Is Vitamin D Deficiency a Confounder in Alcoholic Skeletal Muscle Myopathy?

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Background: Excessive intake of alcohol is often associated with low or subnormal levels of vitamin D even in the absence of active liver disease. As vitamin D deficiency is a well-recognized cause of myopathy, alcoholic myopathy might be related to vitamin D deficiency. Chronic alcoholic myopathy affects approximately half of chronic alcoholics and is characterized by the insidious development of muscular weakness and wasting. Although alcohol or its metabolites may have a direct toxic effect on muscles, the relationship between alcoholic myopathy and vitamin D deficiency has not been examined extensively.

Methods: We reviewed the literature on alcoholic myopathy and hypovitaminosis D myopathy and compared the pathophysiological findings to designate possible mechanisms of vitamin D action in alcohol-related myopathy.

Results and Conclusions: Given the strong interdependency of suboptimal levels of vitamin D, phosphate, and magnesium in chronic alcohol abuse, we hypothesize that combined deficiencies interfere with membrane and intracellular metabolic processes in chronic alcohol-related myopathy; however, it is not yet possible to define exact mechanisms of interaction.

Key Words: Alcoholism, Vitamin D Deficiency, Alcohol-Related Disorders, Myopathy, Muscular Atrophy.

ALCOHOL MAY CAUSE either a life-threatening, acute myopathy, or a subacute to chronic myopathy (Slavin et al., 1983). The acute form probably results from a direct toxic effect of ethanol (EtOH), acetaldehyde, or other EtOH metabolites. The chronic syndrome is characterized by an insidious development of muscular weakness and wasting (Diamond and Messing, 1994; Preedy and Peters, 1994; Slavin et al., 1983).

Most of the literature examining the effect of alcohol abuse and vitamin D has been in alcohol-related osteopenia and osteoporosis, but vitamin D status in patients with muscle weakness associated with alcoholism is scarcely reported and sometimes even contradictory. In an earlier study by Hickish and colleagues (1989), muscle weakness in male alcoholics appeared to be not significantly related to vitamin D deficiency.

In a murine model of alcoholic myopathy, González-Reimers and colleagues (2010) found that low vitamin D levels were related to muscle fiber atrophy, and altered levels of muscle antioxidant enzymes could play a role in alcoholic myopathy.

Aim of Review

We compared the literature on alcoholic myopathy and hypovitaminosis D myopathy to designate possible mechanisms of vitamin D action in chronic, alcohol-related myopathy.

SEARCH STRATEGY AND SELECTION CRITERIA

We conducted a search in PubMed for articles from January 1985 to September 2011. We used the search terms alcohol + myopathy (or sarcopenia, muscle weakness [MeSH], muscle strength [MeSH], falls), and vitamin D + myopathy (or sarcopenia, muscle weakness [MeSH], muscle strength [MeSH], falls) and identified English articles related to alcoholic myopathy or hypovitaminosis D myopathy on basis of titles and abstracts. Studies on vitamin D deficiency in alcoholism were found with combinations of the keywords [MeSH] alcoholism, alcohol drinking, vitamin D, and vitamin D deficiency. Additional articles were identified by means of reference lists. Studies involving animal case

histories, and cardiac or smooth muscles, but not skeletal muscles, were excluded.

The concentration of 25-hydroxyvitamin D (25(OH)D) was defined as insufficient when <50 nM (1 nM 25(OH)D = 0.4 ng/ml), deficient when <25 nM, and severely deficient when <12.5 nM (Bang et al., 2009).

ALCOHOLIC MYOPATHY

Acute Alcoholic Myopathy

Acute alcoholic myopathy can develop after several days of heavy binge drinking (Diamond and Messing, 1994) or may occur in chronic alcoholics after a period of particularly high intake. Repeated EtOH administration to human volunteers for 28 days caused muscle damage despite adequate nutrition (Song and Rubin, 1972). The acute syndrome is characterized by localized or generalized muscular aching and tenderness (Hewitt and Winter, 1995), which is often accompanied by muscle cramps. Weakness is present, but may be difficult to demonstrate because of pain; other features included edema of the muscles and subcutaneous tissues. Massive rhabdomyolysis causes metabolic acidosis and hyperkalemia and can produce myoglobinuria, acute renal failure, and disseminated intravascular coagulation (Diamond and Messing, 1994; Hewitt and Winter, 1995; Preedy and Peters, 1994). The development of a complicating compartment syndrome may be delayed for several days after the initial insult to muscle (Hewitt and Winter, 1995). Recovery of acute myopathy usually occurs within days to weeks of abstinence, but residual weakness in proximal muscles may remain (Diamond and Messing, 1994).

