META-ANALYSIS

Osteoporosis and bone fractures in alcoholic liver disease: A meta-analysis

Chang Seok Bang, In Soo Shin, Sung Wha Lee, Jin Bong Kim, Gwang Ho Baik, Ki Tae Suk, Jai Hoon Yoon, Yeon Soo Kim, Dong Joon Kim

Chang Seok Bang, Sung Wha Lee, Jin Bong Kim, Gwang Ho Baik, Ki Tae Suk, Jai Hoon Yoon, Yeon Soo Kim, Dong Joon Kim, Department of Internal Medicine, Hallym University College of Medicine, Chuncheon 200-704, South Korea
In Soo Shin, College of Education, Jeonju University, Jeonju 560-759, South Korea
Author contributions: Kim DJ and Bang CS designed research; Bang CS, Lee SW, Suk KT, Yoon JH and Kim YS performed research; Shin IS, Kim JB, Baik GH and Kim DJ contributed new reagent/analytic tools; Bang CS and Kim DJ analyzed data; Bang CS wrote the paper.

Correspondence to: Dong Joon Kim, MD, PhD, Department of Internal Medicine, Hallym University College of Medicine, Kyo-dong, Chuncheon 200-704,
South Korea. djkim@hallym.ac.kr
Telephone: +82-33-240-5647
Fax: +82-33-241-8064

Abstract

AIM: To evaluate the association between alcoholic liver disease (ALD) and bone fractures or osteoporosis.

METHODS: Non-randomized studies were identified from databases (PubMed, EMBASE, and the Cochrane Library). The search was conducted using Boolean operators and keywords, which included "alcoholic liver diseases", "osteoporosis", or "bone fractures". The prevalence of any fractures or osteoporosis, and bone mineral density (BMD) were extracted and analyzed using risk ratios and standardized mean difference (SMD). A random effects model was applied.

RESULTS: In total, 15 studies were identified and analyzed. Overall, ALD demonstrated a RR of 1.944 (95%CI: 1.354-2.791) for the development of bone fractures. However, ALD showed a RR of 0.849 (95%CI: 0.523-1.380) for the development of osteoporosis. BMD was not significantly different between the ALD and control groups, although there was a trend toward lower BMD in patients with ALD (SMD in femur-BMD: -0.172, 95%CI: -0.453-0.110; SMD in spine-BMD: -0.169, 95%CI: -0.476-0.138). Sensitivity analyses showed consistent results.

CONCLUSION: Current publications indicate significant associations between bone fractures and ALD, independent of BMD or the presence of osteoporosis.

Key words: Alcoholic liver diseases; Bone fractures; Osteoporosis

Core tip: Excessive alcohol consumption is a well-established risk factor for osteoporosis and bone fractures. However, light amounts of alcohol ingestion is known to be associated with higher bone mineral density (BMD) and low fracture rates. This study evaluated the current evidence regarding osteoporosis and bone fractures in alcoholic liver disease (ALD). In this meta-analysis, there was significant associations between bone fractures and ALD, independent of BMD or the presence of osteoporosis. Although the

mechanism of bone fractures in ALD is not totally understood, further research utilizing a homogenous population and controlling for confounding risk factors for fractures could elucidate the mechanism.

INTRODUCTION

Chronic excessive alcohol consumption is a well-established risk factor for low bone density and bone fractures[1]. This is included in the fracture risk assessment tool (FRAX), which estimates the 10-year probability of bone fractures combined with other clinical risk factors and the bone mineral density (BMD) of the femoral neck[2,3]. It is assumed that the decreases in bone mass and strength resulting from heavy alcohol use are due to an imbalance between bone formation and resorption[4]. However, ingestion of light or moderate amounts of alcohol is known to be associated with higher BMD and decreased fracture rates[5-15], although conflicting results exist because of inconsistent standards of classification of light, moderate, or heavy alcohol consumption[13,16].

Osteoporosis and bone fractures are frequently overlooked complications in patients with chronic liver disease that could result in serious outcomes[17]. However, the exact prevalence or mechanism of osteodystrophy in patients with alcoholic liver disease (ALD), the deleterious outcome of chronic alcohol abuse, have not been described. The aim of this study was to evaluate the association between ALD and bone fractures or osteoporosis.

MATERIALS AND METHODS

Literature search
MEDLINE (through PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library were searched using common keywords related to ALD, osteoporosis, and bone fractures (from inception to April 2014). Medical Subject Headings (MeSH) terminology was used because all 3 databases permit searching using MeSH terminology. The keywords used included "alcoholic liver diseases", "osteoporosis", or "bone fractures" using Boolean operators. Only publications on human subjects were searched, and the bibliographies of relevant articles were also reviewed to identify additional studies. The language of publication was not restricted.

Selection criteria
Due to a lack of randomized-controlled studies relevant to this topic, we included case-control or cohort studies meeting all of the following criteria: (1) designed to evaluate ALD in the target or control group; and (2) included at least one outcome (prevalence of any bone fractures, prevalence of osteoporosis, or BMD) that enabled comparisons of osteodystrophy between patients with ALD and the control group. The exclusion criteria were as follows: (1) incomplete data; (2) review article; or (3) abstract only (study not published as full-text article).

Selection of relevant studies
Two of the authors (C.S.B. and G.H.B.) independently evaluated the eligibility of all studies retrieved from the databases based on the predetermined selection criteria. The abstracts of all identified studies were reviewed to exclude irrelevant articles. Full-text reviews were performed to determine whether the inclusion criteria were satisfied by the remaining studies. Disagreements between the two evaluators were resolved by discussion or by consultation with a third author (D.J.K.).

Assessment of methodological quality
The methodological quality of the enrolled studies was assessed using the Newcastle-Ottawa Scale[18,19]. This tool is categorized into three parameters: the selection of the study population, the comparability of the groups, and the ascertainment of the exposure or outcome. Each parameter consists of subcategorized questions: selection ($n = 4$), comparability ($n = 1$), and exposure or outcome ($n = 3$). Stars awarded for each item serve as a quick visual assessment for the methodological quality of the studies. A study can be awarded a maximum of nine stars, indicating the highest quality[18,19]. The included studies were classified as high-quality ($\geqslant$ 7 stars) or low-quality (< 7 stars). Sensitivity analyses were performed according to the criteria described above.

