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Original article

# Handgrip strength and lean mass are independently related to brain atrophy among alcoholics

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SUMMARY

*Background:* In neurodegenerative disorders or in normal aging humans a relationship between muscle mass and/or performance and brain volume was observed, that is not dependent on age or other confounding factors. The aim of the present study is to analyse the relationship between lean mass and handgrip strength in alcoholics, who frequently show brain and muscle atrophy.

*Methods:* It was included 101 male patients aged 58.35 ± 11.59 years, and 44 controls, all of them workers of our hospital, drinkers of less than 20 g ethanol/day, of similar age. Patients and controls underwent dominant handgrip assessment with a Collins' dynamometer, whole body composition analysis by densitometry, and brain computed tomography (CT) examination, with further calculation of several indices indicative of brain atrophy.

*Main Results:* 1) Brain atrophy is a very common finding among alcoholics, both among cirrhotics and non-cirrhotics. 2) Alcoholics show a marked reduction in handgrip strength, and also in lean mass, especially at the arms and legs −but not in the trunk, even if patients with ascites were excluded.3) There is a relationship between reduced lean mass and brain atrophy, and a close correlation between handgrip strength and brain atrophy, that is independent of age and liver function. 4) Total fat amount is not different among alcoholics and controls, but there are marked differences in fat distribution: alcoholics show less fat in arms, but more fat in trunk, so that if we calculate the peripheral fat/trunk fat index, marked differences were observed among alcoholics and controls. Neither total fat nor fat distribution were related to brain atrophy.

*Conclusion:* among alcoholics, as in other neurodegenerative conditions, there is a relationship between reduced lean mass and brain atrophy, and a close correlation between handgrip strength and brain atrophy, that is independent of age, duration of ethanol consumption and liver function.



## 1. Introduction

Chronic ethanol consumption is associated with both muscle wasting and protein-calorie malnutrition, characterized by a decrease in lean mass and fat mass and also Kwashiorkor-like features [1]. However, not all groups that have analysed this issue have reached similar results [2]. Some have reported preservation or increase in fat mass, especially at the trunk [3] (more markedly in some collectives such as African Americans [4] or women [5]), whereas others have pointed out that fat mass is decreased [6]. By contrast, there is general agreement that 40–60% of heavy alcoholics suffer from chronic myopathy, an entity that was described several decades ago [7] and that is defined by muscle fiber atrophy (mainly type II fibers [8]) and weakness especially affecting proximal muscles. Alcoholic myopathy depends on an imbalance between protein synthesis and protein breakdown, with a possible contributory role of vitamin D deficiency and/or alterations in micronutrients and perhaps inflammation [9].

In recent times it has become progressively clear that muscle is a main source of several hormones and cytokines, functioning as an endocrine organ that exerts important systemic effects [10–12]. A group of these so called myokines are active on the brain [13]. In addition, muscle activity may improve cerebral blood flow, decrease insulin resistance, and exert anti-inflammatory effects and thus may contribute to adequate brain performance [14,15]. On

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the other hand, fat also behaves as an endocrine organ. In parallel with muscle myokines, fat derived adipokines may also affect brain structure and function [16,17]. Burns et al. (2010) found a relationship between lean mass and whole-brain volume, white matter volume and cognitive performance. The relationships of lean mass were especially marked with whole brain volume and white matter volume [18]. Kim et al. (2014) described a relationship between sarcopenia and mild cognitive dysfunction in patients with end-stage renal disease [19], and Nourhashemi et al. (2002) also found a relationship between cognitive impairment and low muscle mass in a large series of community-dwelling elderly women [20]. In accordance with these studies, Colcombe et al. (2003) described a relationship between physical activity and brain volume [21]. In general, the results of all this research raise the possibility of a direct effect of muscle on brain alterations, perhaps mediated by myokines or by the other factors mentioned before.

In addition to alcoholic myopathy, brain atrophy is also an outstanding feature of chronic alcoholism. Based on the previous comments, it is important to examine if there is any association between altered muscle function and/or body composition, and the intensity of brain atrophy in alcoholic patients. This is the aim of the present study.

## 2. Patients and methods

We included 101 male patients aged 58.35 ± 11.59 years, and 44 controls, all of them workers of our hospital, drinkers of less than 20 g ethanol/day, with similar age (56.75 ± 6.50 years, t = 1.01; NS). All patients were heavy drinkers, as recorded in Table 1. The daily amount of ethanol consumed was estimated as follows:

Daily amount of ethanol (g) = volume of ethanol-containing beverage (L) x grades of alcohol/100 × 0.8.

The information about ethanol ingestion (daily ingestion, years of consumption) was obtained by direct inquiry to the patient and relatives. All patients were admitted for alcohol withdrawal syndrome and/or organic complications related to alcohol consumption. Women were not included due to the small number of cases (only 9 during this prospective case collection), and the marked differences in body composition and handgrip strength compared to men.

All patients underwent complete laboratory evaluation and abdominal ultrasound exploration. They were classified as cirrhotics (n = 43) when the liver was irregular in shape, heterogeneous in texture, and splenomegaly and/or portal dilatation were observed. Some clinical and biological features of cirrhotics and non-cirrhotics are shown in Table 1.

All patients underwent, at admission, a brain computed tomography (CT) examination. From the CT images we calculated the indices shown in Fig. 1. In three cases, technical problems (moved images) precluded accurate calculation of these indices. The vast majority of the controls (40) either underwent a CT examination at the inclusion in the study or had undergone a brain CT examination within a 12-month period before inclusion in the study, so indices derived from these CT were compared with those of the patients (Table 2). We also recorded the presence or not of cortical atrophy or cerebellar atrophy, according to the radiological report of the CT examination, performed by an experienced radiologist.

### 2.1. Body composition analysis. Handgrip strength

Patients and controls (Table 2) underwent a body composition analysis assessed with a HOLOGIC QDR-2000 (Waltham, MA, USA) dual-energy X-ray densitometer, that allows measurement of the amount of fat mass and lean mass in different body compartments. Clinical conditions of some patients (mainly agitation in relation to withdrawal syndrome and/or dementia) made this kind of analysis impossible.

Dominant arm handgrip strength was assessed using a Collins hand dynamometer in the 101 patients and in the 44 controls.