Chronic Alcoholic Myopathy

The chronic syndrome affects 40 to 60% of alcoholics (Preedy et al., 2003) and is clinically characterized by muscular weakness and wasting (Diamond and Messing, 1994; Slavin et al., 1983), either diffuse or localized to proximal muscles especially of the pelvic girdle and thighs (Preedy and Peters, 1994). Other common presenting features are frequent falls, difficulties in gait, and muscle cramps. Sometimes pain or tenderness of the proximal muscles occurs (Slavin et al., 1983).

Histologically, a decreased diameter of type II muscle fibers (i.e., fast twitch fibers with predominantly anaerobic glycolytic metabolism) is observed. Type IIb fibers, which have no or scarce mitochondria, were more affected than the type IIa fibers (Preedy and Peters, 1994; Slavin et al., 1983). The ultrastructural changes in muscle fibers included intracellular edema, enlarged and distorted mitochondria, dilatation of sarcoplasmic reticulum, excess of glycogen, and lipid deposits containing triglyceride subjacent to the cell membrane and between muscle fibers (Slavin et al., 1983).

In contrast, the mitochondrial-rich type I fibers (i.e., slow twitch fibers with aerobic or oxidative metabolism) are less sensitive and, at least in the early stages, show a compensatory hypertrophy (Trounce et al., 1987). Atrophy of type I and type IIa fibers, which also use aerobic mitochondrial respiration, only occurred in the most severe cases and to a lesser degree (Slavin et al., 1983). In some patients, muscle biopsies are normal or show minimal changes. Fiber necrosis or inflammatory cellular infiltration is not seen.

Improvement in chronic myopathy usually takes at least 2 to 3 months (Diamond and Messing, 1994), up to 6 to 9 months after abstinence (Preedy and Peters, 1994; Slavin et al., 1983).

Mechanisms in Chronic Alcoholic Myopathy

Patients drinking more than 80 to 100 g alcohol/d for longer than 3 years may develop muscle atrophy (Slavin et al., 1983). When EtOH becomes the main source of energy, the low protein content of alcoholic beverages may lead to nitrogen malnutrition, as reflected by low serum urea nitrogen levels. In chronic alcoholism, protein breakdown exceeded the rate of muscle protein synthesis (Lang et al., 2005), thus compromising the sources of muscle protein and inducing loss of muscle mass. Further details on the biochemical mechanisms in disturbances of protein metabolism were described in a review by Preedy and colleagues (2001). Evidence for increased oxidative stress by free radicals in alcohol-exposed skeletal muscle was inconsistent (Preedy et al., 1999, 2002).

The predominant atrophy of type IIb fibers suggests that an alcohol-induced effect on carbohydrate metabolism in muscle fibers plays a role (Diamond and Messing, 1994; Slavin et al., 1983). However, the glycolytic pathway tends to be reduced in a variety of myopathies (Preedy et al., 1999) and not exclusively in relationship with alcohol abuse.

Several studies of electrolytes in muscles of chronic alcoholic patients as well as in alcohol fed animals showed depletion of electrolytes such as magnesium, potassium, and phosphate (Flink, 1980). Chronic phosphate deficiency has been known to cause subclinical myopathy, and acute hypophosphatemia can lead to proximal myopathy, generalized weakness, and rhabdomyolysis (Berkelhammer and Bear, 1984). Hypokalemia is common in chronic alcoholism and may be associated with myopathy, but its role in the development of alcoholic myopathy is uncertain (Flink, 1980). Hypokalemia, decreased intracellular potassium content, and renal potassium wasting are also encountered frequently in magnesium deficiency. Impaired activity of Na/K-ATPase induced by hypomagnesia would be the cause of these disturbances (Pitts and van Thiel, 1986). Clinically, restoration of potassium cannot be accomplished unless the magnesium deficiency is also corrected (Pall et al., 1987). Furthermore, magnesium deficiency may cause a state of hypocalcemia because of hypoparathyroidism that is resistant to the action of vitamin D or calcium supplements even in substantial doses (Pall et al., 1987; Pitts and van Thiel, 1986). Under these circumstances, supplementation with magnesium

