Vitamin D deficiency and muscle strength in male alcoholics

T. HICKISH, K. W. COLSTON*, J. M. BLAND† AND J. D. MAXWELL

Departments of Medicine, *Chemical Pathology and †Clinical Epidemiology, St George's Hospital and Medical School, London

(Received 14 July/5 December 1988; accepted 6 January 1989)

SUMMARY

1. Chronic alcoholism may be complicated by proximal muscle weakness associated with a selective atrophy of type II skeletal muscle fibres. The histopathological findings are non-specific as identical changes are seen in proximal muscle weakness associated with various metabolic myopathies, including osteomalacia.

2. The maximum voluntary contraction (MVC) of the dominant quadriceps and plasma 25-hydroxycholecalciferol [25-(OH)D] were measured in male alcoholics and control subjects to determine whether vitamin D deficiency contributed to proximal muscle weakness.

3. In both groups MVC declined with age and was related to body build. The distribution of plasma 25-(OH)D was skewed in alcoholics, with the mean significantly lower than in control subjects. Seventeen per cent of patients (but none of the control subjects) had pronounced biochemical deficiency [plasma 25-(OH)D < 10 nmol/l].

4. Alcoholics were significantly weaker than control subjects, even after correcting for the effects of age, height and weight. The severity of associated liver disease (cirrhosis vs no cirrhosis) did not influence muscle strength. Variation in plasma 25-(OH)D and albumin made an insignificant contribution to the difference in MVC observed between patients and control subjects.

5. We conclude that proximal muscle strength is reduced in chronic alcoholism but that this is not due to associated vitamin D [25-(OH)D] deficiency or alcoholic cirrhosis.

Key words: alcoholism, muscle contraction, skeletal muscle, vitamin D, vitamin D deficiency.

Abbreviations: MVC, maximal voluntary contraction; 25-(OH)D, 25-hydroxycholecalciferol.

INTRODUCTION

Muscle weakness may complicate chronic alcohol abuse, but there is no agreement on its prevalence and its pathogenesis is unknown [1–4]. Typically the process involves proximal muscle groups, with an insidious development of weakness and wasting. Although chronic myopathy and neuropathy may both result from alcohol abuse [3–5], available evidence favours the prime importance of myopathy in the development of proximal muscle weakness seen in chronic alcoholics [3]. Histologically the myopathic lesion is a selective atrophy of type II (fast-twitch anaerobic) muscle fibres with reduction in fibre diameter [3, 4].

These histological abnormalities are non-specific, as identical findings are present in the proximal muscle weakness associated with various metabolic myopathies, including osteomalacia [6]. Receptors for vitamin D (1,25-dihydroxycholecalciferol) have been detected in skeletal muscle [7], and in experimental animals vitamin D deficiency has been shown to decrease muscle protein synthesis [8] and to affect muscle physiology [9]. Since vitamin D deficiency and osteomalacia are also recognized complications of chronic alcoholism [10–12], we wondered whether vitamin D deficiency might contribute to muscle weakness in alcohol abusers.

Using a specially designed chair incorporating a strain gauge, we measured the maximum voluntary contraction (MVC) of the dominant quadriceps in alcoholic men who were being investigated for liver disease, and examined the relationship between muscle strength, vitamin D status (as measured by plasma 25-hydroxycholecalciferol [25-(OH)D]), and the severity of alcoholic liver disease.

EXPERIMENTAL

Subjects

Patients. Forty-one male alcohol abusers were recruited from a medical outpatient clinic. Alcohol abuse was diagnosed on the basis of prolonged (> 3 years) excessive (> 80 g of alcohol daily) consumption together with elevated erythrocyte mean corpuscular volume and/or abnormal liver function. Liver biopsy was performed in all patients, of whom 16 (39%) had established cirrhosis. The mean age of the patients was 43.5 years (range 21–72 years) (see Table 1).

