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BONE DENSITY IN PATIENTS WITH HEPATIC CIRRHOSIS & ITS CORRELATION WITH CHOLESTASIS AND GROWTH

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Abstract:

Bone denisy and osteoporosis considered a typical complication of chronic liver disease from cholestatic conditions to autoimmune, alcoholic and post-hepatitic cirrhosis. Its aetiology may inadequately recognize and may also differ in various liver diseases. The majority of symptomatic bone diseases in patients specifically having liver disease tend to be presented only after liver transplantation when initial rapid bone loss triggers a high rate of fracturing the first postoperative year. Limited bone mass prior to after liver transplantation would be the primary risk factor for post-transplant fracturing and, consequently, its comprehending and administration are of leading significance. Optimum administration of post-transplant osteopenia involves concern of pre- and post-transplant aspects.

DXA (Dualenergy X-ray absorptiometry) examination has been carried out in patients with intrahepatic cholestatic diseases. Dualenergy X-ray absorptiometry was carried out on patients aged >5 years (accordingly with native liver) and they are diagnosed with A1AT (alpha-1 antitrypsin deficiency), BASD (bile acid synthetic disorder), CIC (chronic intrahepatic cholestasis) and ALGS (Alagille syndrome).

BMC (bone mineral content) and BMD (Bone mineral density) Z scores were considerably minimal in ALGS and in CIC, as compared with A1AT and BASD ($P < 0.001$). Accordingly, later the adjustment of anthropometric, bone deficits endured in CIC but was not specifically diagnoses in ALGS. In ALGS, height-adjusted and weight-adjusted subtotal BMD and BMC Z scores were negatively correlated with TB ($P < 0.001$) and SBA ($P = 0.02$).

Chronic Intrahepatic Cholestasis patients revealed considerable bone deficits that endured later the adjustment for weight and height and noticeably did not correlate with cholestasis degree. On the other hand low "Bone Mineral Density" and "Bone Mineral Content" reference Z scores were explored and described by weaken growth. Anthropometrically adjusted DXA measures in ALGS correlate with markers of cholestasis and bone fracture history.

Keywords: *Bone Density; Hepatic Cirrhosis;*

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INTRODUCTION:

BMD (Bone mineral density) is a degree of bone density which further reflects the strength of bones as represented by calcium content. Low bone density is when patients' bone density is lower than normal, but not low enough to be considered osteoporosis. It may mean that patients have a greater chance of getting osteoporosis if patient lose bone in the future because the patients have less bone to lose. People with low bone density are more likely to break a bone compared to people with normal bone density (Afessa, 2016).

Aspects triggering bone mineral deficits tend to be based upon the structure as well as intensity of the underlying liver disorder and may also incorporate chronic nutrient and calcium mal-absorption ultimately causing malnutrition and development failure, inadequacies of fat-soluble vitamins, level of physiological exercise, and swirling inflammatory cytokines. High rates of osteoporosis and bone fracture were already discovered in adults with chronic cholestatic liver diseases, including primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC), and cirrhosis of any sort of reason. Metabolic bone disease normally frequent in children with chronic cholestasis or end-stage liver disease, but fewer studies has been conducted to characterize the bone mineral deficits in this vulnerable population (Alam et al., 2013).

Accordingly, bone mass is maintained by a balance between resorption and formation, a process regulated by many hormones and growth factors (as mentioned in Fig. 1).

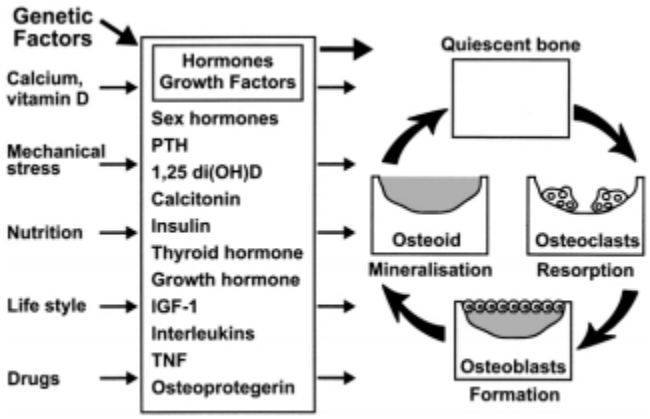

Fig. 1. Bone remodelling cycle.