Table 1. Prevalence of Vitamin D Deficiency in Alcoholic Patients

Studies	Malham and colleagues (2011)	Bang and colleagues (2009)	Kim and colleagues (2003)	Bjørneboe and colleagues (1986)	Hyppönen and colleagues (2010)	Abnet and colleagues (2010)
No. of alcoholic patients	89	13	18	12	?/590	?/512
Details	Cirrhotic patients	–	–	Vitamin D intake[a]	General population	General population
Alcohol misuse	Unspecified	Unspecified	Mean 98 g/d[b]	Unspecified	>21 drinks/wk; ? in 1.1% of participants	>14 g/d;[b] ? in 6.1% of participants
Mean or median 25(OH)D (nM)	Median: 24	Mean: 31	Median: 54	Mean: 56	?	?
25(OH)D <25[c] or <30[d] nM, no. of patients (%)	49/89 (55%)[c]	5/13[d]	3/18[c]	None	63/590 (10.7%)[a,c]	122/512 (23.8%)[a,c]
25(OH)D <12.5 nM,[e] no. of patients (%)	16/89 (18%)	4/13	?	None	?	?

25(OH)D, 25-hydroxyvitamin D; ?, no data; –, no further details.
[a]Not significantly different from controls or nondrinker.
[b]One alcoholic drink is 8 to 14 g ethanol.
[c]25(OH)D < 25 nM, vitamin D deficiency.
[d]25(OH)D < 30 nM.
[e]25(OH)D < 12.5 nM, severe vitamin D deficiency.

corrects the hypocalcemia without the need for calcium supplementation (Pall et al., 1987).

Earlier literature mentioned that features of muscle atrophy in alcoholism would be caused by alcoholic polyneuropathy (Mills et al., 1986), but alternatively coexistent peripheral neuropathy may contribute to muscle atrophy, without a direct causal relation (Diamond and Messing, 1994).

Previous reviews of alcoholic myopathy suggested that muscular atrophy in alcoholics was not primarily related to the patient's nutritional status, or deficiencies of 1 or more of B vitamins (Preedy and Peters, 1994).

ALCOHOLISM AND IMPAIRED VITAMIN D STATUS

The low serum 25(OH)D concentration in alcoholic patients was discussed by Pitts and van Thiel (1986), describing 14 studies concerning 215 alcoholic patients. Mean serum 25(OH)D levels of 40 nM were found in cirrhotic alcoholics, and 62 nM in noncirrhotic alcoholics. In the general population, the prevalence of serum 25(OH)D concentrations below 25 nM ranged from 7.9% (95% CI, 7.3 to 8.5) to 16.4% (95% CI, 15.3 to 17.5) in 2 different cohorts of 7,437 persons with a mean age of 45 years (Hyppönen and Power, 2007) and of 4,030 persons aged 18 to 79 years (Hintzpeter et al., 2008). Studies presenting more detailed data on the prevalence of vitamin D deficiency in alcoholic patients are summarized in Table 1. In a group of 89 cirrhotic alcoholics, 55% (95% CI, 45 to 65) of all patients had 25(OH)D concentrations below 25 nM (Malham et al., 2011). In a recent cohort of 21 male alcoholics living in municipal homeless shelters, we found a mean 25(OH)D concentration of 27.9 nM and a median concentration of 17 nM at baseline. Of these alcoholics, 17/21 (81%) (95% CI, 64 to 97) had concentrations below 25 nM, and 8/21 (38%) (95% CI, 18 to 58) had concentrations below 12.5 nM, indicating severe vitamin D deficiency (Nieuwenhuis, unpublished data).

HYPOVITAMINOSIS D MYOPATHY

Early clinical descriptions of a myopathy associated with severe vitamin D deficiency recognized a potential association between vitamin D and muscles (Ceglia, 2009). Myopathy has been described in severe vitamin D deficiency responsible for rickets in children and osteomalacia in adults. Traditionally, it was felt that this myopathic presentation was secondary to osteomalacia and inactivity, rather than a direct effect of vitamin D on muscles (Hamilton, 2010). The direct association between vitamin D deficiency and myopathy was based on findings of vitamin D receptors (VDRs) present in human muscle tissue (Bischoff et al., 2001) and in VDR knockout mice (Endo et al., 2003).

Biopsies of skeletal muscle in adults with vitamin D deficiency have shown predominantly muscle fiber atrophy of the fast twitch type II fibers (Boland, 1986), fibrosis, enlarged interfibrillar spaces and infiltration of fat, and glycogen granules (Yoshikawa et al., 1979), with no signs of inflammatory reactions. Vitamin D supplementation restored muscle tissue (Annweiler et al., 2010) and was associated with an increase of mean diameter and percentages of type II fibers (Ceglia, 2009).