### 2.2. Statistics

The Kolmogorov–Smirnov test was used to test for normal distribution, a condition fulfilled by most variables. For variables with a non parametric distribution, the tests used were Mann–Whitney's U test, Kruskall–Wallis test, Spearman's correlation analysis or $\chi^2$, whereas Student's t test, variance analysis and Pearson's correlation analysis were used for the variables with a normal distribution. Also, multivariate analyses were also

**Table 1**
Some clinical and biochemical data of cirrhotics and non-cirrhotics.

| | Cirrhotics (n = 43) | Non-cirrhotics (n = 58) | |
|---|---|---|---|
| Age | 58.53 ± 10.42 | 58.21 ± 12.47 | T = 0.051; NS |
| Daily Ethanol (g) consumption | 174 ± 96 | 205 ± 175 | T = 1.28; NS |
| Years of addiction | 33 ± 12 | 34 ± 15 | T = 1.06; NS |
| Handgrip strength | 15.16 ± 10.73 | 17.50 ± 13.99 | T = 0.91; NS |
| Bicaudate index | 0.1629 ± 0.0397[a] | 0.1625 ± 0.0376[b] | T = 0.051; NS |
| Bifrontal index | 0.3550 ± 0.0493[a] | 0.3544 ± 0.0397[b] | T = 0.073; NS |
| Cella index | 0.0653 ± 0.0233[a] | 0.0652 ± 0.0194[b] | T = 0.04; NS |
| Celda Media index | 4.5001 ± 1.0287[a] | 4.3979 ± 0.9685[b] | T = 0.50; NS |
| Ventricular index | 0.4798 ± 0.0856[a] | 0.4830 ± 0.0854[b] | T = 0.78; NS |
| Evans index | 0.3059 ± 0.0431[a] | 0.3025 ± 0.0352[b] | T = 0.43; NS |
| Cortical atrophy (yes/no) | 33/8 | 42/15 | X2 = 0.29; NS |
| Cerebellar atrophy (yes/no) | 31/10 | 40/17 | X2 = 0.13; NS |
| Haemoglobin (g/dl) | 12.09 ± 2.28 | 13.00 ± 2.01 | T = 2.67; p = 0.009 |
| MCV (fl) | 102.16 ± 10.84 | 99.79 ± 7.42 | T = 1.20; NS |
| Prothrombin activity (%) | 66.35 ± 21.19 | 86.83 ± 14.64 | T = 5.74; p < 0.001 |
| Serum albumin (g/dl) | 3.34 ± 0.76 | 3.63 ± 0.63 | T = 2.12; p = 0.033 |
| Serum GGT (U/L) median (IQ range) | 432 ± 732<br>215 (71–416) | 179 ± 208 95 (42.5–233) | Z = 2.44; p = 0.015 |
| Serum bilirubin (mg/dl)<br>median (IQ range) | 3.85 ± 4.78 2.3 (1.0–3.80) | 1.48 ± 1.81 1.0 (1.0–1.18) | Z = 4.90; p < 0.001 |
| Serum creatinine (mg/dl) | 1.07 ± 0.97 | 0.86 ± 0.42 | T = 1.30; NS |
| Serum ASAT (U/L) median (IQ range) | 91.7 ± 86.1 62.0 (33.0–115.0) | 59.1 ± 90.6 31.5 (21.0–75.0) | Z = 2.99; p = 0.003 |
| Serum ALAT (U/L) median (IQ range) | 53.6 ± 51.2 37.0 (23.0–70.0) | 49.4 ± 64.5 31.50 (17.0–54.5) | Z = 1.32; NS |

[a] n = 41.
[b] n = 57.

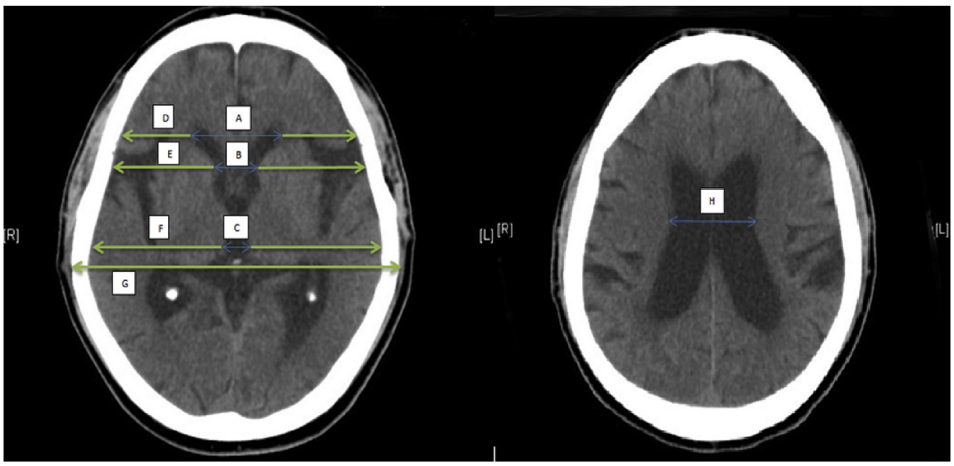


**Fig. 1.** CT indices used in this study. BICAUDATE INDEX = minimum width of lateral ventricles/skull width at the same level = B/E. BIFRONTAL INDEX = maximum width of frontal horns/skull width at the same level = A/D. EVANS INDEX = maximum width of frontal horns/skull width at the level of the third ventricle = A/F. CELLA INDEX = width of the third ventricle/skull width at the same level = C/F. CELDA MEDIA INDEX = maximum width of the skull/width of lateral ventricles = G/H. VENTRICULAR INDEX = minimum width of lateral ventricles/maximum width of frontal horns = B/A.