Main and modifier-based analyses
We investigated the relationship between ALD and bone fractures or osteoporosis using adjusted risk ratios (RRs) and standardized mean difference (SMD). The prevalence of any fractures or osteoporosis assessed by radiologic examinations and BMD assessed by dual-energy X-ray absorptiometry (DXA) or dual-photon absorptiometry (DPA) were extracted and analyzed. Osteoporosis was defined as a value for BMD that was 2.5 standard deviations or more below the reference range[20]. We also performed sensitivity analyses based on methodological quality (high or low), the area measured to determine BMD (femoral neck or spine), the type of control group (normal, healthy control or chronic liver diseases other than
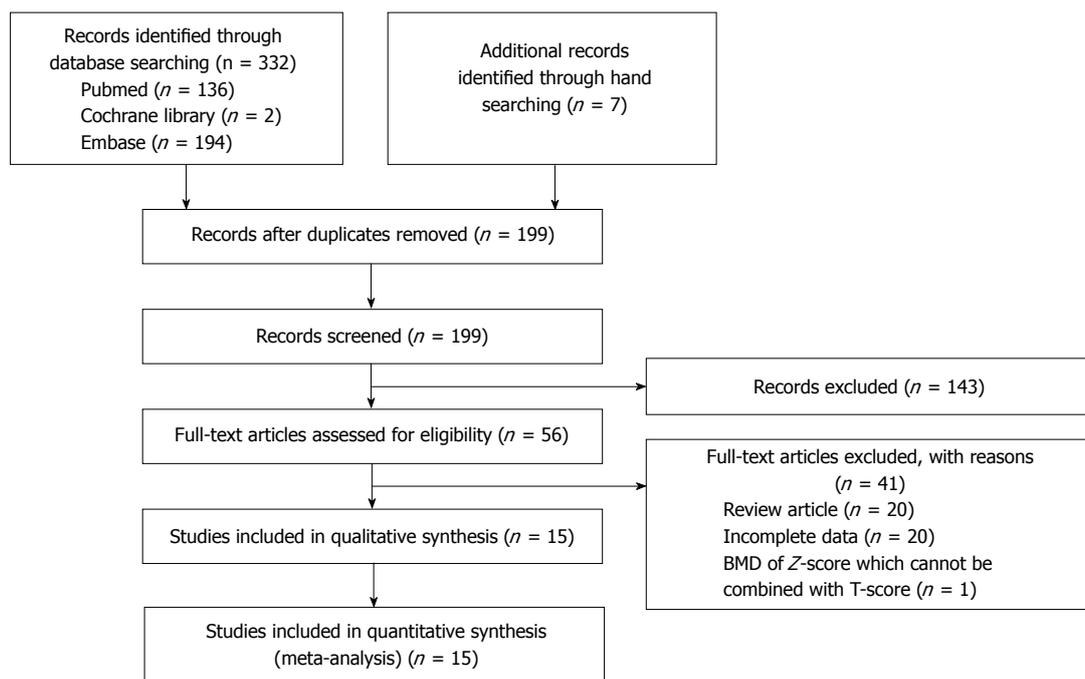
```
┌─────────────────────────┐   ┌─────────────────────────┐
│ Records identified through │   │   Additional records    │
│ database searching (n = 332)│   │ identified through hand │
│   Pubmed (n = 136)      │   │   searching (n = 7)     │
│ Cochrane library (n = 2)│   │                         │
│   Embase (n = 194)      │   │                         │
└─────────────────────────┘   └─────────────────────────┘
            │                              │
            └──────────────┬───────────────┘
                           ▼
        ┌──────────────────────────────────────┐
        │ Records after duplicates removed (n = 199) │
        └──────────────────────────────────────┘
                           │
                           ▼
        ┌──────────────────────────────────────┐
        │      Records screened (n = 199)       │─────────┐
        └──────────────────────────────────────┘         ▼
                           │              ┌─────────────────────────────┐
                           ▼              │ Records excluded (n = 143)  │
        ┌──────────────────────────────────────┐ └─────────────────────────────┘
        │ Full-text articles assessed for eligibility (n = 56) │──┐
        └──────────────────────────────────────┘   ▼
                           │       ┌──────────────────────────────────────┐
                           ▼       │ Full-text articles excluded, with reasons │
        ┌──────────────────────────────────────┐ │          (n = 41)          │
        │ Studies included in qualitative synthesis (n = 15) │ │ Review article (n = 20)    │
        └──────────────────────────────────────┘ │ Incomplete data (n = 20)   │
                           │       │ BMD of Z-score which cannot be │
                           ▼       │ combined with T-score (n = 1)  │
        ┌──────────────────────────────────────┐ └──────────────────────────────────────┘
        │ Studies included in quantitative synthesis │
        │      (meta-analysis) (n = 15)         │
        └──────────────────────────────────────┘
```

Figure 1 Flow diagram for identification of relevant studies.

ALD), and the effect size, excluding outliers whenever possible. Both a cumulative analysis and a one-study-removed analysis were also performed.

Unit of analysis

For the present evaluation, the independent study was the primary unit of analysis. Thus, for the studies that had multiple control groups (reported multiple outcomes)[21-25] or multiple BMD measured at the femoral neck or spine simultaneously[23,26], an approach with a shifting unit of analysis was used for the determination of an independent estimate of the effect[27]. In these studies, the biggest effect sizes of the control groups or the BMD were used.
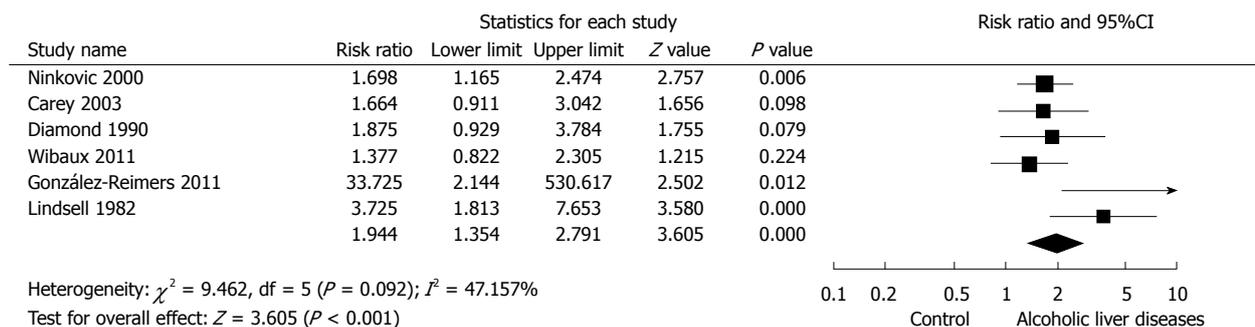
Statistical analysis