Controls. Fifty-nine male controls were recruited from hospital workers (laboratory, medical and paramedical staff) as well as visitors who volunteered to participate. The mean age of the control subjects was 34.5 years (range 19–60 years) (see Table 1). None drank more than 20 g of alcohol daily.
The control subjects were all studied during the months of April and May [an intermediate time in the seasonal variation of 25-(OH)D], while patients were recruited throughout the year. None of the subjects had clinical evidence of hypercorticism or thyroid disease, and all those studied had normal serum potassium, thyroid and renal function. Any subject known to have another metabolic disorder associated with muscle weakness, or receiving drugs which might interfere with muscle function (for example, steroids or thyroxine) or vitamin D metabolism (such as anticonvulsants or other known enzyme inducers), was excluded.

The purpose of the study was fully explained, and written consent was obtained from the alcoholics before liver biopsy. Verbal consent was obtained for the other aspects of the study, which was approved by the Wandsworth Health Authority Ethical Committee.

Methods

Clinical evaluation. Height was measured without shoes, and weight in light indoor clothing. The presence or absence of ankle jerks (after reinforcement) was recorded, and clinically apparent muscle weakness of a degree sufficient to interfere with normal daily activities of living (such as dressing, transferring from bed to chair or rising from a squatting position) was noted.

Muscle strength. Quadriceps MVC was measured using a portable chair incorporating a strain gauge connected to a load cell [13]. Subjects were seated comfortably in the chair with their knees bent at 90%, and the lap belt was fastened. All measurements were made on the leg considered by the subject to be their strongest. The ankle pad was adjusted to lie at the distal end of the tibia and fibula, and just above the malleolus. Subjects were instructed in the correct technique, and encouraged to produce a maximum effort. A display meter provided visual feedback for the subject. The procedure was repeated after a rest period until two similar values were obtained, and MVC was measured as the maximum isometric force exerted on the pad by means of a digital monitor. The quadriceps MVC measurement is reproducible provided the test procedure is performed correctly [14].

Biochemistry. Plasma electrolytes, urea, calcium, phosphate, liver function and thyroid function were measured using standard automated techniques. 25-(OH)D was measured by competitive binding assay [15]. Subjects who were found to have abnormal thyroid function, potassium or elevated urea were excluded from the study.

Statistics

Group means were compared using 95% confidence intervals for differences by the two-sample t method. Relationships between pairs of continuous variables were examined using correlation coefficients. For plasma 25-(OH)D, which had a highly skewed distribution, the log transformation was used in all analyses. Differences in quadriceps MVC between groups were compared using multiple regression to adjust for other factors. Thus the contribution of alcohol to MVC after correcting for height and age was estimated by fitting a regression equation using MVC as outcome and height, age and alcohol as predictors. The effect of alcohol on MVC after adjusting for height and age was judged significant if the reduction in sum of squares obtained by including alcohol as a predictor variable was significant in an F-test. This reduction in the sum of squares, divided by the total sum of squares, gave the proportion of variability explained by alcohol after height and age had been taken into account. The magnitude of the effect was then estimated by its regression coefficient. Analyses were carried out using Nanostat [16].

RESULTS

Clinical and biochemical findings

Table 1 shows physical and biochemical data for the alcoholics and the control subjects. Sixteen out of 41 (39%) alcoholics had established cirrhosis, of whom two had ascites confirmed by ultrasound. Four patients (10%) had weakness limiting activities of daily living, but only two had absent ankle jerks.

There was a large difference in muscle strength between the groups, alcoholics having a mean MVC 220 N less than control subjects. However, there were a number of other differences. The alcoholics were older, shorter and had a higher body mass index (kg/m²) than the control subjects. They also had lower mean plasma 25-(OH)D and albumin, with a greater range. Because 25-(OH)D had a very skewed distribution, it was log transformed for analysis.