**Table 2**
Body composition analysis and CT indices among patients and controls. Lean and fat mass are given in grams.

| | Patients (n = 93) | Controls (n = 44) | T; p |
|---|---|---|---|
| Left arm lean mass | 2760 ± 649 | 3005 ± 461 | T = 2.54; p = 0.012 |
| Left arm fat mass | 905 ± 505 | 1310 ± 513 | T = 4.36; p < 0.001 |
| Right arm lean mass | 2719 ± 632 | 3173 ± 476 | T = 4.22; p < 0.001 |
| Right arm fat mass | 893 ± 528 | 1418 ± 559 | T = 5.33; p < 0.001 |
| Left leg lean mass | 7461 ± 1535 | 8179 ± 1096 | T = 3.13; p = 0.002 |
| Left leg fat mass | 2879 ± 1652 | 3228 ± 1070 | T = 1.48; NS |
| Right leg lean mass | 7483 ± 1547 | 8373 ± 1003 | T = 4.04; p < 0.001 |
| Right leg fat mass | 2885 ± 1641 | 3274 ± 1077 | T = 1.66; NS |
| Trunk lean mass | 25,254 ± 4147 | 26,442 ± 3163 | T = 1.85; NS |
| Trunk fat mass | 12,161 ± 6332 | 11,539 ± 4353 | T = 0.67; NS |
| Total lean mass | 49,505 ± 7610 | 53,256 ± 5941 | T = 2.83; p = 0.005 |
| (excluding ascites) | (49,016 ± 7436) | | (T = 3.17; p = 0.002) |
| Total fat mass | 20,426 ± 10,280 | 21,676 ± 6921 | T = 0.67; NS |
| Trunk fat/peripheral fat | 1.68 ± 0.54 | 1.26 ± 0.37 | T = 4.73; p < 0.001 |
| Trunk lean/peripheral lean (excluding ascites) | 1.25 ± 0.17 | 1.17 ± 0.08 | T = 3.93; p < 0.001 |
| | (1.22 ± 0.16) | | (T = 2.55; p = 0.012) |
| Trunk fat/total fat | 0.5935 ± 0.106 | 0.5230 ± 0.072 | T = 3.99; p < 0.001 |
| Trunk lean/Total lean | 0.5105 ± 0.032 | 0.4966 ± 0.017 | T = 3.26; p = 0.001 |
| (excluding ascites) | 0.5047 ± 0.030 | | (T = 1.87; NS) |
| Bicaudate index | 0.1609 ± 0.0376[a] | 0.1233 ± 0.0236[b] | T = 7.09; p < 0.001 |
| Bifrontal index | 0.3534 ± 0.0430[a] | 0.3195 ± 0.0372[b] | T = 4.37; p < 0.001 |
| Cella index | 0.0639 ± 0.0207[a] | 0.0443 ± 0.0135[b] | T = 6.26; p < 0.001 |
| Celda Media index | 4.4625 ± 0.9870[a] | 4.8767 ± 0.7396[b] | T = 2.27; p = 0.025 |
| Ventricular index | 0.4778 ± 0.0846[a] | 0.4142 ± 0.0846[b] | T = 4.01; p < 0.001 |
| Evans index | 0.3026 ± 0.0384[a] | 0.2746 ± 0.0327[b] | T = 4.05; p < 0.001 |

[a] n = 98.
[b] n = 40.

performed when appropriate. In order to perform logistic regression analyses some continuous variables were transformed into qualitative dychotomic ones according to the median values, unless otherwise specified. These analyses were performed with the SPSS program (Chicago, Ill., USA).

The study protocol was approved by the local ethical committee of our Hospital (number 2017/50) and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All patients (or their relatives in cases of dementia) gave their written informed consent.

## 3. Results

CT indices were similar among cirrhotics and non cirrhotics (Table 1), but markedly different among patients and controls (Table 2). No associations were observed between the presence or not of cortical atrophy or cerebellar atrophy and the presence or not of cirrhosis (Table 1).

CT indices were neither related to liver function tests (Child-Pugh, bilirubin, prothrombin or albumin) nor to creatinine. No differences were observed when the aforementioned liver function variables were compared among patients with or without cerebellar atrophy or cortical atrophy.

### 3.1. Handgrip strength

Handgrip strength was markedly reduced among patients (16.51 ± 12.70 kg vs 39.23 ± 11.05 kg, t = 10.29; p < 0.001). An inverse correlation was observed among age and handgrip strength ($\rho = -0.53$; p < 0.001). Handgrip strength was also inversely related to duration of ethanol addiction ($\rho = -0.42$; p < 0.001), but

**Table 3**
Handgrip strength among patients with CT indices above/below the median.

| | Handgrip strength (UNITS) | | |
|---|---|---|---|
| Ventricular index | 20.22 ± 13.32 | 13.77 ± 11.39 | T = 2.58; p = 0.011 |
| Bicaudate index | 22.36 ± 13.94 | 11.96 ± 9.19 | T = 4.42; p < 0.001 |
| Cella index | 21.64 ± 14.16 | 12.22 ± 9.14 | T = 3.88; p < 0.001 |
| Evans Index | 21.37 ± 12.87 | 13.11 ± 11.36 | T = 3.37; p = 0.001 |
| Bifrontal index | 21.42 ± 13.06 | 12.75 ± 10.96 | T = 3.57; p < 0.001 |
| Celda Media index | 13.27 ± 12.08 | 20.20 ± 12.41 | T = 2.81; p = 0.006 |
| Cortical atrophy (75/23) | 14.81 ± 12.09 | 23.00 ± 12.75 | T = 2.81; p = 0.006 |
| Cerebellar atrophy (71/27) | 15.01 ± 12.20 | 21.26 ± 13.00 | T = 2.22; p = 0.029 |

not with the amount of ethanol consumed, serum GGT or MCV. Multiple regression analyses disclosed that the relationship between handgrip and duration of ethanol addiction was in fact dependent on the relationship between handgrip and age, the variable "duration of ethanol addiction" becoming displaced by the variable "age".

Patients with cortical atrophy showed significantly reduced handgrip strength compared to patients without cortical atrophy (Z = 3.04; p = 0.002). A similar result was observed when handgrip was compared among patients with or without cerebellar atrophy (Z = 2.54; p = 0.011), but these differences disappeared when the variable age was introduced in a logistic regression analysis.

Close relationships were observed between handgrip strength and bicaudate index (ρ = 0.42), bifrontal index (ρ = −0.41), Evans index (ρ = −0.36), cella index (ρ = −0.37; p < 0.001 in all the cases), ventricular index (ρ = −0.32; p = 0.002), and celda media index (ρ = 0.33; p = 0.012). Handgrip strength was also compared among patients with CT indices below or above the median, finding marked differences in all cases (Table 3). With all indices, handgrip strength was markedly reduced among those patients with more intense atrophy. Classifying handgrip strength according to median values, we found that the variable handgrip strength displaced the variables age, duration of ethanol consumption, and Child-Pugh's score in their relationships with ventricular index, remaining as the sole variable related to it (p = 0.015; odds ratio (OR) of handgrip below the median in relation to more dilated ventricular index = 0.37; confidence interval (CI) = 0.16–0.84). The same was observed with cella index (p < 0.001; OR = 0.21; CI = 0.09–0.50). In addition, age and handgrip strength showed an independent relationship with bicaudate index (p = 0.037; OR = 0.34 (0.13–0.86) in the case of handgrip). Age was the only variable selected when Evans and bifrontal indices above or below the median were compared.