Comprehensive meta-analysis software (version 2.2.064, Borenstein M, Hedges L, Higgins J and Rothstein H. Englewood, NJ: Biostat; United States) was used for this meta-analysis. We calculated the RRs with 95%CIs using 2×2 tables from the original articles whenever possible to reveal the relationship between ALD and bone fractures or osteoporosis. To compare the BMD directly between patients with ALD and the control groups, the SMD was also used as another effect size calculation. SMD is the difference in mean value between groups divided by the SD among the populations. Therefore, even if the actual scales for BMD are different across the articles, individual data can be combined. SMD was calculated as follows: SMD = $(M_1 - M_2)$ / pooled SD, where M_1 is the mean BMD in the ALD group and M_2 is the mean BMD in the control group[28]. A negative value of SMD means the ALD group has a lower BMD than the control group. Heterogeneity was tested using the I^2 test, which measures the percentage of total variation across studies[29]. I^2 was calculated as follows: I^2 (%) = 100 × (Q-df)/Q, where Q is Cochrane's heterogeneity statistic and df means the degree of freedom. Negative values for I^2 were set to zero, and an I^2 value over 50% was considered to be of substantial heterogeneity (range of 0-100%)[30]. Pooled RRs with 95%CIs were calculated using a random effects model and the method of DerSimonian and Laird because of methodological heterogeneity[31]. These results were confirmed again by the I^2 test. A fixed effects model using the inverse variance-weighted (Woolf's) method was used in the sensitivity analyses, including cumulative and one-study-removed analyses, based on the assumption of a common effect size shared by the subgroup studies[32,33]. Significance was set at $P = 0.05$ in both models. Publication bias was evaluated using Begg's funnel plot, Egger's test of the intercept, Duval and Tweedie's trim and fill, and Begg and Mazumdar's rank correlation test[34-38].

RESULTS

Identification of relevant studies

Figure 1 shows a flow diagram of how relevant studies were identified. A total of 339 articles was identified by a search of 3 core databases and a manual search of relevant bibliographies. In all, 140 duplicate studies and an additional 143 studies were excluded during the initial screening through a review of the titles and abstracts. The full texts of the remaining 56 studies were thoroughly reviewed. Among these studies, 41

Study name	Risk ratio	Lower limit	Upper limit	*Z* value	*P* value
Ninkovic 2000	1.698	1.165	2.474	2.757	0.006
Carey 2003	1.664	0.911	3.042	1.656	0.098
Diamond 1990	1.875	0.929	3.784	1.755	0.079
Wibaux 2011	1.377	0.822	2.305	1.215	0.224
González-Reimers 2011	33.725	2.144	530.617	2.502	0.012
Lindsell 1982	3.725	1.813	7.653	3.580	0.000
	1.944	1.354	2.791	3.605	0.000

Heterogeneity: χ^2 = 9.462, df = 5 (P = 0.092); I^2 = 47.157%

Test for overall effect: Z = 3.605 (P < 0.001)

Figure 2 Association between alcoholic liver diseases and bone fractures. The size of each square is proportional to the study's weight. Diamond is the summary estimate from the pooled studies with 95% CI. ALD: Alcoholic liver diseases; CI: Confidence interval (random effect model).

were excluded from the final analysis. The reasons for study exclusion during the final review were as follows: review article (n = 20), incomplete data (n = 20), or use of Z-score for BMD, which cannot be combined with T-score (n = 1). The remaining 15 non-randomized studies were included in the final analysis.

Characteristics of studies included in the final analysis

Within the 15 studies, we identified a total of 726 participants (313 patients with ALD *vs* 413 controls) in the analysis of bone fractures, 470 participants (260 patients with ALD *vs* 210 controls) in the analysis of osteoporosis, and 769 participants (391 patients with ALD *vs* 378 controls) in the analysis of BMD. The clinical characteristics of the enrolled studies are shown in Table 1.

The enrolled studies were published between 1982 and 2011. Eight studies were conducted in Europe[21,25,39-44], whereas the remaining studies were conducted in the United States (n = 3)[22,23,45], Canada (n = 1)[24], Australia (n = 1)[46], India (n = 1)[26], and Korea (n = 1)[47]. All 15 articles were written in English. The study format of each study was as follows; cohort study (10)[21-26,39,40,42,45] and case-control study (5)[41,43,44,46,47]. Three studies included a normal healthy population as the control group[40,41,44], although the remaining studies included patients with chronic liver diseases other than alcoholic etiologies as the control groups[21-26,39,42,43,45-47].

Among the included studies, 4 studies[22,25,26,42] had ALD groups that consisted only of cirrhotic patients, whereas 2 studies[44,47] included no alcoholic cirrhotic patients, and in 5 studies[23,24,39,45,46], the presence or absence of cirrhosis was not specified.

As for the measurement of BMD, only 1 study used DPA using Prodigy: DPX-NT /DPX-MD + (General Electric, Milwaukee, WI)[22], and the remaining studies[21,24,25,40,41,43,45,47] used DXA.

In terms of the methodological quality, the authors classified the included studies as high-quality ($\geqslant$ 7 stars) or low-quality (< 7 stars). Six studies[26,39,40,45-47] were classified as high-quality, whereas the remaining 9 studies[21-25,41-44] were classified into the low-quality group (Table 2).

Association between ALD and bone fractures or osteoporosis

The overall association of ALD and bone fractures was evaluated by a random effects model-based meta-analysis of 6 studies[39,41,42,44-46]. Overall, ALD showed a RR of 1.944 (95%CI: 1.354-2.791, P < 0.001) for the development of bone fractures (Figure 2).

The relationship between ALD and osteoporosis was assessed by a random effects model-based meta-analysis of 5 studies[23,26,43,45,47]. ALD showed a RR of 0.849 (95%CI: 0.523-1.380, P = 0.509) for the development of osteoporosis (Figure 3).

To compare the BMD directly between patients with ALD and the control groups, the authors performed a random effects model-based meta-analysis of 7 studies[21,22,24,25,40,43,47] in which the BMD was measured at the femoral neck and 9 studies[21,22,24,25,40,41,43,45,47] in which the BMD was measured at the spine. BMD was not significantly different between the ALD and control groups, although there was a trend toward lower BMD in patients with ALD (SMD in the femoral neck BMD: -0.172, -0.453-0.110, P = 0.233; SMD in the spine BMD: -0.169, -0.476-0.138, P = 0.282).
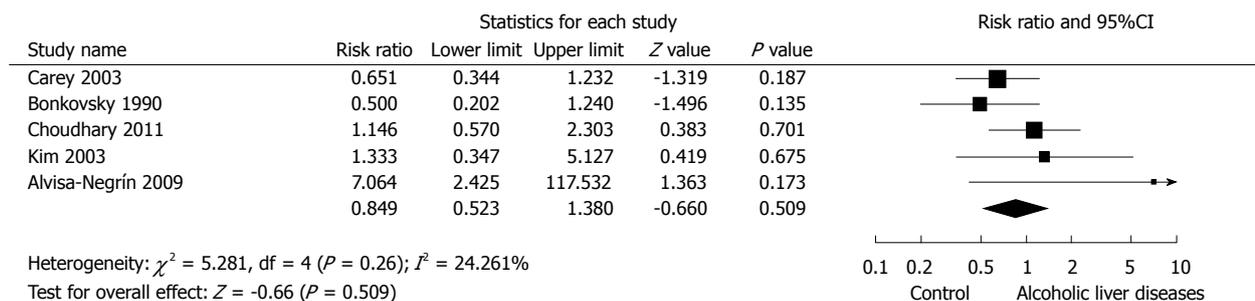
Sensitivity meta-analysis

The cumulative meta-analysis of the enrolled studies in the order of published year showed a decreasing trend of RRs, but a consistent and statistically significant increase in bone fractures. With regard to osteoporosis, the cumulative meta-analysis of the enrolled studies showed an increasing trend of RRs that was consistently non-statistically significant. For the measurement of BMD, cumulative meta-analyses of enrolled studies showed a decreasing trend in SMD, although there was still no difference in BMD *vs* the control group. The one-study-removed meta-analyses of the enrolled studies also showed consistent results.

