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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301

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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302

INTEGRATIVE CLINICAL NUTRITION DIALYSIS SCORE (ICNDS) FOR PREDICTION OF NUTRITIONAL RISK IN HEMODIALYSIS PATIENTS

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The Integrative Clinical Nutrition Dialysis Score is a new quantitative method for identifying nutritional risk in hemodialysis patients. It is based on biochemical measures and weight change taken as a part of the patient's monthly routine care and can be accomplished within a short time following completion of laboratory results. The Scoring result is a number between 0-100 given for each patient. A higher Score indicates a good nutritional status, a lower Score represents malnutrition. The Score identifies also a monthly change in nutritional status, and patients who should receive nutritional intervention. In 59 patients, Score results were found to be significantly correlated with nutrition evaluation by the Subjective Global Assessment taken within the same month. In 165 patients, baseline *score* emerged as a significant inverse predictor of mortality and hospitalization: each 1-unit increase in score reduced mortality risk by 7.1%, and reduced hospitalization risk by 6.5%. A 1- unit increase of *slope of monthly scores* reduced mortality risk by 23.6% and reduced hospitalization risk by 20.1%. A *threshold* of Score greater or equal to 75 reduced mortality by 64.2%. Patients were divided into four categories based on baseline *score* (above/equal or below a threshold of 75) and *slope* of monthly scores (smaller or larger/equal to 0). Worsening nutrition status over time as indicated by both *score* and *slope*, significantly increased death hazard. Results confirm that Integrative Clinical Nutrition Dialysis Score (ICNDS) is a simple, useful prognostic tool to reflect hemodialysis patients nutrition status, and nutrition deterioration at its very commencement.

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303

DOSE ADJUSTMENT PRACTICES OF PEGINESATIDE VS. EPOETIN IN EMERALD 1 AND 2 PIVOTAL TRIALS

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Peginesatide (P) is a synthetic, pegylated, peptide-based ESA approved for treatment of anemia due to chronic kidney disease in adult patients (pts) on dialysis. P demonstrated noninferiority to epoetin (E) in maintenance of Hb levels in hemodialysis (HD) pts in two Phase 3 randomized, active-controlled, open-label trials (EMERALD 1,2). A large dialysis organization (LDO) recently reported an ESA dose adjustment rate of 12.1/pt-year (Bond et al, ISPOR 2012). This post hoc analysis evaluated dosing practices for maintaining Hb with P vs E.

Pooled data from the two trials compared P (1x monthly; N=1066) with E (1-3x wkly; N=542) in HD pts previously on stable doses of E. Hb was measured during screening, at baseline and wkly (evaluation period, wks 29-36) or every 2 wks (all other periods). Dose adjustments were not to be made more frequently than every 4 wks, unless required for safety purposes. Dose adjustments (defined as change $> \pm 20\%$ from last dose) were evaluated during the titration (wks 0-28), evaluation, and long-term follow-up (LT, wks 36-52) periods. Dose postponements were defined as $>$ 35d for P; for E, they were $>$ 4d, 6d, or 9d for TIW, BIW, and QW, respectively.

Across the entire study period, P doses were adjusted $\sim$3 times less frequently and held $\sim$8 times less than P (Table).

	P (per pt-year)	E (per pt-year)	E/P ratio
Total Dose Adjustments	3.5	10.3	2.9
Dose Increases	1.7	5.3	3.0
Dose Decreases	1.8	5.0	2.8
Dost Postponements	0.6	5.0	8.3

Within each treatment arm, dose adjustment and postponement rates (including corresponding E/P ratios) were similar across titration, evaluation, and LT periods.

E dose adjustment rate was similar to that of real world practice in an LDO. E doses were adjusted and held more frequently than P despite similar protocol specifications for dose alteration and Hb maintenance.

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304

SHIFT IN BALANCE OF IV IRON-TO-EPOETIN USE: 2008-2011

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Recent post hoc analyses of large randomized clinical trials have suggested an association between high ESA dose and cardiovascular events