No differences were observed in handgrip strength among cirrhotics and non-cirrhotics (15.16 ± 10.73 vs 17.50 ± 13.99; t = 0.91). No relationships were observed between handgrip strength and liver function parameters (prothrombin, bilirubin, Child-Pugh score), besides a direct correlation with serum albumin (ρ = 0.323; p = 0.001).

### 3.2. Body composition

In Table 2 we show that significant differences were observed among patients and controls regarding lean mass, always reduced among patients. Total lean mass was by far higher among controls than among patients (t = 4.36; p < 0.001), especially if we excluded patients with ascites (t = 4.50; p < 0.001). Close, significant relationships were observed between handgrip strength and right arm lean mass (ρ = 0.40; p < 0.001), left arm lean mass (ρ = 0.29; p = 0.01), right leg lean mass (ρ = 0.44; p < 0.001), left leg lean mass (ρ = 0.36; p = 0.001), trunk lean mass (ρ = 0.30; p = 0.007) and total lean mass (ρ = 0.38; p < 0.001).

Total lean mass was inversely related to age (ρ = −0.30; p = 0.004), as was right arm lean mass (ρ = −0.29; p = 0.006), left arm lean mass (ρ = −0.27; p = 0.008), left leg lean mass (ρ = −0.38; p < 0.001) and right leg lean mass (ρ = −0.36; p < 0.001). Left leg lean mass (ρ = −0.24; p = 0.016), right leg lean mass (ρ = −0.28; p < 0.006) and total lean mass (ρ = −0.23; p = 0.022) were all inversely related to duration of ethanol addiction, but these relationships were displaced by the variable age in all cases. No relationships were observed among the daily amount of ethanol consumed, MCV or GGT values and lean mass variables.

Significant differences were observed when the diverse variables related to lean mass were compared with the bicaudate, bifrontal and cella indices (Table 4), but not with ventricular, Evans, and cella media indices (Fig. 2a–f). However, logistic regression analyses disclosed that the relationships between the CT indices and lean mass variables were dependent on age in all cases. The exception was the relationship observed between cella index and right leg lean mass. This variable was selected after age with a borderline significance (p = 0.051), so that reduced right leg lean mass was associated with a more dilated cella index with an OR of 0.40 and CI ranging 0.159–1.003.

In general, there were trends to lower lean mass among patients with cortical atrophy or cerebellar atrophy (Fig. 3 a, b), that were not significant.

Lean mass parameters were not related to liver function, besides weak correlations between trunk lean mass and bilirubin (ρ = 0.21;

**Table 4**
Lean mass and fat mass compared with CT indices.

| | Bicaudate index | | | Bifrontal index | | | Cella index | | |
|---|---|---|---|---|---|---|---|---|---|
| | Below the median (less atrophy; n = 49) | Over the median (more atrophy; n = 43) | | Below the median (less atrophy; n= 49) | Over the median (more atrophy; n = 43) | | Below the median (n = 46; less atrophy) | Over the median (more atrophy; n = 46) | |
| Left arm lean (g) | 2828 ± 711 | 2671 ± 571 | 1.16 | 2789 ± 701 | 2714 ± 591 | 0.55 | 2778 ± 698 | 2731 ± 604 | 0.34 |
| Left arm fat (g) | 965 ± 568 | 815 ± 360 | 1.45 | 917 ± 572 | 870 ± 402 | 0.45 | 969 ± 578 | 821 ± 396 | 1.43 |
| Right arm lean (g) | 2896 ± 670 | 2505 ± 524 | 3.09*** | 2786 ± 694 | 2631 ± 553 | 1.17 | 2835 ± 678 | 2592 ± 567 | 1.87 |
| Right arm fat (g) | 944 ± 600 | 813 ± 410 | 1.21 | 882 ± 582 | 883 ± 449 | 0.13 | 933 ± 584 | 832 ± 450 | 0.93 |
| Left leg lean (g) | 7896 ± 1574 | 6897 ± 1259 | 3.33*** | 7759 ± 1614 | 7053 ± 1309 | 2.29* | 7793 ± 1623 | 7065 ± 1313 | 2.37* |
| Left leg fat (g) | 2909 ± 1765 | 2775 ± 1480 | 0.39 | 2946 ± 1765 | 2733 ± 1475 | 0.63 | 3101 ± 1888 | 2591 ± 1295 | 1.51 |
| Right leg lean (g) | 7920 ± 1542 | 6909 ± 1308 | 3.37*** | 7774 ± 1596 | 7076 ± 1345 | 2.25* | 7847 ± 1606 | 7048 ± 1322 | 2.61* |
| Right leg fat (g) | 2923 ± 1762 | 2765 ± 1442 | 0.47 | 2952 ± 1756 | 2732 ± 1444 | 0.65 | 3122 ± 1875 | 3576 ± 1264 | 1.64 |
| Trunk lean (g) | 25,864 ± 3893 | 24,380 ± 4209 | 1.76 | 25,830 ± 4279 | 24,419 ± 3772 | 1.67 | 26,108 ± 4222 | 24,233 ± 3768 | 2.25* |
| Trunk fat (g) | 12,659 ± 6604 | 11,359 ± 5880 | 0.99 | 11,909 ± 6658 | 12,214 ± 5885 | 0.23 | 12,399 ± 6763 | 11,704 ± 5803 | 0.53 |
| Total lean (g) | 51,384 ± 7474 | 47,020 ± 6881 | 2.90** | 50,904 ± 7982 | 47,567 ± 6535 | 2.18* | 51,380 ± 7863 | 47,308 ± 6571 | 2.70** |
| Total fat (g) | 21,304 ± 10996 | 18,979 ± 9048 | 1.09 | 20,089 ± 10838 | 20,367 ± 9420 | 0.32 | 20,980 ± 11148 | 19,424 ± 9082 | 0.73 |

*p < 0.05.
**p < 0.01.
***p < 0.005.