In the sensitivity analyses of high-quality[39,45,46] and low-quality[41,42,44] studies for bone fractures, consistent results were noted (RR = 1.719, 95%CI: 1.285-2.299, P < 0.001; RR = 2.058, 95%CI: 1.360-3.114, P = 0.001). Consistent results were also noted in the

Table 1 Clinical data of included studies

Ref.	Population characteristics	LC in ALD	Bone fractures — Fracture site	Bone fractures — ALD fracture	Bone fractures — Total ALD	Bone fractures — Control fracture	Bone fractures — Total control	Osteoporosis — ALD osteoporosis	Osteoporosis — Total ALD	Osteoporosis — Control osteoporosis	Osteoporosis — Total control	ALD BMD	Control BMD
Lindsell et al[44]	149 CLD (72 ALD, 77 non-alcoholic CLD), 149 normal controls	0	Rib or clavicle	18	72	10	149 (normal control)						
Diamond et al[46]	115 CLD (M: 72, F: 43), 113 Controls (M: 52, F: 61)	Unidentifiable	Peripheral bone	12	40	12	75 (other CLD)						
Bonkovsky et al[23]	133 CLD (M: 70, F: 63, Mean age: 47 ± 1.1)	Unidentifiable						5 (L), 4 (FN)	32	15 (L), 5 (FN)	48 (other LC)		
Ninkovic et al[39]	37 CLD (6 ALD, 31 other CLD) (M: 20, F: 17, Mean age: 51.3, range: 32-65)	Unidentifiable	Vertebra	6	6	17	31 (other CLD)						
Ninkovic et al[21]	243 CLD (M: 128, F: 115, Mean age: 51.1 ± 10.9)	Predominantly LC			46		55 (HCV)					T (L1-4): -0.94 ± 1.38, T (FN): -1.49 ± 1.15	T (L1-4): -1.59 ± 1.6, T (FN): -1.66 ± 1.27
Carey et al[45]	207 CLD (66 ALD, 73 HCV + ALD, 68 HCV) (M: 131, F: 76, Mean age: 51, range: 32-68)	Unidentifiable	Overall fractures	21	66	13	68 (HCV)	12	66	19	68 (HCV)	T (L1-4): -0.87 ± 1.61	T (L1-4): -1.43 ± 1.68
Kim et al[47]	18 ALD (Mean age: 50.2 ± 9.5), 18 normal controls (Mean age: 51.2 ± 14)	0						4	18	3	18 (normal control)	T (L2-4): 1.04 ± 0.14, T (FN): 0.844 ± 0.12	T (L2-4): 1.131 ± 0.22, T (FN): 0.908 ± 0.15
Sokhi et al[22]	104 CLD (M: 54, F: 50, Mean age: 54.4 ± 12.9)	All (17)			17		69 (LC-HCV)					T (L2-4): -1.17 ± 0.16, T (FN): 0.97 ± 0.18	T (L2-4): 1.23 ± 0.25, T (FN): 0.98 ± 0.16
Alvisa-Negrin et al[43]	77 ALD (M: 68, F: 9, Mean age: 50.43 ± 10.81), 28 normal controls (M: 25, F: 3, Mean age: 49.83 ± 9.24)	41 ALC, 30 Non-LC						9	77	0	28 (normal control)	[1]T (L): -1.2 ± 1.16, T (FN): -1.1 ± 1.28	[1]T (L): -0.49 ± 0.89, T (FN): -0.5 ± 1.23
González-Reimers et al[40]	124 ALD (Mean age: 50.5 ± 11.23), 38 Controls (Mean age: 48.47 ± 11.08)	51 ALC, 61 Non-LC			124		38 (normal control)					[2]T (L5): -1.17 ± 1.22, T (FN): -1.24 ± 1.38	[2]T (L5): -0.5 ± 0.86, T (FN): -0.36 ± 1.34
Mitchell et al[24]	117 CLD (M: 74, F: 43, Mean age: 50.4 ± 10.5)	Unidentifiable			20		46 (viral CLD)					T (L1-4): -1.51 ± 1.35, T (FN): -1.31 ± 1.02	T (L1-4): -1.08 ± 1.35, T (FN): -1.11 ± 1.07
Mahmoudi et al[25]	109 CLD (M: 72, mean age: 55.3 ± 11.4, F: 37, mean age: 65.2 ± 11)	All (31)			31		43 (LC-HCV)					T (L1-4): -0.34 ± 1.46, T (FN): -0.07 ± 1.45	T (L1-4): -0.83 ± 1.66, T (FN): -0.56 ± 1.49
Wibaux et al[42]	99 CLD (M: 79, F: 20, mean age: 55 ± 8)	All (39)	Vertebra	17	39	19	60 (other CLD)						
Choudhary et al[26]	115 LC (M: 107, F: 8, mean age: 49 ± 5.5)	All (67)						16	67	10	48 (viral LC)		
González-Reimers et al[41]	90 ALD (Mean age: 50.14 ± 10.49), 30 normal controls (Mean age: 50.11 ± 10.4)	40 ALC, 48 Non-LC	Overall fractures	49	90	0	30 (normal control)					[3]T (L): -1.15 ± 1.18	[3]T (L): -0.56 ± 0.9

[1]Measured only in 23 patients for each group; [2]Measured in 117 patients with ALD and 24 patients in control group; [3]Measured in 85 patients with ALD and 28 patients in control group. BMD: Bone mineral density; LC: Liver cirrhosis; ALD: Alcoholic liver disease; CLD: Chronic liver disease; Other CLD: CLD of etiology other than alcohol; L: Lumbar spine; FN: Femoral neck bone; Other LC: Liver cirrhosis of etiology other than alcohol; HCV: Chronic hepatitis C.

Study name	Risk ratio	Lower limit	Upper limit	Z value	P value	Risk ratio and 95%CI
		Statistics for each study				
Carey 2003	0.651	0.344	1.232	-1.319	0.187	
Bonkovsky 1990	0.500	0.202	1.240	-1.496	0.135	
Choudhary 2011	1.146	0.570	2.303	0.383	0.701	
Kim 2003	1.333	0.347	5.127	0.419	0.675	
Alvisa-Negrín 2009	7.064	2.425	117.532	1.363	0.173	
	0.849	0.523	1.380	-0.660	0.509	

Heterogeneity: χ^2 = 5.281, df = 4 (P = 0.26); I^2 = 24.261%

Test for overall effect: Z = -0.66 (P = 0.509)

Figure 3 Association between alcoholic liver diseases and osteoporosis. The size of each square is proportional to the study's weight. Diamond is the summary estimate from the pooled studies with 95%CI. ALD: Alcoholic liver diseases; CI: Confidence interval (Random effect model).