Source: (Afessa, 2016)

The major influences on bone metabolism are genetic, but also essential are mechanical stress (exercise and muscle activity), good nutrition, adequate calcium and vitamin D and a normal hormonal environment (Afessa, 2016).

Regardless of understanding metabolic bone disease on incidence and standard of living in pediatric patients along with chronic liver disease, limited comprehensive trials have been done to measure bone deficits and identify risk aspects for osteopenia and fracture. In one released research, ALGS patients (n = 31) and 80 healthy control respondents experienced examination by dual-energy X-ray absorptiometry (DXA). The ALGS children had been small for age and had lowered bone mineral content (BMC) for age and BMC for height, with bone mineralization favourably relevant to coefficient of fat absorption but not to dietary consumption (Alam et al., 2013).

In an additional research of twenty non-jaundiced children with biliary atresia, whole-body and lumbar spine BMC standards had been discovered to declination with age, signifying that children enduring with native liver are at risk of affected bone health, additionally in the absence of improved bilirubin levels. Till now, there have been no published studies of DXA analysis in children with other inherited chronic liver diseases, such as alpha-1 antitrypsin deficiency (A1AT) or PFIC (Alam et al., 2013).

METHODS:

Participants:

Informed consent was obtained from parents or guardians or participants 18 years or older, and assent was obtained from participants >7 years of age, per local guidelines. This study designed to assess the natural history of several genetic causes of cholestasis, including ALGS, A1AT, BASD, and PFIC.

Inclusion Criteria:

All participants must be according to "1" and "2":
(1)
1. Must have family history of ALGS
2. Bile duct paucity
3. Other clinical criteria such as evidence of cholestasis, cardiac involvement, ocular findings, butterfly vertebrae and functional or structural renal anomalies

(2)

Clinical, biochemical or histologic evidence of liver disease

Measurement of DXA:

Dualenergy X-ray absorptiometry (DXA) the equivalent phantom was adopted for longitudinal substance correction whenever essential. Researchers applied a couple of models of scanners and manipulation between the two brands of scanners was performed with patient-based correction formulas. Standard Z scores were determined established on age, sex, and race reference data.(scanning of the whole body, spine, and femur was performed using specific equipment. Accordingly, adjusted Z scores were calculated based on age, sex, race, height, and weight.

Statistical Approaches:

The pre-planned examines of the DXA data incorporated everyone in the group with their indigenous liver for whom a DXA was carried out. Descriptive statistics are exhibited as methods and standard deviations or median along with initial and third quartiles for prolonged variables in addition to being frequencies and percentages for categorical variables. Researchers categorized DXA Z scores in two ways—as a continuous variable and as a dichotomous variable based on the proportion of participants <-1.5 and >-1.5.

Pearson correlation coefficients and their corresponding P values were put to use while assessing the relationships between participant anthropometric parameters (height, weight, and body mass index [BMI] Z scores) and research DXA Z scores (characterized whilst the standard approach to adjust for age, sex, and race) and between DXA Z score and laboratory standards. Laboratory standards were acquired within one year of DXA scan. Due to the large number of comparisons being made, researcher deemed P values.

RESULTS:

Attributes of the Study:

This research overall comprised with the total of 148 respondents registered in the study. Respondents possessed ALGS (n = 49), CIC (n = 41), A1AT (n = 44), or BASD (n = 14). Table 1 demonstrates traits of respondents in the study by disease group. The A1AT and BASD groups had greater proportions of male respondents than the ALGS and CIC groups: 70% and 79% versus 57% and 44%, correspondingly.

The rate of bone fracture happening had not been statistically unique among disease groups. Anthropomorphic dimensions were considerably assorted across disease groups ($P < 0.001$), with ALGS and CIC participants having lower mean height, weight, and BMI Z scores than participants with A1AT or BASD (Gallego-Rojo et al., 2017).

