] and humans with chronic alcoholism, malnutrition and low muscle P [7].

Our balance studies further confirm the role of acute fall of extracellular P in muscle cell derangement during TPN; in fact, significant changes in muscle water and electrolytes, at least in well-nourished subjects, were seen only when AH supervened during P-deficient TPN, while the subjects submitted to an identical TPN schedule, but without development of AH, did not show significant alterations. Moreover, changes of muscle P were equally slight in group A and B, excluding any possible effect of a muscle P depletion on muscle water and electrolytes at least in well-nourished subjects. However, one cannot exclude that in malnourished subjects, muscle P depletion contribute to muscle cell derangement, as suggested by the greater modifications seen in malnourished, muscle P-depleted group; it is possible also that TPN induces a more pronounced fall of muscle P in underfed than in well-nourished subjects.

Also the effects of P replacement in TPN induced AH (group C) support the assumption of a protective effect of adequate P intake against muscle cell alterations during TPN; however, even in this group, because of the presence of two subjects with severe malnutrition and muscle P depletion, it is conceivable that recovery not only of extracellular Pi, but also of muscle cell P plays a role in the restoration of cell composition.

The intracellular pattern observed in AH is consistent with an impairment of active Na efflux from (and K influx into) the cells, due to reduced activity of NaKATPase — dependent pump, as previously supposed by Others [2, 12]. This interpretation can be supported by the finding of a constant reduction of K_i/K_e ratio, as an index of the hability of muscle cell membrane to mantain a normal intra/extracellular gradient for K, as well as by the impairment of Na-K pump previously found by us in red blood cells from subjects with AH [10]. The presence of such a membrane defect also in muscle cells as well as its pathogenetic role in biochemical features of AH — associated muscle cell dysfunction must be further investigated. The strict correlation between the changes of muscle K and those of muscle Mg in balance studies strongly suggests a reciprocal dependence of these cations in muscle cells, as previously observed [1, 9]. In our previous work [9] we studied in 21 chronically ill, malnourished subjects with severe muscle K depletion the relationship between muscle Mg and K. Although the correction of K depletion alone, without any positivity of external balance of Mg, was able to restore also muscle Mg content, no direct relationship between the variations of muscle Mg and K was found; changes of muscle Mg were on the contrary well correlated with the protein content of muscle cells (Alkali Soluble Protein Nitrogen) which was generally depressed in this series; this was in agreement with the assumption of a large binding of Mg to different "stable" intracellular compounds, as myofibrillar proteins or ATP [13]. In the present work it is possible that the dependence of muscle Mg on muscle K is even more evident because of a generally normal muscle ASPN in our well-nourished subjects.

In summary, the present metabolic studies demonstrate some cellular effects of acute depletion of extracellular Pi; these latter, perhaps through an impairment of a primary cellular function, i.e. transmembrane Na-K transport by ATP dependent pump, involve all the intracellular cations as Na, K and Mg.

Under various clinical conditions, frequently associated with AH, a correct management of P homeostasis appears to be necessary to prevent alterations of cell composition and function.

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