VDR null mutant mice (Bouillon et al., 2008) show growth retardation, osteomalacia, diffuse muscle fiber loss (differing from the human hypovitaminosis D myopathy with a predominance of type II fiber loss), and metabolic changes such as secondary hyperparathyroidism and hypocalcemia (Ceglia, 2009).

Clinical Findings

Myopathy associated with vitamin D–deficient osteomalacia is presenting predominantly as a proximal muscle weakness, muscle wasting, and difficulty in walking upstairs (Hamilton, 2010). Apart from severe cases, hypovitaminosis D myopathy is generally underdiagnosed because of the

nonspecific symptoms and signs (Annweiler et al., 2010). The first observed symptoms often are muscle weakness and musculoskeletal pain. Generally, the pain is symmetrical and starts in the lower back then spreads to the pelvis, upper legs, and ribs. It is felt mainly in the bones; not in the joints (de Torrenté de la Jara et al., 2004). Muscle weakness can exist during deficiency without biochemical signs of bone involvement (Glerup et al., 2000). The course of myopathic symptoms varied, usually improving within 3 months (de Torrenté de la Jara et al., 2004), or lasting 6 to 12 months (Annweiler et al., 2010), mainly depending upon baseline serum 25(OH)D levels and dosage of subsequent vitamin D treatment.

Vitamin D Deficiency

Normal serum 25(OH)D levels proved to be necessary for maintaining adequate muscle function in a group of 55 vitamin D–deficient women (Glerup et al., 2000). Serum 25(OH)D concentrations below 50 nM were associated with poorer physical performance in 1,234 persons aged 65 years and older in the Longitudinal Aging Study Amsterdam (Wicherts et al., 2007), and concentrations below 25 nM were associated with an increased risk of falling in the same study.

The required serum 25(OH)D concentration is defined by the Institute of Medicine (IOM) as higher than 50 nM (Ross et al., 2011). Others have defined the optimal serum 25(OH)D concentration as ≥ 75 nM (Sievenpiper et al., 2008). Even though a traditional reference range of mean ± 2 standard deviations is difficult to determine, because serum 25(OH)D varies with season and geography, concentrations below 20 nM indicated severe deficiency (Compston, 1998; de Torrenté de la Jara et al., 2004). To prevent increased bone turnover, serum 25(OH)D should be higher than 40 nM according to Kuchuk and colleagues (2009), whereas physical performance increased up to 25(OH)D levels of 60 nM in the Longitudinal Aging Study Amsterdam including 1,319 persons aged 65 or older. Concentrations of at least 50 nM were needed to prevent secondary hyperparathyroidism and low bone mineral density in other studies (Malabanan et al., 1998).

Various authors recommend a daily vitamin D intake of 800 to 1,000 IU (50 to 62.5 nmol; 20 to 25 μg) for benefits in health (Compston, 1998; Vieth, 1999). The new report on dietary requirements for calcium and vitamin D from the IOM recommends 600 IU/d of vitamin D for adults, and 800 IU/d for >70 years old persons, corresponding to a serum 25(OH)D concentration of at least 50 nM based on the requirements for bone health in $\geq 97.5\%$ of the population (Ross et al., 2011; www.iom.edu).

Mechanisms in Vitamin D—Related Myopathy

The etiology of the myopathy is multifactorial and attributed to secondary hyperparathyroidism, hypocalcemia, hypophosphatemia, and vitamin D deficiency itself (Holick,

2006; Pfeifer et al., 2002). Studies in rodents have demonstrated that parathyroid hormone induces muscle catabolism (Garber, 1983) and reduces calcium transport, intracellular phosphate, creatinine phosphokinase, mitochondrial oxygen consumption, and oxidation of long-chain fatty acids in skeletal muscles (Annweiler et al., 2010).