TABLE 1. Demographic and Clinical Characteristics* of Participant Population by Disease Group

Liver Disease	AIGS (n = 49[†])	CIC (n = 41[†])	A1AT Deficiency (n = 44[†])	BASD (n = 14[†])	p[‡]
Number (%) of participants					
Male sex	28 (57%)	18 (44%)	31 (70%)	11 (79%)	0.04
Race					0.16
White	38 (78%)	34 (83%)	43 (98%)	11 (79%)	
Black	5 (10%)	2 (5%)	0 (0%)	1 (7%)	
Other	6 (12%)	5 (12%)	1 (2%)	2 (14%)	
Ethnicity					0.62
Hispanic	4 (8%)	7 (17%)	3 (7%)	3 (21%)	
Non-Hispanic	44 (90%)	33 (80%)	40 (91%)	11 (79%)	
Not reported	1 (2%)	1 (2%)	1 (2%)	0 (0%)	
Any bone fractures[#]					0.20
No	30 (61%)	31 (76%)	35 (80%)	11 (79%)	
Yes	19 (39%)	10 (24%)	9 (20%)	3 (21%)	
Frequency of bone fractures					0.06
0 or 1	40 (82%)	38 (93%)	43 (98%)	13 (93%)	
2 or more	9 (18%)	3 (7%)	1 (2%)	1 (7%)	
Spleen size >2 cm and platelet count <150 x $10^3/\mu L$**	6 (16%)	4 (13%)	5 (12%)	0 (0%)	0.59
BMI Z score <-2**	3 (6%)	2 (5%)	1 (2%)	1 (7%)	0.73
Mean (SD)					
Median (Q1, Q3)					
Age (years)	10.8 (4.6)	11.0 (5.0)	11.0 (5.3)	12.0 (6.7)	0.90
	9.8 (7.7, 13.1)	10.9 (6.6, 15.0)	8.7 (6.5, 14.5)	8.4 (6.8, 20.0)	
Weight Z score	-1.3 (1.3)	-1.1 (1.5)	0.6 (0.9)	0.9 (1.4)	<0.001
	-1.1 (-2.3, -0.4)	-1.1 (-2.0, 0.0)	0.7 (0.1, 1.2)	1.1 (-0.2, 1.7)	
Height Z score	-1.5 (1.1)	-1.3 (1.8)	0.5 (1.2)	-0.1 (0.7)	<0.001
	-1.6 (-2.1, -0.7)	-1.2 (-2.3, -0.3)	0.5 (-0.1, 1.1)	0.1 (-0.5, 0.2)	
BMI Z score	-0.6 (1.2)	-0.2 (1.0)	0.4 (1.0)	1.0 (1.4)	<0.001
	-0.3 (-1.3, 0.3)	-0.1 (-0.8, 0.4)	0.6 (-0.2, 0.9)	1.3 (0.4, 1.9)	

Source: (Gallego-Rojo et al., 2017)

Normal lab specifications of bilirubin, gamma-glutamyl transpeptidase, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and serum bile acids (SBAs) happen to be optimum in participants with ALGS, medium for nearly all those with CIC, and minimal in participants with A1AT and BASD. Mean albumin and haemoglobin happen to be diminished in ALGS and CIC in comparison along with A1AT and BASD. There initially were no statistical variants in international normalized ratio (INR), white blood cell count, and platelet count in between groups.

DXA Scores:

The participants of A1AT and BASD been unsuccessful to own significant bone mineral deficits as established by DXA; consequently, the results are targeted on the ALGS and CIC groups. Table 2 displays review methods of research along with height-adjusted and weight-adjusted BMD and BMC Z scores producing from DXA scans by disease group for ALGS and CIC participants. The research ratings consider the participants' age, sex, and race. Mean DXA reference Z scores had been equivalent regarding ALGS and CIC respondents, other than for spine BMD that has been lowered in the CIC group (as mentioned in Table 2). Due to the fact that some of the respondents through the research possess important advancement insufficiencies, researcher analysed correlations in between DXA reference Z scores and height, weight, and BMI Z scores by disease group (presented in Table 3) (Gallego-Rojo et al., 2017).