Quadriceps MVC in alcoholics

Among the alcoholics there was a significant relationship between MVC and age and height. Strength decreased with age and increased with height (Figs. 1 and 2). The multiple regression equation was:

\[
MVC = -464 - 3.08 \text{age} + 5.40 \text{height} \quad (1)
\]

This accounted for 26% of the variation in quadriceps MVC and was highly significant (\(F=6.72, \text{degrees of freedom}=3 \text{ and } 37, P<0.01\)).

Quadriceps MVC was also significantly correlated with log 25-(OH)D and albumin, but not with calcium or erythrocyte mean corpuscular volume. However, albumin was also correlated with age (Table 2). After adjustment for age and height, albumin still had a significant relationship with quadriceps MVC, accounting for a further 8% of the variation (\(F=4.3, \text{degrees of freedom}=1 \text{ and } 37, P<0.05\)).

Although log 25-(OH)D was not so strongly related to age and height, there was no significant relationship between quadriceps MVC and log 25-(OH)D after age and height were allowed for. Log 25-(OH)D accounted for 5% of the variation in quadriceps MVC (\(F=2.9, \text{degrees of freedom}=1 \text{ and } 37, 0.05<P<0.10\)).

Severity of alcoholic liver disease and quadriceps MVC

There was only a small difference in MVC between cirrhotic and non-cirrhotic alcoholics (Table 3). Mean
Vitamin D and muscle strength in alcoholics

Table 1. Characteristics of subjects and results of objective measurements

Abbreviation: ND, not determined.

<table>
<thead>
<tr>
<th></th>
<th>Alcohols (A)</th>
<th>Control subjects (C)</th>
<th>Difference A-C</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.5 ± 11.3</td>
<td>34.5 ± 10.1</td>
<td>9.0</td>
<td>4.7 to 13.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.7 ± 6.5</td>
<td>176.0 ± 6.6</td>
<td>-5.3</td>
<td>-7.9 to -2.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.5 ± 14.8</td>
<td>73.0 ± 8.6</td>
<td>1.5</td>
<td>-3.1 to 6.2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.5 ± 4.6</td>
<td>23.6 ± 2.7</td>
<td>1.9</td>
<td>0.5 to 3.4</td>
</tr>
<tr>
<td>MVC (N)</td>
<td>322 ± 112</td>
<td>542 ± 104</td>
<td>-220</td>
<td>-264 to -177</td>
</tr>
<tr>
<td>25-(OH)D (nmol/l)</td>
<td>31.1 ± 29.9</td>
<td>36.9 ± 17.2</td>
<td>-5.8</td>
<td>-0.35 to -0.03</td>
</tr>
<tr>
<td>log 25-(OH)D</td>
<td>1.33 ± 0.39</td>
<td>1.52 ± 0.20</td>
<td>-0.19</td>
<td>-0.31 to 0.03</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.34 ± 0.17</td>
<td>2.37 ± 0.15</td>
<td>-0.03</td>
<td>-0.11 to 0.03</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>38.4 ± 10.3</td>
<td>44.6 ± 3.6</td>
<td>-6.2</td>
<td>-9.4 to -3.0</td>
</tr>
<tr>
<td>Mean corpuscular volume (fl)</td>
<td>95.0 ± 6.6</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inspection of Fig. 1, which shows the relationship between MVC and age for alcoholics and control subjects, suggests that control subjects were stronger at each age. Fig. 2 shows MVC and height for alcoholics and control subjects. Again the difference in quadriceps MVC between alcoholics and control subjects of the same height is apparent.

Quadriceps MVC in control subjects

Among the control subjects there was also a significant relationship between MVC and age and height ($F = 4.52$, degrees of freedom = 2 and 55, $P < 0.05$) (Figs. 1 and 2).

The multiple regression equation was:

$$MVC = 70 - 2.29 \text{age} + 3.26 \text{height}$$ (2)

However, age and height together accounted for only 14% of the variation in quadriceps MVC.