Research on the VDRs suggested the existence of lower muscle strength in different single-nucleotide polymorphisms of the VDR gene and differences of responders and nonresponders to vitamin D (Annweiler et al., 2010). The biologically active form of vitamin D, 1,25-dihydroxyvitamin D $(1,25(OH)_2D)$, is critical for the regulation of calcium and phosphate levels that in turn support mineralization and neuromuscular activity (Wang and DeLuca, 2011). In addition to the nuclear $1,25(OH)_2D$ VDR, a less clearly defined cell membrane receptor has been reported (Ceglia, 2009) that mediates the rapid nongenomic actions. The genomic pathway of vitamin D action in muscle involves genomic control (Ceglia, 2009) to regulate the synthesis of proteins responsible for multiple phenomena such as calcium influx into the cell (de Boland and Boland, 1985), membrane phosphate transport, phospholipids metabolism (Drittanti et al., 1988), and muscle fiber proliferation and differentiation (Wu et al., 2000). Rapid responses to $1,25(OH)_2D$ are mediated by a membrane-bound VDR, through second-messenger pathways that influence calcium transport and regulate intracellular calcium (Ceglia, 2008). According to current investigations; however, identification of tissues expressing VDRs has been controversial (Wang et al., 2010) because of false-positive results in detecting specific VDRs in muscle tissue. Wang and DeLuca (2011) therefore suggested that underlying mechanisms of vitamin D action in muscles are either of an indirect nature or do not involve the known receptor.

Finally, vitamin D may act on the peripheral nervous system, because a reduction of nerve conduction velocity has been reported in cases of severe vitamin D insufficiency (Skaria et al., 1975).

VITAMIN D AND CHRONIC ALCOHOLIC MYOPATHY

Although alcoholics in the general population may have normal serum 25(OH)D concentrations (Abnet et al., 2010; Hyppönen et al., 2010), in-hospital and outpatient ambulatory settings the majority had subnormal levels even in the absence of active liver disease (Bang et al., 2009; Pitts and van Thiel, 1986).

Articles specifically addressing vitamin D in relation to myopathy in alcoholism are rare. Previous studies suggested that changes in alcoholic muscle disease were not attributable to dietary deficiencies, but effects of severe vitamin D deficiency in alcoholic myopathy have not been extensively examined. Low $1,25(OH)_2D$ levels were related to reduced handgrip strength and reduced lean mass in a study performed on 90 alcoholics (González-Reimers et al., 2011). Hickish and colleagues (1989) concluded that muscle weakness in 41 male alcoholics was not significantly related to
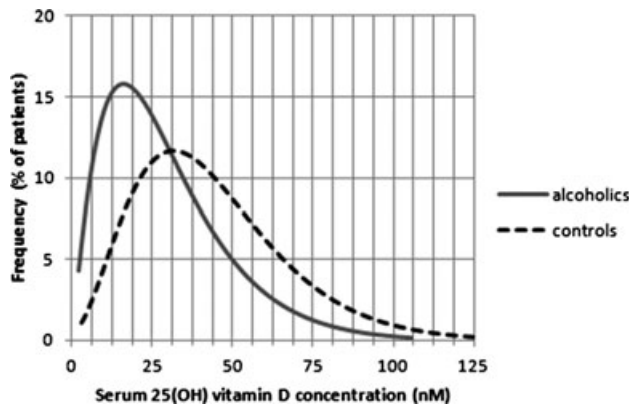
Fig. 1. Distribution of vitamin D status in alcoholics and controls. Example of right-skewed distribution of vitamin D concentrations in 74 alcoholic patients (pooled data from: Bjørneboe et al., 1986; Hickish et al., 1989; Nieuwenhuis, unpublished data) and 1,066 controls: median age 61 years, male 73%/female 27%, serum 25(OH)D concentration median 39.1 nM, interquartile range 25.8 to 56.7 nM, season of blood draw: winter 52%/ summer 48% (Abnet et al., 2010). Areas under curves represent 100% of cases. Lowest serum 25(OH)D concentrations are unspecified <7 nM.

vitamin D deficiency. For serum 25(OH)D concentrations, which had a highly skewed distribution, a transformation of data was used in statistical analysis. However, in smaller patient groups, 25(OH)D distributions frequently appeared right-skewed, corresponding with fewer high values in the right tail of the distribution (Fig. 1), and median < mean values. Serum 25(OH)D concentrations were below 12.5 nM and maximum voluntary contractions (MVC) of the dominant quadriceps ranging from 70 to 390 N in 10/41 (24%) of the alcoholic patients. The quadriceps MVC of controls ranged from 310 to 800 N (Hickish et al., 1989).