Table 2 Methodological quality of included studies measured by Newcastle-Ottawa scale				
Study	**Selection**	**Comparability**	**Exposure or outcome**	**Total**
Lindsell *et al*[44]	2		3	5
Diamond *et al*[46]	3	1	3	7
Bonkovsky *et al*[23]	3		2	5
Ninkovic *et al*[39]	4		3	7
Ninkovic *et al*[21]	3		3	6
Carey *et al*[45]	3	1	3	7
Kim *et al*[47]	3	2	3	8
Sokhi *et al*[22]	3		3	6
Alvisa-Negrín *et al*[43]	3	1	2	6
González-Reimers *et al*[40]	3	1	3	7
Mitchell *et al*[24]	3		3	6
Mahmoudi *et al*[25]	3		3	6
Wibaux *et al*[42]	3		3	6
Choudhary *et al*[26]	3	2	3	8
González-Reimers *et al*[41]	3	1	2	6

sensitivity analysis of osteoporosis in both the high-quality[26,45,47] and low-quality[23,43] studies (RR = 0.885, 95%CI: 0.568-1.381, P = 0.592; RR = 0.642, 95%CI: 0.271-1.523, P = 0.315).

When analyzing the included studies by the characteristics of the control, the association between ALD and bone fractures was statistically significant both in studies utilizing the normal healthy population as the control arm[41,44] (RR = 7.379, 95%CI: 1.001-54.391, P < 0.05) and studies with CLD (etiology other than alcohol) serving as the control arm[39,42,45,46] (RR = 1.629, 95%CI: 1.265-2.099, P < 0.001).

In the analysis of the association between ALD and bone fractures, the outlier[41] was noted to have an effect size of 33.725 (RR) (Figure 2). After excluding this outlier[41] in the analysis of the association between ALD and bone fractures, the result was unchanged and was statistically significant (RR = 1.811, 95%CI: 1.370-2.395, P < 0.001).

For the association between ALD and osteoporosis, studies using a normal, healthy control-arm[43,47] showed a RR = 1.908 (95%CI: 0.498-7.300, P = 0.346), and studies with CLD (etiology other than alcohol) as a control arm[23,26,45] showed a RR = 0.751 (95%CI: 0.474-1.188, P = 0.221), which did not differ from the general analysis (Figure 3).

Currently, DXA is recommended for the measurement or monitoring of BMD[48]. A T-score measured by DPA, a different tool for the measurement of BMD, could result in significant bias. Thus, an analysis excluding the study[22] that utilized DPA for the measurement of BMD was performed. The sensitivity analysis for BMD excluding the study that measured BMD by DPA demonstrated results consistent with the full analysis (SMD in femoral neck BMD: -0.157, -0.357-0.043, P = 0.123; SMD in spine BMD: -0.073, -0.234-0.088, P = 0.375).

Analysis of publication bias

A funnel plot for the enrolled studies was asymmetrical. Egger's regression test revealed that the intercept was 2.442 [95%CI: -0.282-5.167, *t*-value: 2.489, df: 4, P = 0.034 (1-tailed) and P = 0.068 (2-tailed)]. A trim and fill analysis showed that 1 study was missed or trimmed. The rank correlation test showed a Kendall's tau of 0.800 with a continuity correction [P = 0.012 (1-tailed) and P = 0.024 (2-tailed)].

A funnel plot for the enrolled studies of the analysis of the association between ALD and osteoporosis is also asymmetrical. However, Egger's regression test revealed that the intercept was 1.644 [95%CI: -2.081-5.368, *t*-value: 1.405, df: 3, P = 0.127 (1-tailed) and P = 0.255 (2-tailed)]. A trim and fill analysis showed that 2 studies were missed or trimmed. The rank correlation test showed a Kendall's tau of 0.300 with a continuity correction [P = 0.231 (1-tailed) and P = 0.462 (2-tailed)].

In the evaluation of the BMD measured at the femoral neck between the ALD and control groups, the resulting funnel plot was of a symmetrical shape. Egger's regression test revealed that the intercept was -3.701 [95%CI: -12.537-5.135, *t*-value: 1.076, df: 5, P = 0.165 (1-tailed) and P = 0.331 (2-tailed)]. A trim and fill analysis showed that no study was missed or trimmed. The rank correlation test showed a Kendall's tau of -0.19 with a continuity correction [P = 0.274 (1-tailed) and P = 0.548 (2-tailed)].

In the evaluation of the BMD measured at the spine between the ALD and control groups, the funnel plot showed a symmetrical shape. Egger's regression test revealed that the intercept was -6.231 [95%CI:

-12.759-0.296, *t*-value: 2.257, df: 7, *P* = 0.029 (1-tailed) and *P* = 0.059 (2-tailed)]. A trim and fill analysis showed that no study was missed or trimmed. The rank correlation test showed a Kendall's tau of -0.25 with a continuity correction [*P* = 0.174 (1-tailed) and *P* = 0.348 (2-tailed)].

Overall, publication bias was detected in the analysis of bone fractures and osteoporosis. However, there was no evidence of publication bias in the analysis of BMD.

DISCUSSION

In this meta-analysis, bone fracture was associated with ALD, whereas osteoporosis was not associated with ALD. This signifies that the fractures occurring in patients with ALD could be BMD-independent fractures. This result is consistent with the findings of a previous meta-analysis by Kanis *et al*[49]. This study concluded that high intake of alcohol confers a substantial risk for fractures and that this risk is largely independent of BMD[49]. However, there are several considerations when interpreting the results of these studies. The meta-analysis by John A. Kanis *et al*[49] aimed to quantify the fracture risk associated with alcohol consumption in the normal population. As demonstrated in previous studies, light to moderate amounts of alcohol use decrease fracture rates and increase bone density, which is contrary to the results of heavy alcohol consumption[5-15]. This is known as the threshold effect, indicating a J-shaped relationship between alcohol consumption and fracture risk, which was confirmed by another meta-analysis[15]. However, studies in the normal population have the problem of spectrum bias. The proportion of heavy alcoholics in the cohort dictates the threshold, and studies with a low proportion of heavy alcohol users lack the power required to examine this effect[49]. Moreover, these studies have the limitation of timing for alcohol consumption measurement and self-reported alcohol consumption, which could be inaccurate[15]. Contrary to the studies consisting of the normal population, our study enrolled articles utilizing the ALD population. Considering that ALD is the deleterious outcome of chronic alcohol abuse, these limitations could be minimized in our study.