TABLE 2. DXA Reference and Height-Adjusted and Weight-Adjusted *Z* Scores by Disease Group

Mean (SD) % with *Z* <–1.5	ALGS (n = 46-49)	CIC (n = 39-41)	*P**	Winsorized† Values, n (%)
BMD measures				
Total body minus head				
Reference *Z* score	–1.10 (1.57) 46.9%	–1.58 (1.11) 56.1%	0.10	13 (14%)
Adjusted *Z* score	0.23 (1.65) 20.8%	–0.37 (1.45) 20.0%	0.07	9 (10%)
Spine				
Reference *Z* score	–0.08 (1.66) 20.4%	–1.01 (1.36) 43.9%	0.005	9 (10%)
Adjusted *Z* score	0.13 (1.65) 20.8%	–1.15 (0.98) 40.0%	<0.001	4 (5%)
Total hip				
Reference *Z* score	–0.78 (1.38) 23.4%	–1.17 (1.23) 47.5%	0.16	10 (11%)
Adjusted *Z* score	–0.46 (1.41) 21.7%	–1.17 (1.30) 43.6%	0.02	7 (8%)
BMC measures				
Total body minus head				
Reference *Z* score	–1.23 (1.45) 44.9%	–1.80 (1.33) 63.4%	0.06	25 (28%)
Adjusted *Z* score	0.36 (1.34) 10.4%	–0.76 (1.16) 27.5%	<0.001	7 (8%)

Tests for differences DXA *Z* scores between disease groups were performed using two-sample *t* tests.
†Values <–3 were set to –3, and values >3 were set to 3.

TABLE 3. Pearson Correlations Between DXA Reference *Z* Scores* and Height, Weight, and BMI *Z* Scores for ALGS and CIC

	ALGS (n = 47-49)			CIC (n = 40-41)		
	Height	Weight	BMI	Height	Weight	BMI
BMD measures						
Total body	0.62§	0.53§	0.18	0.56‡	0.55‡	0.23
Total body minus head	0.67§	0.59§	0.24	0.59§	0.55‡	0.19
Spine	0.58§	0.44†	0.09	0.53‡	0.54‡	0.29
Total hip	0.57§	0.48‡	0.19	0.33	0.32	0.18
Hip neck	0.56§	0.42†	0.16	0.33	0.35	0.24
BMC measures						
Total body	0.76§	0.69§	0.34	0.73§	0.68§	0.28
Total body minus head	0.81§	0.73§	0.34	0.74§	0.68§	0.27

*Reference *Z* score is adjusted for age, sex, and race (black versus nonblack).
†$P < 0.01$.
‡$P < 0.001$.
§$P < 0.0001$.

Source: (Gallego-Rojo et al., 2017)

In the ALGS group, weight Z scores also correlated strongly with total body and total body minus head BMD and BMC DXA reference Z scores (P < 0.0001) and, to a lesser extent with spine, total hip, and hip neck DXA reference Z scores (as above mentioned Table 3).

Relation between laboratory measurement and DXA:

Researchers examined potential associations between DXA height-adjusted and weight-adjusted Z scores and laboratory measurements using Pearson correlation coefficients. The correlations for ALGS and CIC are shown in Table 4. In ALGS participants, all of the height-adjusted and weight-adjusted BMD and BMC measures were negatively correlated with serum total bilirubin (TB; P < 0.001). In the ALGS group, many of the DXA measurements were also correlated with INR and albumin. There were no significant correlations found in the CIC (Table 4), A1AT, or BASD groups (data not shown). There were no significant differences found in the CIC group. In ALGS, albumin was lower in participants with height-adjusted and weight-adjusted BMD Z scores.

TABLE 4. Pearson Correlations Between DXA Height-Adjusted and Weight-Adjusted *Z* Scores and Laboratory Measures of Cholestasis and Liver Synthetic Function

	ALGS (n = 37-47*)					CIC (n = 32-40*)				
	TB (mg/dL)	SBA (μmol/L)	Vitamin D (ng/mL)	INR	Albumin (g/dL)	TB (mg/dL)	SBA (μmol/L)	Vitamin D (ng/mL)	INR	Albumin (g/dL)
BMD										
Total body minus head	−0.54‡	−0.37	0.07	−0.41†	0.35	−0.12	−0.29	0.19	0.08	−0.08
Spine	−0.59§	−0.31	0.27	−0.33	0.44†	−0.36	−0.29	0.09	0.00	0.20
Total hip	−0.66§	−0.36	0.14	−0.44†	0.53‡	−0.24	−0.09	0.03	0.13	0.22
BMC										
Total body minus head	−0.63§	−0.39	0.33	−0.31	0.48‡	−0.39	−0.23	−0.09	0.01	0.29

*Number of participants varies due to missing values for DXA or lab measurements.
†$P < 0.01$.
‡$P < 0.001$.
§$P < 0.0001$.
Abbreviations: INR, international normalized ratio.