The causes of 25(OH)D deficiencies in alcoholics may include reduced hepatic 25-hydroxylase activity, lack of sun exposure, inadequate dietary intake, and malabsorption. Low vitamin D activity may contribute significantly to the calcium and phosphate deficiencies observed in chronic alcoholism. In a female rat model, Shankar and colleagues (2008) showed that there was a reduction in $1,25(OH)_2D$ due altered metabolism in possible relation with EtOH-induced oxidative damage. Alcohol-related osteoporosis responded well to vitamin D therapy (Pitts and van Thiel, 1986). Likewise, chronic alcoholic myopathy might be treated by vitamin D therapy, but a clear understanding of the exact role of vitamin D in alcoholic myopathy is currently lacking. Vitamin D appears to be important for normal skeletal muscle development and optimal muscle strength (Pfeifer et al., 2002), and this may imply a protective role of vitamin D in alcoholic myopathy (cf., vitamin D and nervous system; Annweiler et al., 2010).

Overlap and Differences

Similarities between hypovitaminosis D myopathy and chronic alcoholic myopathy were found in: (i) clinical

descriptions of predominantly proximal myopathy, (ii) morphological descriptions of muscle fiber atrophy, lower protein content, and accumulation of glycogen and lipid deposits, and (iii) were also found in suggested pathological mechanisms comprising free radicals or muscle antioxidant enzymes. Finally, (iv) in both conditions comorbidity of polyneuropathy was observed. Similarities between hypovitaminosis D myopathy and alcoholic myopathy suggest an association between the two, but this does not prove a causal relationship of vitamin D deficiency in alcoholic myopathy. The association of vitamin D deficiency and alcoholism with type II fiber atrophy may be nonspecifically related to a similar final pathway of disease occurring in various metabolic myopathies (Slavin et al., 1983).

Differences between hypovitaminosis D myopathy and chronic alcoholic myopathy were found in multiple deficiencies in alcoholic myopathy, such as magnesium, phosphate, and thiamine deficiencies. Given the strong interdependency of suboptimal levels of vitamin D, phosphate, and magnesium in chronic alcohol abuse, combined deficiencies may possibly interfere with membrane and intracellular metabolic processes in chronic alcohol-related myopathy; however, it is difficult to identify exact mechanisms of action.

CONCLUSION

Vitamin D supplementation may possibly be an effective target in prevention and treatment for alcoholic myopathy. However, the underlying mechanisms remain unclear. Further research is needed to determine whether vitamin D supplementation additionally can improve muscle function in alcoholic myopathy if alcohol is stopped, and if so, to estimate optimal vitamin D dosages for treatment and prevention of alcohol-related myopathy.

REFERENCES

Abnet CC, Chen Y, Chow WH, Gao YT, Helzlsouer KJ, Le Marchand L, McCullough ML, Shikany JM, Virtamo J, Weinstein SJ, Xiang YB, Yu K, Zheng W, Albanes D, Arslan AA, Campbell DS, Campbell PT, Hayes RB, Horst RL, Kolonel LN, Nomura AM, Purdue MP, Snyder K, Shu XO (2010) Circulating 25-hydroxyvitamin D and risk of osophageal and gastric cancer: Cohort Consortium Vitamin D Pooling Project of Rare Cancers. Am J Epidemiol 172:94–106.

Annweiler C, Montero-Odasso M, Schott AM, Berrut G, Fantino B, Beauchet O (2010) Fall prevention and vitamin D in the elderly: an overview of the key role of the non-bone effects [review]. J Neuroeng Rehabil 7:50.

Bang UC, Semb S, Nordgaard-Lassen I, Jensen JE (2009) A descriptive cross-sectional study of the prevalence of 25-hydroxyvitamin D deficiency and association with bone markers in a hospitalized population. Nutr Res 29:671–675.

Berkelhammer C, Bear RA (1984) A clinical approach to common electrolyte problems: 3. Hypophosphatemia. Can Med Assoc J 130:17–23.

Bischoff HA, Borchers M, Gudat F, Duermueller U, Theiler R, Stähelin HB, Dick W (2001) In situ detection of 1,25-dihydroxyvitamin D receptor in human skeletal muscle tissue. Histochem J 33:19–24.

Bjørneboe GE, Johnson J, Bjørneboe A, Rousseau B, Pederson JI, Norum KR, Mørland J, Drevon CA (1986) Effect of alcohol consumption on serum concentration of 25-hydroxyvitamin D3, retinol, and retinol-binding protein. Am J Clin Nutr 44:678–682.

de Boland AR, Boland R (1985) In vitro cellular muscle calcium metabolism. Characterization of effects of 1,25-dihydroxy-vitamin D3 and 25-hydroxy-vitamin D3. Z Naturforsch C 40:102–108.

Boland R (1986) Role of vitamin D in skeletal muscle function. Endocr Rev 7:434–448.

Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, Lieben L, Mathieu C, Demay M (2008) Vitamin D and human health: lessons from vitamin D receptor null mice. Endocr Rev 29:726–776.

Ceglia L (2008) Vitamin D and skeletal muscle tissue and function. Mol Aspects Med 29:407–414.

Ceglia L (2009) Vitamin D and its role in skeletal muscle [review]. Curr Opin Clin Nutr Metab Care 12:628–633.

Compston JE (1998) Vitamin D deficiency: time for action. Evidence supports routine supplementation for elderly people and others at risk. BMJ 317:1446–1447.

Diamond I, Messing RO (1994) Neurologic effects of alcoholism. West J Med 161:279–287.

Drittanti L, de Boland AR, Boland RL (1988) Effects of 1,25-dihydroxyvitamin D-3 on phospholipid metabolism in chick myoblasts. Biochim Biophys Acta 962:1–7.

Endo I, Inoue D, Mitsui T, Umaki Y, Akaike M, Yoshizawa T, Kato S, Matsumoto T (2003) Deletion of vitamin D receptor gene in mice results in abnormal skeletal muscle development with deregulated expression of myoregulatory transcription factors. Endocrinology 144:5138–5144.

Flink EB (1980) Nutritional aspects of magnesium metabolism. West J Med 133:304–312.

Garber AJ (1983) Effects of parathyroid hormone on skeletal muscle protein and amino acid metabolism in the rat. J Clin Invest 71:1806–1821.

Glerup H, Mikkelsen K, Poulsen L, Hass E, Overbeck S, Andersen H, Charles P, Eriksen EF (2000) Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. Calcif Tissue Int 66:419–424.

González-Reimers E, Alvisa-Negrín J, Santolaria-Fernández F, Candelaria Martín-González M, Hernández-Betancor I, Fernández-Rodríguez CM, Viña-Rodríguez J, González-Díaz A (2011) Vitamin D and nutritional status are related to bone fractures in alcoholics. Alcohol Alcohol 46:148–155.

González-Reimers E, Durán-Castellón MC, López-Lirola A, Santolaria-Fernández F, Abreu-González P, Alvisa-Negrín J, Sánchez-Pérez MJ (2010) Alcoholic myopathy: vitamin D deficiency is related to muscle fibre atrophy in a murine model. Alcohol Alcohol 45:223–230.

Hamilton B (2010) Vitamin D and human skeletal muscle [review]. Scand J Med Sci Sports 20:182–190.

Hewitt SM, Winter RJ (1995) Rhabdomyolysis following acute alcohol intoxication. J Accid Emerg Med 12:143–144.

Hickish T, Colston KW, Bland JM, Maxwell JD (1989) Vitamin D deficiency and muscle strength in male alcoholics. Clin Sci 77:171–176.

Hintzpeter B, Mensink GB, Thierfelder W, Müller MJ, Scheidt-Nave C (2008) Vitamin D status and health correlates among German adults. Eur J Clin Nutr 62:1079–1089.

Holick MF (2006) High prevalence of vitamin D inadequacy and implications for health [review]. Mayo Clin Proc 81:353–373.

Hyppönen E, Berry D, Cortina-Borja M, Power C (2010) 25-hydroxyvitamin D and pre-clinical alterations in inflammatory and hemostatic markers: a cross sectional analysis in the 1958 British Birth Cohort. PLoS ONE 5: e10801.

Hyppönen E, Power C (2007) Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr 85:860–868.

Kim MJ, Shim MS, Kim MK, Lee Y, Shin YG, Chung CH, Kwon SO (2003) Effect of chronic alcohol ingestion on bone mineral density in males without liver cirrhosis. Korean J Intern Med 18:174–180.

Kuchuk NO, Pluijm SM, van Schoor NM, Looman CW, Smit JH, Lips P (2009) Relationships of serum 25-hydroxyvitamin D to bone mineral density and serum parathyroid hormone and markers of bone turnover in older persons. J Clin Endocrinol Metab 94:1244–1250.

Lang CH, Frost RA, Summer AD, Vary TC (2005) Molecular mechanisms responsible for alcohol-induced myopathy in skeletal muscle and heart [review]. Int J Biochem Cell Biol 37:2180–2195.

Malabanan A, Veronikis IE, Holick MF (1998) Redefining vitamin D insufficiency. Lancet 351:805–806.

Malham M, Jørgensen SP, Ott P, Agnholt J, Vilstrup H, Borre M, Dahlerup JF (2011) Vitamin D deficiency in cirrhosis relates to liver dysfunction rather than aetiology. World J Gastroenterol 17:922–925.