In the present study, however, there was also substantial methodological heterogeneity between the enrolled studies, which had a potential effect on the risk estimates. This phenomenon was evaluated by sensitivity analyses for the confirmation of the robustness of this meta-analysis. The most noticeable modifier was the different populations used as control groups among the enrolled studies. Previous studies have suggested that metabolic bone disease is prevalent in CLD, especially in cholestatic liver disease[17,50]. Thus, studies with CLD as a control group run the potential risk of reporting an underestimated

effect size (*vs* ALD). Moreover, CLD is a complex and vague terminology that cannot include specific populations. ALD may include alcoholic fatty liver, alcoholic hepatitis, and liver cirrhosis of alcoholic origin. Despite the anticipated problems described above, the main analysis and the sensitivity analyses divided by control-group (normal population *vs* CLD) showed consistent results regarding bone fractures, osteoporosis, and BMD. The proportion of liver cirrhosis in ALD was unidentifiable in most of the enrolled studies. Future studies using homogenous populations are needed to determine the applicability of these results to the subpopulations of ALD or CLD.

Another modifier was the quality of the enrolled studies. The included studies were classified as being either in the high-quality (≥ 7 stars) or the low-quality group (< 7 stars). This standard was decided by the authors. The average number of stars awarded in 15 studies was 6.4 (Table 2). Of note, 8 studies were awarded zero stars in the section of comparability. Despite the pitfalls of methodological quality, the sensitivity analyses divided by study quality showed consistent results. High-quality studies are needed for the wide application of these results.

During the main and sensitivity analyses, a significant outlier[41] was observed. In the analysis of the association between ALD and bone fractures, the effect size of the outlier (RR = 33.725) was more than 10 times the adjusted effect size (RR = 1.944) (Figure 2). The analysis excluding the outlier showed consistent results. The reason for the large effect size of the outlier is postulated to be a methodological problem. In this study, the presence of fracture was recorded by anamnesis and chest X-ray film[41]. This inaccurate methodology could overestimate the rate of bone fractures. Moreover, the quality measured by NOS was low (6 stars) in this study.

In terms of the main mechanism behind the pathophysiology of bone fractures and osteoporosis in ALD, it is inferred that alcohol causes an imbalance in bone remodeling with a predominant decrease in bone formation[4,15,51]. Alcohol is known to cause direct effects on the numbers and activity of osteoblasts and osteoclasts[4]. In addition to the direct effects of alcohol on the osteoblasts and osteoclasts, many indirect effects have also been reported. These indirect effects are mainly linked to impaired nutrition, which leads to weight loss, decreased fat and lean body mass, and hormone alterations, which may change in bone cell activity[4,15,51]. More recent studies indicated the effects that alcohol have on bone mass may be due to a suppression of the Wnt/DKK1 signaling pathway through the stimulation of oxidative stress[52,53]. With an accumulating body of evidence regarding the effects alcohol has on the skeletal system, a more detailed pathophysiology could be confirmed in the near future.

This study is the first meta-analysis examining the association between ALD and bone fractures

or osteoporosis. The strength of this study is the evaluation of 3 effect sizes. The main result was confirmed, compared, and interpreted with regard to the other effect sizes. Another strength of this analysis is the selection of ALD for the study population. As described above, biases from various standards of alcohol consumption (light, moderate, heavy, or binge drinking), inaccurate amounts of alcohol consumption from self-reporting, and inconsistent timing for the measurement of alcohol consumption could be minimized. Potential modifiers were detected whenever possible from the articles and evaluated through the sensitivity analyses.

Despite its strengths, there are several limitations within the present study. First, there was no consideration given to any potential confounders, which could be influential to bone fractures and osteoporosis. These include sex, age, menopausal status, bone fracture history, family history of bone diseases or fractures, smoking, medications such as corticosteroids and body composition. However, most the important confounder is assumed to be trauma, such as frequent falls in patients with ALD. As noted in many studies, this powerful but easily overlooked confounder should be included *via* a thorough history in the studies relevant to this topic[4,15]. Second, the Newcastle-Ottawa scale was used to assess the methodological quality of the studies. This scale has been criticized for its low agreement between authors and reviewers[54]. Alternative tools such as the risk of bias table by the Cochrane group have been proposed as an alternative approach. However, this particular tool has strength in the evaluation of randomized studies, and poor inter-rater agreement was also noted[55]. Additional validated and commonly used tools are needed.

In conclusion, current publications indicate a significant association between bone fractures and ALD, independent of BMD or the presence of osteoporosis. Due to the qualitative and quantitative heterogeneity among studies, further studies utilizing homogenous populations and controlling for confounding risk factors for fractures are needed to elucidate the underlying mechanism of bone fractures in ALD.

COMMENTS

Background
Chronic excessive alcohol consumption is a well-established risk factor for low bone density and bone fractures. However, ingestion of light or moderate amounts of alcohol is known to be associated with higher bone density and decreased fracture rates. Osteoporosis and bone fractures are frequently overlooked complications in patients with chronic liver disease that could result in serious outcomes. However, the exact prevalence or mechanism of osteodystrophy in patients with alcoholic liver disease (ALD), which is the deleterious outcome of chronic alcohol abuse, have not been described

Research frontiers
Meta-analysis by John A. Kanis concluded that high intake of alcohol confers a substantial risk for fractures and that this risk is largely independent of bone mineral density (BMD). However, this study included normal population and there has been no such analysis in the ALD population.

Innovations and breakthroughs
From the fifteen non-randomized studies, ALD demonstrated a RR =1.944 (95%CI: 1.354-2.791) for the development of bone fractures. However, ALD showed a RR = 0.849 (95%CI: 0.523-1.380) for the development of osteoporosis.

Applications
Current publications indicate significant associations between bone fractures and ALD, independent of BMD or the presence of osteoporosis. Although the mechanism of bone fractures in ALD is not totally understood, further research utilizing a homogenous population and controlling for confounding risk factors for fractures could elucidate the mechanism.

Terminology
ALD: Excessive alcohol consumption is associated with a spectrum of hepatic manifestations, including alcoholic fatty liver, alcoholic hepatitis, and cirrhosis. These diseases share the core cause of hepatic injury which is an excessive alcohol consumption and generally refers to alcoholic liver disease.

Peer-review
The study addresses an interesting topic and merit. However, it has some intrinsic methodological limitations which decrease its potential clinical impact.