Listed below Table 5 reveals variations in DXA height-adjusted and weight-adjusted Z scores, TB, and SBAs by regardless or perhaps not the individual possessed a bone fracture. There had been no immense variations observed for virtually any of the DXA specifications or the laboratory values in the CIC group. In ALGS, adjusted spine BMD and total body minus head BMC Z scores were lower in the fracture group (–0.6 versus 0.6, P = 0.02; and –0.2 and 0.7, P = 0.02). Serum TB and SBAs were both higher in the fracture group (6.1 versus 2.0, P = 0.03; and 157 versus 80, P = 0.02) for ALGS participants. However, the P value of 0.02 for these comparisons does not meet our cut-off for statistical significance of P < 0.01.

TABLE 5. Differences in DXA Height-Adjusted and Weight-Adjusted Z Score Measures and Lab Values by Occurrence of Bone Fracture*

	ALGS (n = 49)			CIC (n = 41)		
	n	Mean (SD)	P†	n	Mean (SD)	P†
BMD						
Total body minus head			0.07			0.33
Bone fracture	19	−0.3 (1.8)		10	−0.8 (1.7)	
No bone fracture	29	0.6 (1.5)		30	−0.2 (1.4)	
Spine			0.02			0.12
Bone fracture	19	−0.6 (1.7)		10	−1.6 (1.0)	
No bone fracture	29	0.6 (1.4)		30	−1.0 (0.9)	
Total hip			0.21			
Bone fracture	18	−0.8 (1.6)		10	−1.5 (1.5)	0.41
No bone fracture	28	−0.2 (1.3)		29	−1.1 (1.2)	
BMC						
Total body minus head			0.02			0.96
Bone fracture	19	−0.2 (1.4)		10	−0.8 (1.2)	
No bone fracture	29	0.7 (1.2)		30	−0.8 (1.2)	
Lab measures						
TB			0.03			0.89
Bone fracture	17	6.1 (6.8)		9	1.5 (1.4)	
No bone fracture	25	2.0 (2.7)		29	1.6 (2.1)	
SBA			0.02			0.58
Bone fracture	19	156.9 (119.2)		8	87.6 (95.7)	
No bone fracture	20	79.7 (77.9)		26	64.3 (105.3)	

*Bone fracture could have occurred before or after the DXA scan.
†*P* value based on two-sample *t* test.

Accordingly, Table 6 shows mean DXA height-adjusted and weight-adjusted Z scores for ALGS and CIC by the diversion status. The spine DXA Z score was lower in ALGS participants with biliary diversion compared to those without (–1.1 versus 0.4, P = 0.013). In participants with CIC, the mean total body minus head BMD Z score was higher in the diversion group (0.1 versus –1.0, P = 0.03). However, these differences did not reach the threshold of P < 0.01 for statistical significance in this study.

TABLE 6. Differences in DXA Height-Adjusted and Weight-Adjusted *Z* Score Measures by Biliary Diversion*

	ALGS (n = 49)			CIC (n = 41)		
	n	Mean (SD)	$P^{\dagger}$	n	Mean (SD)	$P^{\dagger}$
BMD						
Total body minus head			0.34			0.03
Diversion	9	−0.2 (1. 9)		23	0.1 (1.5)	
No diversion	39	0.4 (1.6)		17	−1.0 (1.2)	
Spine			0.013			0.90
Diversion	9	−1.1 (1. 5)		23	−1.1 (1.0)	
No diversion	39	0.4 (1.6)		17	−1.2 (1.0)	
Total hip			0.10			
Diversion	9	−1.1 (1.1)		22	−1.0 (1.4)	0.40
No diversion	37	−0.3 (1.4)		17	−1.4 (1.1)	
BMC						
Total body minus head			0.13			0.65
Diversion	9	−0.2 (1.5)		23	−0.7 (1.2)	
No diversion	39	0.5 (1.3)		17	−0.9 (1.2)	

*All diversions were performed prior to DXA scans. The median (interquartile range) times between diversion and scan for ALGS and CIC were 7 (7-10) and 6 (5-10) years, respectively.
†*P* value based on two-sample *t* test.