There was no evidence of a relationship between MVC and log 25-(OH)D, albumin or calcium (Table 2). This difference between the control subjects and alcoholics may be because none of the control subjects had abnormal plasma biochemistry and the distributions were less widely scattered about the mean (Figs. 3 and 4).

**Fig. 1.** Relationship between age and quadriceps MVC for male alcoholics (●) and control subjects (○).

**Fig. 2.** Relationship between height and quadriceps MVC for male alcoholics (●) and control subjects (○).

**Difference in quadriceps MVC between alcoholics and control subjects**

When the difference between alcoholic and control subjects was adjusted for age and height, age and height accounted for 36% of the variability in MVC and group for a further 24% ($F = 58.07$, degrees of freedom = 3 and 95, $P < 0.001$). The regression equation was:

$$MVC = -72 - 3.09 \text{age} + 4.10 \text{height} - 171 \text{group}$$ (3)

(where group = 1 for alcoholics, and 0 for control subjects.) Thus the adjusted difference in quadriceps MVC between alcoholics and controls was 171 N (SEM 22, 95% confidence interval 127–215 N). This is less than the unadjusted difference of 220 N because the alcoholics were older and shorter than the control subjects.
Fig. 3 shows scattergrams of MVC and log 25-(OH)D, and Fig. 4 MVC and albumin, for alcoholics and control subjects. There is a clear difference between groups which is not explained by vitamin D or albumin levels. The estimated difference between groups after adjustment was given by the regression equation:

\[
\text{MVC} = 194 - 2.81 \text{ age} + 1.49 \text{ height} + 2.00 \text{ albumin} + 67.2 \log 25-(\text{OH})D - 170 \text{ group} \quad (4)
\]

(where group = 1 for alcoholics and 0 for controls). Thus after adjusting for vitamin D status and albumin, the estimated difference between alcoholics and control subjects is 170 N. This compares with the difference of 171 N between alcoholics and control subjects before adjusting for vitamin D and albumin, suggesting that their effect on quadriceps strength is negligible.

However, analysis after pooling the groups (resulting in a greater range of vitamin D and albumin values) indicates that both vitamin D and albumin have small effects on quadriceps MVC, which persist after controlling for age, height, and weight.

After controlling for age, height and group, log 25-(OH)D accounted for a further 4% of the variation in MVC \((F = 6.64, \text{ degrees of freedom} = 1 \text{ and} 59, P < 0.05)\) and albumin for 3\% \((F = 4.96, \text{ degrees of freedom} = 1 \text{ and} 59, P < 0.05)\).

These effects are small. For example, the coefficient of 67.2 for log 25-(OH)D indicates an increase of only 67.2 N for a tenfold increase in plasma vitamin D. Because vitamin D and albumin are correlated \((r = 0.49)\) their regression effects are also correlated and the coefficients are poorly estimated. It is not possible to decide which is the more important in relation to quadriceps MVC.

**DISCUSSION**

Anecdotal reports in nineteenth century medical literature drew attention to an association between muscle weakness and chronic alcoholism. However, this complication of alcohol abuse received relatively little attention until recent developments in muscle biopsy, histology and electrophysiology allowed more detailed scrutiny of the mechanisms involved. It is now clear that alcoholism may be associated with a chronic myopathy, due to selective atrophy of the type II (fast-twitch anaerobic) muscle fibres, as well as a peripheral neuropathy. Although many patients with histological abnormalities of skeletal muscle are asymptomatic, the occurrence of clinically apparent weakness and wasting of proximal muscles is well recognized [1–5].