REFERENCES

1 **Kanis JA**, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, Oden A, Zethraeus N, Pfleger B, Khaltaev N. Assessment of fracture risk. *Osteoporos Int* 2005; **16**: 581-589 [PMID: 15616758 DOI: 10.1007/s00198-004-1780-5]
2 **Kanis JA**, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008; **19**: 385-397 [PMID: 18292978 DOI: 10.1007/s00198-007-0543-5]
3 WHO Fracture Risk Assessment Tool (FRAX). Available from: URL: http://www.shef.ac.uk/FRAX
4 **Maurel DB**, Boisseau N, Benhamou CL, Jaffre C. Alcohol and bone: review of dose effects and mechanisms. *Osteoporos Int* 2012; **23**: 1-16 [PMID: 21927919 DOI: 10.1007/s00198-011-1787-7]
5 **Feskanich D**, Korrick SA, Greenspan SL, Rosen HN, Colditz GA. Moderate alcohol consumption and bone density among postmenopausal women. *J Womens Health* 1999; **8**: 65-73 [PMID: 10094083 DOI: 10.1089/jwh.1999.8.65]
6 **Jugdaohsingh R**, O'Connell MA, Sripanyakorn S, Powell JJ. Moderate alcohol consumption and increased bone mineral density: potential ethanol and non-ethanol mechanisms. *Proc Nutr Soc* 2006; **65**: 291-310 [PMID: 16923313 DOI: 10.1079/PNS2006508]
7 **Orwoll ES**, Bauer DC, Vogt TM, Fox KM. Axial bone mass in older women. Study of Osteoporotic Fractures Research Group. *Ann Intern Med* 1996; **124**: 187-196 [PMID: 8533993 DOI: 10.7326/0003-4819-124-2-199601150-00001]
8 **Ilich JZ**, Brownbill RA, Tamborini L, Crncevic-Orlic Z. To drink or not to drink: how are alcohol, caffeine and past smoking related to bone mineral density in elderly women? *J Am Coll Nutr* 2002; **21**: 536-544 [PMID: 12480799 DOI: 10.1080/07315724.2002.10719252]
9 **Pedrera-Zamorano JD**, Lavado-Garcia JM, Roncero-Martin R, Calderon-Garcia JF, Rodriguez-Dominguez T, Canal-Macias ML. Effect of beer drinking on ultrasound bone mass in women. *Nutrition* 2009; **25**: 1057-1063 [PMID: 19527924 DOI: 10.1016/j.nut.2009.02.007]
10 **Williams FM**, Cherkas LF, Spector TD, MacGregor AJ. The effect of moderate alcohol consumption on bone mineral density: a study of female twins. *Ann Rheum Dis* 2005; **64**: 309-310 [PMID: 15231511 DOI: 10.1136/ard.2004.022269]
11 **Tucker KL**, Jugdaohsingh R, Powell JJ, Qiao N, Hannan MT, Sripanyakorn S, Cupples LA, Kiel DP. Effects of beer, wine, and liquor intakes on bone mineral density in older men and women. *Am J Clin Nutr* 2009; **89**: 1188-1196 [PMID: 19244365 DOI: 10.3945/ajcn.2008.26765]
12 **Venkat KK**, Arora MM, Singh P, Desai M, Khatkhatay I. Effect of alcohol consumption on bone mineral density and hormonal parameters in physically active male soldiers. *Bone* 2009; **45**: 449-454 [PMID: 19450718 DOI: 10.1016/j.bone.2009.05.005]

13   **Ganry O**, Baudoin C, Fardellone P. Effect of alcohol intake on bone mineral density in elderly women: The EPIDOS Study. Epidémiologie de l'Ostéoporose. *Am J Epidemiol* 2000; **151**: 773-780 [PMID: 10965974 DOI: 10.1093/oxfordjournals.aje.a010277]

14   **Høidrup S**, Grønbæk M, Gottschau A, Lauritzen JB, Schroll M. Alcohol intake, beverage preference, and risk of hip fracture in men and women. Copenhagen Centre for Prospective Population Studies. *Am J Epidemiol* 1999; **149**: 993-1001 [PMID: 10355374 DOI: 10.1093/oxfordjournals.aje.a009760]

15   **Berg KM**, Kunins HV, Jackson JL, Nahvi S, Chaudhry A, Harris KA, Malik R, Arnsten JH. Association between alcohol consumption and both osteoporotic fracture and bone density. *Am J Med* 2008; **121**: 406-418 [PMID: 18456037 DOI: 10.1016/j.amjmed.2007.12.012]

16   **Hernández ER**, Revilla M, Rico H. Total body bone mineral and pelvis bone mineral content as parameters of bone mass in men. A dual-energy X-ray absorptiometry study. *Acta Anat* (Basel) 1991; **142**: 227-230 [PMID: 1796737 DOI: 10.1159/000147193]

17   **Goel V**, Kar P. Hepatic osteodystrophy. *Trop Gastroenterol* 2010; **31**: 82-86 [PMID: 20862980]

18   **Deeks JJ**, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003; **7**: iii-x, 1-173 [PMID: 14499048 DOI: 10.3310/hta7270]

19   **Stang A**. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; **25**: 603-605 [PMID: 20652370 DOI: 10.1007/s10654-010-9491-z]

20   **Kanis JA**, McCloskey EV, Johansson H, Oden A, Melton LJ, Khaltaev N. A reference standard for the description of osteoporosis. *Bone* 2008; **42**: 467-475 [PMID: 18180210 DOI: 10.1016/j.bone.2007.11.001]

21   **Ninkovic M**, Love SA, Tom B, Alexander GJ, Compston JE. High prevalence of osteoporosis in patients with chronic liver disease prior to liver transplantation. *Calcif Tissue Int* 2001; **69**: 321-326 [PMID: 11800228 DOI: 10.1007/s00223-001-2028-4]

22   **Sokhi RP**, Anantharaju A, Kondaveeti R, Creech SD, Islam KK, Van Thiel DH. Bone mineral density among cirrhotic patients awaiting liver transplantation. *Liver Transpl* 2004; **10**: 648-653 [PMID: 15108256 DOI: 10.1002/lt.20104]

23   **Bonkovsky HL**, Hawkins M, Steinberg K, Hersh T, Galambos JT, Henderson JM, Millikan WJ, Galloway JR. Prevalence and prediction of osteopenia in chronic liver disease. *Hepatology* 1990; **12**: 273-280 [PMID: 2391068 DOI: 10.1002/hep.1840120214]

24   **Mitchell R**, McDermid J, Ma MM, Chik CL. MELD score, insulin-like growth factor 1 and cytokines on bone density in end-stage liver disease. *World J Hepatol* 2011; **3**: 157-163 [PMID: 21860675 DOI: 10.4254/wjh.v3.i6.157]

25   **Mahmoudi A**, Sellier N, Reboul-Marty J, Chalès G, Lalatonne Y, Bourcier V, Grando V, Barget N, Beaugrand M, Trinchet JC, Ganne-Carrié N. Bone mineral density assessed by dual-energy X-ray absorptiometry in patients with viral or alcoholic compensated cirrhosis. A prospective study. *Clin Res Hepatol Gastroenterol* 2011; **35**: 731-737 [PMID: 21873139 DOI: 10.1016/j.clinre.2011.07.009]