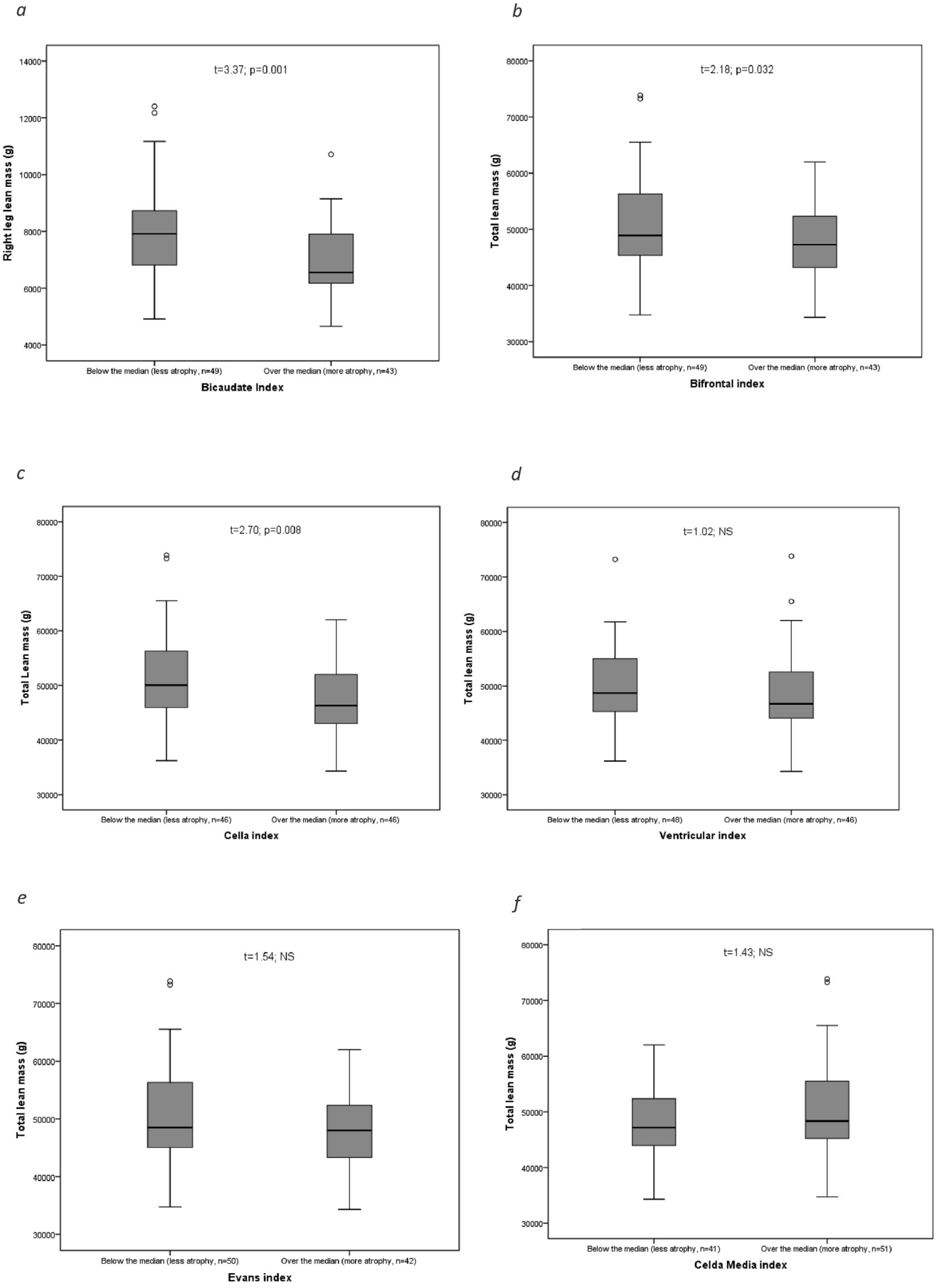


**Fig. 2.** (a–f): several variables related to lean mass compared with the indices derived from brain computed tomography examination.

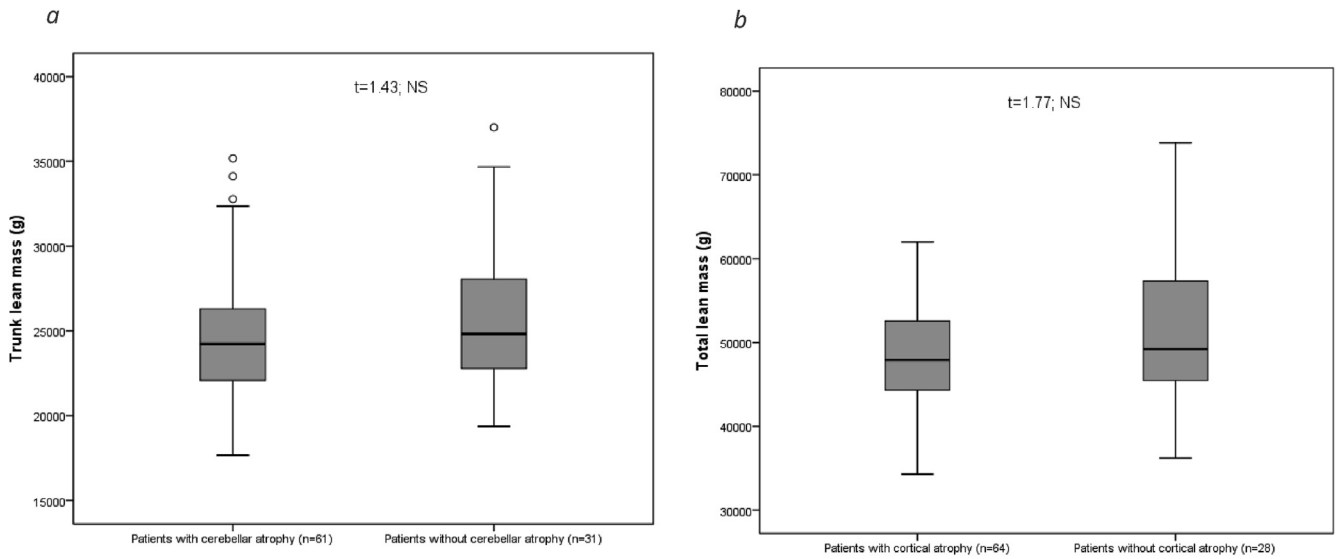


**Fig. 3.** (a,b): several variables related to lean mass among patients with or without cortical atrophy or with or without cerebellar atrophy were not significant.