Mills KR, Ward K, Martin F, Peters TJ (1986) Peripheral neuropathy and myopathy in chronic alcoholism. Alcohol Alcohol 21:357–362.

Pall HS, Williams AC, Heath DA, Sheppard M, Wilson R (1987) Hypomagnesaemia causing myopathy and hypocalcaemia in an alcoholic. Postgrad Med J 63:665–667.

Pfeifer M, Begerow B, Minne HW (2002) Vitamin D and muscle function. Osteoporos Int 13:187–194.

Pitts TO, van Thiel DH (1986) Disorders of divalent ions and vitamin D metabolism in chronic alcoholism. Recent Dev Alcohol 4:357–377.

Preedy VR, Adachi J, Asano M, Koll M, Mantle D, Niemela O, Parkkila S, Paice AG, Peters T, Rajendram R, Seitz H, Ueno Y, Worrall S (2002) Free radicals in alcoholic myopathy: indices of damage and preventive studies [review]. Free Radic Biol Med 32:683–687.

Preedy VR, Ohlendieck K, Adachi J, Koll M, Sneddon A, Hunter R, Rajendram R, Mantle D, Peters TJ (2003) The importance of alcohol-induced muscle disease. J Muscle Res Cell Motil 24:55–63.

Preedy VR, Paice A, Mantle D, Dhillon AS, Palmer TN, Peters TJ (2001) Alcoholic myopathy: biochemical mechanisms [review]. Drug Alcohol Depend 63:199–205.

Preedy VR, Patel VB, Reilly ME, Richardson PJ, Falkous G, Mantle D (1999) Oxidants, antioxidants and alcohol: implications for skeletal and cardiac muscle. Front Biosci 4:e58–e66.

Preedy VR, Peters TJ (1994) Alcohol and muscle disease. J R Soc Med 87:188–190.

Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA (2011) The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 96:53–58.

Shankar K, Liu X, Singhal R, Chen JR, Nagarajan S, Badger TM, Ronis MJ (2008) Chronic ethanol consumption leads to disruption of vitamin D3 homeostasis associated with induction of renal 1,25 dihydroxyvitamin D3-24-hydroxylase (CYP24A1). Endocrinology 149:1748–1756.

Sievenpiper JL, McIntyre EA, Verrill M, Quinton R, Pearce SH (2008) Unrecognised severe vitamin D deficiency. BMJ 336:1371–1374.

Skaria J, Katiyar BC, Srivastava TP, Dube B (1975) Myopathy and neuropathy associated with osteomalacia. Acta Neurol Scand 51:37–58.

Slavin G, Martin F, Ward P, Levi J, Peters T (1983) Chronic alcohol excess is associated with selective but reversible injury to type 2B muscle fibres. J Clin Pathol 36:772–777.

Song SK, Rubin E (1972) Ethanol produces muscle damage in human volunteers. Science 175:327–328.

de Torrenté de la Jara G, Pécoud A, Favrat B (2004) Musculoskeletal pain in female asylum seekers and hypovitaminosis D3. BMJ 329:156–157.

Trounce I, Byrne E, Dennett X, Santamaria J, Doery J, Peppard R (1987) Chronic alcoholic proximal wasting: physiological, morphological and biochemical studies in skeletal muscle. Aust N Z J Med 17:413–419.

Vieth R (1999) Vitamin D supplementation, 25–hydroxyvitamin D concentrations, and safety [review]. Am J Clin Nutr 69:842–856.

Wang Y, Becklund BR, DeLuca HF (2010) Identification of a highly specific and versatile vitamin D receptor antibody. Arch Biochem Biophys 494:166–177.

Wang Y, DeLuca HF (2011) Is the vitamin D receptor found in muscle? Endocrinology 152:354–363.

Wicherts IS, van Schoor NM, Boeke AJ, Visser M, Deeg DJ, Smit J, Knol DL, Lips P (2007) Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab 92:2058–2065.

Wu Z, Woodring PJ, Bhakta KS, Tamura K, Wen F, Feramisco JR, Karin M, Wang JY, Puri PL (2000) p38 and extracellular signal-regulated kinases regulate the myogenic program at multiple steps. Mol Cell Biol 20:3951–3964.

Yoshikawa S, Nakamura T, Tanabe H, Imamura T (1979) Osteomalacic myopathy. Endocrinol Jpn 26:65–72.