Numerous explanations have been offered for the pathogenesis of chronic myopathy and muscle weakness in alcohol abusers [2–4], but it is still not clear whether this is due to a direct toxic effect of alcohol on muscle, is mediated indirectly through some other effect of alcohol (e.g. associated liver disease or hormonal changes), or is due to alcohol associated malnutrition or malabsorption. Most recent work has been on histological, biochemical and electrophysiological changes in muscle, and few studies have addressed the functional consequences of muscle disease in chronic alcoholics. Available reports have been limited either by an absence of adequate controls [17] or failure to take account of confounding effects of age, body build, sex or race of the subjects studied [14]. This may explain why no difference in muscle strength between male alcoholics and control subjects was observed in a recent report despite clear differences in muscle histology [3]. The varying reported prevalence of alcoholic myopathy has been explained both by differences in the definition of myopathy, and differences between study populations.

Direct electrical stimulation of muscle to elicit maximal contraction independent of nerve transmission is a useful

Table 2. Correlations with quadriceps MVC in male alcoholics and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Alcoholics</th>
<th></th>
<th>Control subjects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(r)</td>
<td>(P)</td>
<td>(r)</td>
<td>(P)</td>
</tr>
<tr>
<td>Age</td>
<td>-0.42</td>
<td>0.007</td>
<td>-0.31</td>
<td>0.02</td>
</tr>
<tr>
<td>Height</td>
<td>0.25</td>
<td>0.06</td>
<td>0.25</td>
<td>0.06</td>
</tr>
<tr>
<td>Weight</td>
<td>0.45</td>
<td>0.006</td>
<td>0.17</td>
<td>0.2</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.31</td>
<td>0.05</td>
<td>0.00</td>
<td>0.97</td>
</tr>
<tr>
<td>log 25-(OH)D</td>
<td>0.38</td>
<td>0.01</td>
<td>0.13</td>
<td>0.4</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.14</td>
<td>0.4</td>
<td>0.13</td>
<td>0.4</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.45</td>
<td>0.003</td>
<td>0.14</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>-0.10</td>
<td>0.5</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Table 3. Comparison of cirrhotic and non-cirrhotic alcoholics

<table>
<thead>
<tr>
<th></th>
<th>Non-cirrhotic alcoholics (NCA)</th>
<th>Cirrhotic alcoholics (CA)</th>
<th>Difference NCA–CA</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean 42.2  sd 11.2  n 25</td>
<td>Mean 45.7  sd 11.6  n 16</td>
<td>-3.5</td>
<td>-10.9 to 3.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Mean 170.2  sd 6.9  n 25</td>
<td>Mean 171.6  sd 6.0  n 16</td>
<td>-1.4</td>
<td>-5.6 to 2.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean 73.1  sd 13.9  n 25</td>
<td>Mean 76.8  sd 16.4  n 16</td>
<td>-3.7</td>
<td>-13.3 to 6.0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>Mean 25.2  sd 4.4  n 25</td>
<td>Mean 26.0  sd 4.9  n 16</td>
<td>-0.8</td>
<td>-3.8 to 2.2</td>
</tr>
<tr>
<td>MVC (N)</td>
<td>Mean 336.4  sd 150.1  n 25</td>
<td>Mean 300.1  sd 122.6  n 16</td>
<td>36.3</td>
<td>-36.4 to 108.9</td>
</tr>
<tr>
<td>25-(OH)D (nmol/l)</td>
<td>Mean 37.0  sd 35.3  n 25</td>
<td>Mean 22.0  sd 15.8  n 16</td>
<td>-15.0</td>
<td>-24.4 to -5.6</td>
</tr>
<tr>
<td>log 25-(OH)D</td>
<td>Mean 1.40  sd 0.39  n 25</td>
<td>Mean 1.22  sd 0.35  n 16</td>
<td>0.18</td>
<td>0.06 to 0.43</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>Mean 2.34  sd 0.16  n 23</td>
<td>Mean 2.34  sd 0.20  n 14</td>
<td>-0.00</td>
<td>-0.13 to 0.12</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>Mean 42.4  sd 5.5  n 25</td>
<td>Mean 32.2  sd 13.0  n 16</td>
<td>10.2</td>
<td>4.3 to 16.1</td>
</tr>
<tr>
<td>Mean corpuscular volume (fl)</td>
<td>Mean 94.1  sd 5.2  n 25</td>
<td>Mean 96.6  sd 8.5  n 15</td>
<td>-2.5</td>
<td>-6.8 to 1.9</td>
</tr>
</tbody>
</table>
Vitamin D deficiency is one of the best documented nutritional deficiency syndromes affecting muscle [3]. The proximal myopathy of osteomalacia, like that of chronic alcoholic myopathy, consists of type II fibre atrophy [6]. Earlier reports indicated that subclinical vitamin D deficiency (and even osteomalacia) may occur in chronic alcoholics [10–12], but the relationship between vitamin D deficiency and muscle weakness or fibre atrophy in alcoholics was not specifically examined.