$p = 0.046$), and between total lean mass and bilirubin ($\rho = 0.21$; $p = 0.048$), but these correlations became non-significant if patients with ascites were excluded.

Differences in fat mass among patients and controls are also evident, but only in arms (Table 2). Despite this, total fat amount was similar among patients and controls, because we observed a trend to higher amount of trunk fat among alcoholics. Indeed, when we calculate a trunk fat/(arms fat + legs fat) index, marked differences were observed among alcoholics and controls regarding fat distribution ($t = 6.71$; $p<<0.001$), with alcoholics accumulating more fat in the trunk than controls. A similar relationship was found when the trunk fat/total fat index was calculated ($t = 5.89$; $p<<0.001$). Smaller, but still significant differences were observed when the trunk lean mass/(arms lean mass + legs lean mass) index was compared among patients and controls, even if the patients with ascites were excluded ($t = 2.76$; $p = 0.007$). Patients showed higher values of this index despite a by far lower total lean mass and lean mass at the arms and legs.

No relationships were observed among CT indices and body fat (either total or by body compartments). No differences at all were observed when fat mass was compared among patients with or without cortical atrophy, or with or without cerebellar atrophy (Fig. 4a,b).

No differences were observed in body fat parameters among cirrhotics and non-cirrhotics, and there were no relationships between fat variables and liver function, assessed by Child-Pugh's score.

## 4. Discussion

Our results clearly show that: 1) Brain atrophy is a very common finding among alcoholics, both among cirrhotics and non-cirrhotics. 2) Alcoholics show a marked reduction in handgrip strength, and also in lean mass, especially at the arms and legs –but not in the trunk, even if patients with ascites were excluded. 3) There is a relationship between reduced lean mass and brain

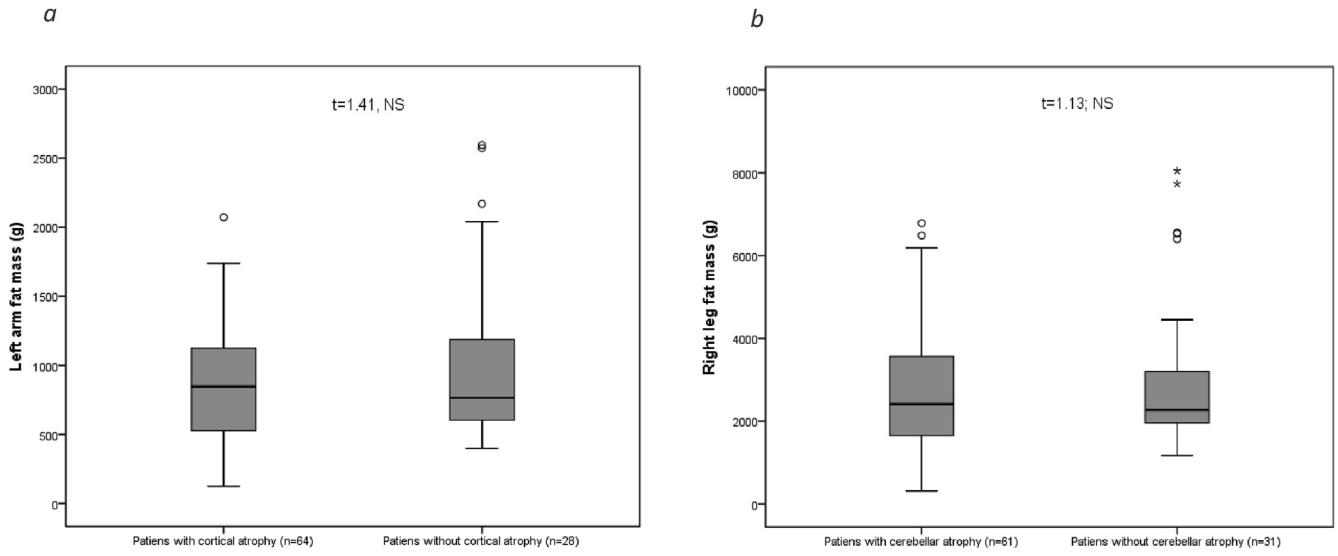


**Fig. 4.** (a,b): several variables related to fat mass among patients with or without cortical atrophy or with or without cerebellar atrophy were not significant.

atrophy, and a close correlation between handgrip strength and brain atrophy, that is independent of age and liver function. 4) Total fat amount is not different among alcoholics and controls, but there are marked differences in fat distribution: alcoholics show less arm fat, but more trunk fat, so that if we calculate the peripheral fat/trunk fat index, marked differences were observed among alcoholics and controls. Neither total fat nor fat distribution were related to brain atrophy.

The first two conclusions are fully in accordance with other reports, and confirm a well established fact. It is generally accepted that ethanol mainly alters brain white matter, but also causes neurodegeneration, especially in the prefrontal areas and some hippocampal regions [22]. The pathogenesis of these alterations is incompletely understood, although many factors seem to play a role including a direct effect of ethanol on the myelin-synthesizing ability of oligodendrocytes leading to disproportionate white matter atrophy, alterations in brain inflammatory milieu [23], oxidative damage, associated vitamin deficiency [24], or altered blood flow [25]. Regarding the second conclusion, Lang et al. [26] showed that muscle atrophy depends on ethanol-mediated inhibition of protein synthesis, mainly related to a translational inefficiency. Increased protein breakdown may also contribute [9], although some controversy exists regarding this item [27], as well as regarding the possible sexual differences in the effect of ethanol on muscle protein metabolism [28]. Reduction in protein synthesis is especially marked in fast-twitch skeletal muscle but is not observed in slow-twitch muscle [29].