26   **Choudhary NS**, Tomar M, Chawla YK, Bhadada SK, Khandelwal N, Dhiman RK, Duseja A, Bhansali A. Hepatic osteodystrophy is common in patients with noncholestatic liver disease. *Dig Dis Sci* 2011; **56**: 3323-3327 [PMID: 21573732 DOI: 10.1007/s10620-011-1722-y]

27   **Cooper H**. Synthesizing research: A guide for literature reviews. Thousand Oaks, CA: Sage, 1998

28   **Higgins JPT**, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1. 0. UK, London: The Cochrane Collaboration, 2011

29   **Higgins JP**, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539-1558 [PMID: 12111919 DOI: 10.1002/sim.1186]

30   **Higgins JP**, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-560 [PMID: 12958120 DOI: 10.1136/bmj.327.7414.557]

31   **DerSimonian R**, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177-188 [PMID: 3802833 DOI: 10.1016/0197-2456(86)90046-2]

32   **Borenstein M**, Hedges LV, Higgins J, Rothstein HR. Fixed - Effect Versus Random - Effects Models. Introduction to Meta-analysis. Chichester: Wiley, 2009: 77-86 [DOI: 10.1002/9780470743386.ch13]

33   **Olkin I**. Statistical methods for meta-analysis. San Diego, CA: Academic, 1985

34   **Duval S**, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; **56**: 455-463 [PMID: 10877304 DOI: 10.1111/j.0006-341X.2000.00455.x]

35   **Sutton AJ**, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for meta-analysis in medical research. Chichester: Wiley, 2000

36   **Sterne JA**, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001; **54**: 1046-1055 [PMID: 11576817 DOI: 10.1016/S0895-4356(01)00377-8]

37   **Begg CB**, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**: 1088-1101 [PMID: 7786990 DOI: 10.2307/2533446]

38   **Egger M**, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629-634 [PMID: 9310563 DOI: 10.1136/bmj.315.7109.629]

39   **Ninkovic M**, Skingle SJ, Bearcroft PW, Bishop N, Alexander GJ, Compston JE. Incidence of vertebral fractures in the first three months after orthotopic liver transplantation. *Eur J Gastroenterol Hepatol* 2000; **12**: 931-935 [PMID: 10958221 DOI: 10.1097/00042737-200012080-00013]

40   **González-Reimers E**, Alvisa-Negrín J, Santolaria-Fernández F, Ros-Vilamajó R, Martín-González MC, Hernández-Betancor I, García-Valdecasas-Campelo E, González-Díaz A. Prognosis of osteopenia in chronic alcoholics. *Alcohol* 2011; **45**: 227-238 [PMID: 21051177 DOI: 10.1016/j.alcohol.2010.09.002]

41   **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. Vitamin D and nutritional status are related to bone fractures in alcoholics. *Alcohol Alcohol* 2011; **46**: 148-155 [PMID: 21248027 DOI: 10.1093/alcalc/agq098]

42   **Wibaux C**, Legroux-Gerot I, Dharancy S, Boleslawski E, Declerck N, Canva V, Mathurin P, Pruvot FR, Cortet B. Assessing bone status in patients awaiting liver transplantation. *Joint Bone Spine* 2011; **78**: 387-391 [PMID: 21565541 DOI: 10.1016/j.jbspin.2011.03.001]

43   **Alvisa-Negrín J**, González-Reimers E, Santolaria-Fernández F, García-Valdecasas-Campelo E, Valls MR, Pelazas-González R, Durán-Castellón MC, de Los Angeles Gómez-Rodríguez M. Osteopenia in alcoholics: effect of alcohol abstinence. *Alcohol Alcohol* 2009; **44**: 468-475 [PMID: 19535494 DOI: 10.1093/alcalc/agp038]

44   **Lindsell DR**, Wilson AG, Maxwell JD. Fractures on the chest radiograph in detection of alcoholic liver disease. *Br Med J* (Clin Res Ed) 1982; **285**: 597-599 [PMID: 6819030 DOI: 10.1136/bmj.285.6342.597]

45   **Carey EJ**, Balan V, Kremers WK, Hay JE. Osteopenia and osteoporosis in patients with end-stage liver disease caused by hepatitis C and alcoholic liver disease: not just a cholestatic problem. *Liver Transpl* 2003; **9**: 1166-1173 [PMID: 14586877 DOI: 10.1053/jlts.2003.50242]

46   **Diamond T**, Stiel D, Lunzer M, Wilkinson M, Roche J, Posen S. Osteoporosis and skeletal fractures in chronic liver disease. *Gut* 1990; **31**: 82-87 [PMID: 2318434 DOI: 10.1136/gut.31.1.82]

47   **Kim MJ**, Shim MS, Kim MK, Lee Y, Shin YG, Chung CH, Kwon SO. Effect of chronic alcohol ingestion on bone mineral density in males without liver cirrhosis. *Korean J Intern Med* 2003; **18**: 174-180 [PMID: 14619387]

48   **El Maghraoui A**, Roux C. DXA scanning in clinical practice. *QJM* 2008; **101**: 605-617 [PMID: 18334497 DOI: 10.1093/qjmed/hcn022]

49   **Kanis JA**, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H, Tenenhouse A. Alcohol intake as a risk factor for fracture.

Osteoporos Int 2005; **16**: 737-742 [PMID: 15455194 DOI: 10.1007/s00198-004-1734-y]

50   **Rouillard S**, Lane NE. Hepatic osteodystrophy. *Hepatology* 2001; **33**: 301-307 [PMID: 11124849 DOI: 10.1053/jhep.2001.20533]

51   **Chakkalakal DA**. Alcohol-induced bone loss and deficient bone repair. *Alcohol Clin Exp Res* 2005; **29**: 2077-2090 [PMID: 16385177]

52   **Chen JR**, Lazarenko OP, Shankar K, Blackburn ML, Badger TM, Ronis MJ. A role for ethanol-induced oxidative stress in controlling lineage commitment of mesenchymal stromal cells through inhibition of Wnt/beta-catenin signaling. *J Bone Miner Res* 2010; **25**: 1117-1127 [PMID: 20200986 DOI: 10.1002/jbmr.7]

53   **Callaci JJ**, Himes R, Lauing K, Wezeman FH, Brownson K. Binge alcohol-induced bone damage is accompanied by differential expression of bone remodeling-related genes in rat vertebral bone. *Calcif Tissue Int* 2009; **84**: 474-484 [PMID: 19330277 DOI: 10.1007/s00223-009-9240-z]

54   **Lo CK**, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC Med Res Methodol* 2014; **14**: 45 [PMID: 24690082 DOI: 10.1186/1471-2288-14-45]

55   **Hartling L**, Ospina M, Liang Y, Dryden DM, Hooton N, Krebs Seida J, Klassen TP. Risk of bias versus quality assessment of randomised controlled trials: cross sectional study. *BMJ* 2009; **339**: b4012 [PMID: 19841007 DOI: 10.1136/bmj.b4012]

Baishideng®

9 771007 932045