Poor diet and reduced solar exposure have been held responsible for the low 25-(OH)D levels found in many alcoholic patients [10–12]. The role of impaired hepatic 25-hydroxylation of vitamin D in alcoholics is more controversial [11], but there is some evidence that this may be true for alcoholic patients with severe hepatocellular dysfunction. Furthermore 1α-hydroxylation may be impaired in alcoholics with concomitant renal impairment [12].

Mean plasma 25-(OH)D concentrations were significantly reduced in our alcoholic population, and the distribution skewed, but there was no difference between cirrhotic and non-cirrhotic alcoholics (Table 2). The lower limit of the normal range in our laboratory for plasma 25-(OH)D is 20 nmol/l, and as privational osteomalacia is thought to occur when plasma 25-(OH)D concentrations are at or below 10 nmol/l, we consider such concentrations as indicative of vitamin D deficiency [18]. Seven (17%) of the alcoholics had concentrations of <10 nmol/l, while none of the controls had such low levels. However, multiple regression analysis indicated that differences in plasma 25-(OH)D concentrations between alcoholics and control subjects made only a negligible contribution to differences in muscle strength observed between these groups.

The relationship between muscle bulk and muscle strength is well established [19]. While muscle wasting may be a prominent feature of malnutrition associated with decompensated cirrhosis, our outpatient population of alcoholics was relatively fit, and multiple regression analysis revealed no relationship between quadriceps MVC and either plasma albumin or the severity of underlying alcoholic liver disease. Our finding that there was no association between muscle weakness and the presence or absence of cirrhosis is in keeping with previous reports that type II fibre atrophy was not significantly more common in cirrhotic than in non-cirrhotic alcoholics [3, 4]. It is also consistent with other observations indicating varying target organ sensitivity to the effects of chronic alcohol abuse [20].

There is no evidence of increased muscle breakdown rates in cirrhotic or non-cirrhotic alcoholics, with or without severe muscle wasting [21]. Preliminary studies indicate that muscle protein synthesis rates are lower in alcoholics [22]. Specific atrophy of type II fibres is also
seen in iatrogenic or spontaneous Cushing’s syndrome, but excess glucocorticoid secretion associated with alcoholism (pseudo-Cushing’s syndrome) could not be implicated in the development of chronic alcoholic myopathy [23]. We have no data on plasma 1,25-dihydroxycholecalciferol, but we could not implicate deficiency of plasma 25-(OH)D, or associated liver disease. Another possible interpretation of our results is that proximal muscle weakness of chronic alcoholism is due to a direct toxic effect of alcohol on skeletal muscle. New laboratory techniques should allow a better understanding of the biochemical changes which are ultimately responsible for skeletal muscle weakness and fibre atrophy in alcohol abusers. Since a high proportion of these patients are vitamin D deficient, rational management should include repletion of vitamin D stores, in addition to advising abstinence.

ACKNOWLEDGMENTS

We are grateful for support from the St George’s Hospital Research Fund, and for a contribution towards expenses from Leo Laboratories. We thank Ms Linda Hadcocks for technical assistance, and Ms Marion Amos for typing the manuscript. A preliminary communication was presented to the Medical Research Society.

REFERENCES