However, our last conclusions, relative to the relationships between altered body composition and brain atrophy deserve some commentary. In an observational cross-sectional study like this, the possibility exists that the relationships observed are merely derived from what can be expected when a toxic compound, as ethanol, exerts its deleterious effects simultaneously both on muscle and brain. This possibility cannot be fully disclosed, but multivariate analyses suggest the existence of an independent role of reduced muscle strength on brain atrophy. Indeed, in the current study several CT indices that indicate brain atrophy are related to handgrip strength independently of age, liver function and ethanol consumption. Other authors have also studied the association between brain atrophy and sarcopenia and/or altered muscle strength in conditions other than alcoholism. As commented, Burns et al. [18] found that brain atrophy (assessed by magnetic resonance imaging) was related to brain atrophy in Alzheimer's disease, independent of age and sex, and Nourashemi et al., in a study on community-dwelling normal women aged 75 years and older, found that women in the lowest quartile of lean mass had an OR of 1.43 for cognitive impairment compared with those in the highest quartile [20]. In 2016, Chang et al. [30] performed a meta-analysis of research in which the relationship between sarcopenia and cognitive impairment was assessed. In this meta-analysis seven studies, including collectives of community dwelling older adults or patients with end-stage renal disease, were analyzed. Handgrip strength was assessed in 4 of them, and cognitive impairment was assessed by minimental state examination or similar scales. The authors concluded that sarcopenia was independently related to cognitive impairment. To our knowledge, there are no studies dealing with alcoholism, but the results observed are similar to those reported here: sarcopenia, including altered muscle function, was related to impaired cognitive function or brain atrophy. These results open the discussion of whether atrophied/functional impaired muscle may exert a direct effect on brain or *vice-versa*, as the data provided by Pruznak et al. [31] suggest. These authors showed that intraventricular injection of ethanol led to an inhibition of muscle protein synthesis, so acute ethanol administration in the brain could affect muscle protein synthesis and breakdown. To our knowledge there are no studies that explored what happens with the chronic administration of ethanol.

But, as commented, a likely possibility includes the altered secretion of myokines on the brain [10–12]. The role of muscle-derived factors, especially brain derived neurotrophic factor (BDNF) on brain structure and function has been explored in several neurodegenerative processes such as Huntington's disease [32], Alzheimer's disease [33], psychiatric conditions or merely age related cerebral changes [34]. Although altered BDNF levels have been reported in alcoholics in relation to craving and dependence [35], the potential role of BDNF and/or other myokines on the inverse relationship between muscle strength and brain atrophy in chronic alcoholics is not known and needs future research.

It is also of interest the lack of relationship between fat mass and brain atrophy. It is remarkable that fat mass at the arms and, to a lesser extent, at the legs, is lower among alcoholics, something that is just the opposite with respect to trunk fat. That is, alcoholics have, in general, less fat in the appendicular areas, but more fat in the trunk, so a simple index such as trunk fat/peripheral fat shows very marked differences among alcoholics and controls. Accumulation of fat in the trunk among alcoholics is not a novel finding, since many authors have reported it in the last decades [6], but the relationship between brain atrophy and trunk fat has not been explored in alcoholics, but indeed in other conditions, such as diabetes [16]. Trunk fat is a source of proinflammatory cytokines. From a theoretical point of view it is not surprising that excessive TNF or IL-6 or decreased adiponectin secretion – a profile usually associated with trunk fat accumulation could contribute to neurodegeneration, although in our study no relationship was found between fat amount and/or distribution and brain atrophy.

This study has some limitations. As previously commented, its cross-sectional design does not allow the establishment of causal links between brain atrophy and sarcopenia. Interventional studies, including witnessed ethanol abstinence are needed, as well as longitudinal observational studies. Dietary assessment and determination of serum levels of some parameters such as vitamin D, could also aid to disclose the presence of confounding factors potentially involved both in muscle and brain atrophy in alcoholics. It would also be important to assess if the results observed in this study are also present among alcoholic women. Nevertheless, the results here presented, fully in accordance with the observations derived from studies performed in other conditions characterized by sarcopenia and brain atrophy and/or cognitive impairment, suggest the possibility of a cross-talk between muscle and brain, in which perhaps myokines play a relevant role, a matter that deserves future research.

Therefore the main conclusion of this study is that among alcoholics, as in other neurodegenerative conditions, there is a relationship between reduced lean mass and brain atrophy, and a close correlation between handgrip strength and brain atrophy, that is independent of age, duration of ethanol consumption and liver function. Future research should be aimed to disclose whether or not there is a causal link between both sarcopenia and brain changes, and to clarify the eventual role of myokines in these alterations.

## Statement of authorship

L Romero-Acevedo, D Martínez-Martínez, G Quintero-Platt and MC Martin-González collected the data of the included patients. A González-Díaz (Nuclear Medicine service) performed the body composition analysis. MC Martín- González, F Santolaria-Fernández and E González-Reimers performed statistical analysis. E González-

Reimers drafted the manuscript. E González-Reimers and F Santolaria-Fernández designed the study (senior authors).

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## Conflict of interest

The authors declare that there are no conflicts of interest.