DISCUSSION:

As part of this multicentre research, researcher describe the particular results of DXA evaluation in participants along with four sorts of intrahepatic cholestasis—ALGS, CIC (including genetically established PFIC), A1AT, and BASD. Significantly, respondents with A1AT or BASD were without significant bone mineral deficits detected by DXA; however, these participants have been also only moderately cholestatic at the time of the DXA scan (Table 1) (Harnois, 2017).

In comparison, research respondents with ALGS and CIC possessed important bone mineral deficits that correlated extremely with development parameters. Modification for height and weight stabilized DXA BMD and BMC Z scores in ALGS but up to a reduced degree in CIC. In ALGS, weight-adjusted and height-adjusted DXA Z scores associated along with laboratory indications of cholestasis and hepatic synthetic function. Bone fracture happening was correlated with DXA parameters and laboratory values in the ALGS group, who have been likely to develop fractures. In this study, biliary diversion did not have a major impact on DXA Z scores (Harnois, 2017).

One of the key findings in this study is the strong correlation between weight-adjusted and height-adjusted DXA Z scores and laboratory measures of cholestasis and liver synthetic function, specifically in ALGS (Table 4). Similar correlations were not identified in the CIC group. Notably, OH vitamin D levels were not correlated with DXA Z scores in this cholestatic population. The effect of cholestasis on bone metabolism has been studied both in vitro and in vivo (Hultberg, Isaksson and Jansson, 2016).

Ruiz-Gaspà et al. treated human primary osteoblasts with bilirubin or serum from jaundiced patients and found decreased osteoblast viability and differentiation, reduced expression of osteogenic transcription factors, and up-regulation of factors inducing osteoclastogenesis. Histomorphometric analysis of 50 patients with PBC and PSC at the time of liver transplantation showed decreased bone formation in both male and female patients and increased bone resorption only in female patients. These studies support the hypothesis that cholestasis has direct effects on bone remodelling. The divergent results for the ALGS and CIC groups with respect to correlations between DXA measures and cholestasis are not well understood but may be explained to some extent by the fact that ALGS participants in this

study had higher mean TB and SBA levels compared with the CIC group. However, the majority of the CIC participants (56%) had undergone biliary diversion, indicating a history of long-standing and profound cholestasis at some point in the past, which is unlikely to be reflected by current laboratory values. Varying clinical response to biliary diversion, ranging from complete resolution of cholestasis to ongoing issues with fat-soluble vitamin deficiencies, complicates interpretation of these results (Hultberg, Isaksson and Jansson, 2016).

In this study, researcher found no statistically significant differences in height-adjusted and weight-adjusted DXA Z scores between participants with and without biliary diversion. Variable clinical response to biliary diversion significantly complicates the interpretation of the results of these analyses. Some patients may respond to biliary diversion with normalization of bilirubin and bile acids, but low intestinal luminal bile acid levels may lead to profound fat-soluble vitamin deficiencies. Limited numbers of participants who underwent biliary diversion precluded sub analysis of bile flow after the procedure with regard to clinical response and vitamin D status. After successful drainage procedures, some patients develop bouts of cholestasis that can last months, akin to benign recurrent intrahepatic cholestasis. As such, the timing of DXA scanning relative to intermittent cholestasis events could affect the DXA findings (Le Gars, 2017).

CONCLUSION:

While summarizing the content, researchers' outcomes describe very large study, up to now, of DXA evaluation in a proper-recognized research of participants with intrahepatic cholestatic liver diseases. In specific, respondents with ALGS and CIC possess important bone mineral deficits which will impede clinical results. There are obviously complicated and inadequately recognized multi-factorial impacts on bone mineralization in this populace, with varying effects on growth, degree of cholestasis, fracture vulnerability, and direct contribution of underlying genetic etiology. Fractures in this population are unlikely to be simple manifestations of vitamin D deficiency but are the result of a much more complex pathophysiology.

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