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PHOSPHATE BINDER THERAPY AND SERUM PHOSPHATE CONTROL FOLLOWING INITIATION OF HAEMODIALYSIS

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Hyperphosphataemia is associated with increased all-cause mortality in patients with chronic kidney disease (CKD), but serum phosphate (P) levels can be managed by dialysis, diet and the use of P binders. Serum P data were obtained retrospectively from a US dialysis provider for the 9 months following initiation of haemodialysis (HD) in CKD patients, who were then grouped according to the variations in their serum P. Group baseline characteristics and changes in P binder use over time were described.

Variations in average monthly serum P values from months 4 to 9 were classified as either consistently in the target range (CT, 3.5–5.5 mg/dL), consistently low (CL, < 3.5 mg/dL), consistently high (CH, > 5.5 mg/dL), or varying between the low and target (LT), target and high (TH) or the low and high ranges (LH). For each group, baseline characteristics and changes in P binder use during the study were compared with CT (the reference group) to identify differences.

In total, 47742 eligible patients were allocated to the six groups: CT, 7301; CL, 131; CH, 5001; LT, 6469; TH, 24469; LH, 4371. CH, TH, and LH were significantly younger than CT, with fewer comorbidities, higher incidence of elevated parathyroid hormone (PTH) and higher mean serum P; CH and TH also had higher levels of P binder use. CL and LT were older, with more comorbidities, lower PTH levels and lower levels of P binder use than CT. Overall, comparing months 8–9 with baseline (months 1–3), more patients received P binder therapy (51.7 vs 35.0%), on a larger percentage of days (50.0 vs 30.9%), but with little change in mean serum P (5.3 vs 5.2 mg/dL). By group, mean serum P increased numerically in CH (7.5 vs 6.6 mg/dL) and TH (5.6 vs 5.4 mg/dL) but decreased in other groups.

Serum P can be difficult to control following initiation of HD. Patients with elevated serum P were younger, and most had higher P binder use than the reference group. Overall, binder use was lower than in other studies of HD patients. Dietary education and higher doses of the most effective P binders may be needed to improve P management.

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RELATIVE DOSING OF PHOSPHATE BINDERS FOR EFFECTIVE MANAGEMENT OF PHOSPHATE AND PROTEIN INTAKE IN CHRONIC KIDNEY DISEASE

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Patients with chronic kidney disease undergoing haemodialysis have a maximum recommended dietary phosphate (P) intake of 1000 mg/day and a recommended protein intake of 1.2 g/kg/day. Achieving this level of protein intake is associated with the best patient outcomes. However, protein-containing foods also contain P, and elevated serum P is associated with increased all-cause mortality. It is therefore important to manage the levels of serum P while maintaining adequate levels of nutrition.

For different P binders, we estimated the dose and associated tablet burden needed to remove excess P based on the maximum recommended daily P intake. We also examined the implications for patient nutrition.

Published binding capacities of different P binders in healthy volunteers ingesting up to 2000 mg/day P, are in the range of 26–135 mg P/g binder. Assuming that 60% of ingested P is absorbed, and that haemodialysis three-times weekly will remove 2400 mg P, a haemodialysis patient ingesting 1000 mg/day P will have a residual P burden of 257 mg/day. To bind this, patients would require a maximum of 3 x 1000 mg lanthanum carbonate tablets, or approximately 9 x 400 mg calcium carbonate tablets, or approximately 9 x 800 mg sevelamer hydrochloride tablets.

The recommended protein intake for a 70 kg haemodialysis patient is 84 g/day. A realistic estimate of the average P content of a typical diet is 15 mg/g protein, which equates to a P intake of 1260 mg/day. This is considerably in excess of the recommended limit and, depending on vitamin D status more than 60% may be absorbed, further adding to the residual P burden.

The availability of binding capacity data for P binders, presents physicians with the possibility of tailoring doses of binder to a patient's diet, facilitating sufficient intake of dietary protein while maintaining a neutral P balance. Use of high-capacity binders, such as lanthanum carbonate, would minimize the tablet burden faced by patients and this may also encourage adherence.

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DOCOSAHEXAENOIC ACID (DHA) PREVENTS ATROPHY-RELATED SIGNALING IN PALMITATE-TREATED C2C12 MUSCLE CELLS

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Hypertriglyceridemia is a comorbidity of chronic kidney disease (CKD) that contributes to insulin resistance and dysfunctional protein metabolism in skeletal muscle, resulting in debilitating muscle atrophy. The saturated fatty acid palmitate (PA) induces muscle insulin resistance and promotes apoptosis and atrophic signaling pathways. In contrast, omega-3 polyunsaturated fatty acids like docosahexaenoic acid (DHA) improve insulin sensitivity and may attenuate activation of pathways that lead to muscle atrophy. The purpose of this study was to examine the effects of saturated and omega-3 fatty acids on atrophy-related signaling pathways in skeletal muscle cells. Our hypothesis was that DHA prevents the detrimental effects of PA. C2C12 myotubes were treated with 0.1mM DHA and/or 0.5mM PA for 48 h. Insulin (100nM; 15 min) was added to cells to activate signaling pathways. The expression of proteins involved in atrophic and apoptotic signaling pathways was examined by Western analysis. PA reduced myotube size and number. PA also reduced insulin-stimulated Akt and Foxo3a phosphorylation plus induced caspase-3 and actin-fragmentation. All of these responses were blocked by the addition of DHA; DHA alone had minimal effects on these pathways. In conclusion, these data suggest that DHA protects muscle cells from activation of atrophic signaling pathways by high levels of saturated fatty acids. Therefore, protein-energy wasting during CKD may be improved by DHA supplements.Support: NIH DK007734

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CALCINEURIN-NFAT SIGNALING REGULATES ATROGIN-1 AND MURF1 VIA MICRORNA-23A (MIR-23A) DURING MUSCLE ATROPHY

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Muscle atrophy is prevalent in chronic kidney disease (CKD) patients. MicroRNAs play a critical role in biological processes including muscle atrophy. MicroRNA-23a (miR-23a) negatively regulates the expression of two atrophy-related ubiquitin ligases, atrogin-1 and MuRF1; it is reduced in muscle during atrophy. Although miR-23a expression was recently shown to be positively regulated by NFATc3, the underlying mechanism of miR-23a suppression during atrophy remains unknown. We previously reported that the activity of calcineurin (Cn), the calcium-activated phosphatase that regulates NFATc proteins, is decreased when insulin signaling is decreased. Since CKD causes muscle atrophy, and glucocorticoids are required for the response, we investigated how dexamethasone (DEX) affects Cn activity, NFATc3 signaling, and miR-23a expression. C2C12 or L6 myotubes were treated with 100 uM DEX to induce atrophy. Within 1 h, Cn activity was reduced and less NFATc3 was located in the nucleus. Further, miR-23a was also decreased within 30 minutes. After 48 h, expression of the NFATC3 target gene, MCIP1.4, and miR-23a were decreased. Expression of atrogin-1 and MuRF1 were also increased 48 h after DEX. Collectively, these findings indicate the Cn-NFAT signaling pathway may play an important role in the regulation of atrogin-1 and MuRF1 by suppressing miR23a during CKD and glucocorticoid-related muscle atrophy. Support: NIH DK007656; AHA GRNT7660020

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