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## References

[1] Mendenhall CL, Anderson S, Weesner RE, Goldberg SJ, Crolic KA. Protein-calorie malnutrition associated with alcoholic hepatitis. Veterans administration cooperative study group on alcoholic hepatitis. Am J Med 1984;76:211–22.
[2] Suter PM. Is alcohol consumption a risk factor for weight gain and obesity? Crit Rev Clin Lab Sci 2005;42:197–227.
[3] Laws A, Terry RB, Barrett-Connor E. Behavioral covariates of waist-to-hip ratio in Rancho Bernardo. Am J Public Health 1990;80:1358–62.
[4] Slattery ML, McDonald A, Bild DE, Caan BJ, Hilner JE, Jacobs Jr DR, et al. Associations of body fat and its distribution with dietary intake, physical activity, alcohol, and smoking in blacks and whites. Am J Clin Nutr 1992;55:943–9.
[5] Greenfield JR, Samaras K, Jenkins AB, Kelly PJ, Spector TD, Campbell LV. Moderate alcohol consumption, dietary fat composition, and abdominal obesity in women: evidence for gene-environment interaction. J Clin Endocrinol Metab 2003;88:5381–6.
[6] Addolorato G, Capristo E, Greco AV, Stefanini GF, Gasbarrini G. Influence of chronic alcohol abuse on body weight and energy metabolism: is excess ethanol consumption a risk factor for obesity or malnutrition? J Intern Med 1998;244:387–95.
[7] Slavin G, Martin F, Ward P, Levi J, Peters T. Chronic alcohol excess is associated with selective but reversible injury to type 2B muscle fibres. J Clin Pathol 1983;36:772–7.
[8] Preedy VR, Peters TJ. The effect of chronic ethanol ingestion on protein metabolism in type-I- and type-II-fibre-rich skeletal muscles of the rat. Biochem J 1988;15(254):631–9.
[9] Simon L, Jolley SE, Molina PE. Alcoholic myopathy: pathophysiologic mechanisms and clinical implications. Alcohol Res 2017;38:207–21.
[10] Iizuka K, Machida T, Hirafuji M. Skeletal muscle is an endocrine organ. Pharmacol Sci 2014;125:125–31.
[11] Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol 2005;98:1154–62.
[12] Pedersen BK, Akerström TC, Nielsen AR, Fischer CP. Role of myokines in exercise and metabolism. J Appl Physiol 2007;103:1093–8.
[13] Eldomiaty MA, Almasry SM, Desouky MK, Algaidi SA. Voluntary running improves depressive behaviours and the structure of the hippocampus in rats: a possible impact of myokines. Brain Res 2017;1657:29–42. https://doi.org/10.1016/j.brainres.2016.12.001.
[14] Phillips C, Baktir MA, Srivatsan M, Salehi A. Neuroprotective effects of physical activity on the brain: a closer look at trophic factor signaling. Front Cell Neurosci 2014 Jun 20;8:170. https://doi.org/10.3389/fncel.2014.00170. eCollection 2014.
[15] Kohut ML, McCann DA, Russell DW, Konopka DN, Cunnick JE, Franke WD, et al. Vanderah EAerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. Brain Behav Immun 2006;20:201–9.
[16] Climie RE, Moran C, Callisaya M, Blizzard L, Sharman JE, Venn A, et al. Abdominal obesity and brain atrophy in type 2 diabetes mellitus. PLoS One 2015;10(11). https://doi.org/10.1371/journal.pone.0142589. e0142589.
[17] Razay G, Vreugdenhil A, Wilcock G. Obesity, abdominal obesity and Alzheimer disease. Dement Geriatr Cogn Disord 2006;22:173–6.
[18] Burns JM, Johnson DK, Watts A, Swerdlow RH, Brooks WM. Reduced lean mass in early Alzheimer disease and its association with brain atrophy. Arch Neurol 2010;67:428–33. https://doi.org/10.1001/archneurol.2010.38.
[19] Kim JK, Choi SR, Choi MJ, Kim SG, Lee YK, Noh JW, et al. Prevalence of and factors associated with sarcopenia in elderly patients with end-stage renal disease. Clin Nutr 2014;33:64–8. https://doi.org/10.1016/j.clnu.2013.04.002.
[20] Nourhashémi F, Andrieu S, Gillette-Guyonnet S, Reynish E, Albarède JL, Grandjean H, et al. Is there a relationship between fat-free soft tissue mass and low cognitive function? Results from a study of 7,105 women. J Am Geriatr Soc 2002;50:1796–801.
[21] Colcombe SJ, Erickson KI, Raz N, Webb AG, Cohen NJ, McAuley E, et al. Aerobic fitness reduces brain tissue loss in aging humans. J Gerontol A Biol Sci Med Sci. 2003;58:176–80.
[22] de la Monte SM, Kril JJ. Human alcohol-related neuropathology. Acta Neuropathol 2014;127:71–90.
[23] Qin L, He J, Hanes RN, Pluzarev O, Hong JS, Crews FT. Increased systemic and brain cytokine production and neuroinflammation by endotoxin following ethanol treatment. J Neuroinflammation 2008;18(5):10. https://doi.org/10.1186/1742-2094-5-10.
[24] He X, Sullivan EV, Stankovic RK, Harper CG, Pfefferbaum A. Interaction of thiamine deficiency and voluntary alcohol consumption disrupts rat corpus callosum ultrastructure. Neuropsychopharmacology 2007;32:2207–16.
[25] Crews FT, Nixon K. Mechanisms of neurodegeneration and regeneration in alcoholism. Alcohol Alcohol 2009;44:115–27. https://doi.org/10.1093/alcalc/agn079.
[26] Lang CH, Frost RA, Kumar V, Wu D, Vary TC. Impaired protein synthesis induced by acute alcohol intoxication is associated with changes in eIF4E in muscle and eIF2B in liver. Alcohol Clin Exp Res 2000;24:322–31.
[27] Steiner JL, Lang CH. Dysregulation of skeletal muscle protein metabolism by alcohol. Am J Physiol Endocrinol Metab 2015;308:E699–712. https://doi.org/10.1152/ajpendo.00006.2015.
[28] Steiner JL, Kimball SR, Lang CH. Acute alcohol-induced decrease in muscle protein synthesis in female mice is REDD-1 and mTOR-independent. Alcohol Alcohol 2016;51:242–50. https://doi.org/10.1093/alcalc/agv105.
[29] Lang CH, Wu D, Frost RA, Jefferson LS, Kimball SR, Vary TC. Inhibition of muscle protein synthesis by alcohol is associated with modulation of eIF2B and eIF4E. Am J Physiol 1999;277:E268–76.
[30] Chang KV, Hsu TH, Wu WT, Huang KC, Han DS. Association between sarcopenia and cognitive impairment: A systematic review and meta-analysis. J Am Med Dir Assoc 2016;17. https://doi.org/10.1016/j.jamda.2016.09.013. 1164.e7–1164.e15.
[31] Pruznak AM, Nystrom J, Lang CH. Direct central nervous system effect of alcohol alters synthesis and degradation of skeletal muscle protein. Alcohol Alcohol 2013;48:138–45. https://doi.org/10.1093/alcalc/ags113.
[32] Ferrer I, Goutan E, Marín C, Rey MJ, Ribalta T. Brain-derived neurotrophic factor in Huntington disease. Brain Res 2000;866:257–61.
[33] Borba EM, Duarte JA, Bristot G, Scotton E, Camozzato AL, Chaves ML. Brain-derived neurotrophic factor serum levels and hippocampal volume in mild cognitive impairment and dementia due to alzheimer disease. Dement Geriatr Cogn Dis 2016;6:559–67. https://doi.org/10.1159/000450601.
[34] Hashizume M, Hachisu M, Yoshida H, Kim M, Kim HK, Amano Y, et al. Serum brain-derived neurotrophic factor level in elderly women depression: a community-based study. Prog Neuro-Psychopharmacol Biol Psychiatry 2015;56:109–16. https://doi.org/10.1016/j.pnpbp.2014.08.012.
[35] Costa MA, Girard M, Dalmay F, Malauzat D. Brain-derived neurotrophic factor serum levels in alcohol-dependent subjects 6 months after alcohol withdrawal. Alcohol Clin Exp Res 2011;35:1966–73. https://doi.org/10.1111/j.1530-0277.2011.01548.x.