doi: 10.3978/j.issn.2095-6959.2020.03.022
View this article at: http://dx.doi.org/10.3978/j.issn.2095-6959.2020.03.022

2 型糖尿病合并非酒精性脂肪性肝病肝纤维化与骨密度的相关性

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[摘　要]　**目的：**探讨2型糖尿病(type 2 diabetes mellitus，T2DM)合并非酒精性脂肪性肝病(non-alcoholic fatty liver disease，NAFLD)肝纤维化与骨密度的关系。**方法：**筛选T2DM患者539例，依据腹部超声分为T2DM组(n=234)、T2DM+NAFLD组(n=305)，再依据非酒精性脂肪肝肝纤维化评分(non-alcoholic fatty liver disease fibrosis score，NAFLDFS)分为<−1.455排除纤维化亚组、−1.455~0.676可疑纤维化亚组、>0.676诊断纤维化亚组，行骨密度检查并测定空腹血糖(fasting blood glucose，FBG)、空腹C肽(fasting C-peptide，F-CP)、空腹胰岛素(fasting insulin，FINS)、糖化血红蛋白(HbA1c)、肝功能及血脂等血清学指标。**结果：**与T2DM组相比，T2DM+NAFLD组股骨颈、Ward's三角、大粗隆、股骨干及全部股骨的骨密度及T值下降(P<0.05)。与−1.455~0.676亚组及<−1.455亚组相比，>0.676亚组股骨颈、Ward's三角的骨密度及T值下降(P<0.05)。T2DM组和T2DM+NAFLD组骨量异常(骨量减少和骨质疏松)发生率存在差异(48.29% vs 65.90%，P<0.01)；<−1.455亚组，−1.455~0.676亚组，>0.676亚组骨量异常发生率存在差异(48.39% vs 67.98% vs 82.5%，两两比较均P<0.01)。相关性分析示：NAFLDFS与股骨颈、Ward's三角的骨密度及T值呈负相关(P<0.05)。Logistic回归分析示：在控制年龄、性别、BMI、病程、FBG、ALT、HDLC、HbA1C及载脂蛋白B(APOB)后，NAFLDFS评分是骨量减少的独立危险因素。−1.455~0.676亚组相对于<−1.455亚组骨量减少的风险增加(OR=2.235，95%CI 1.040~4.803，P<0.05)；>0.676亚组相对于<−1.455亚组骨量减少的风险增加(OR=4.463，95%CI 1.221~16.308，P<0.05)。**结论：**T2DM合并NAFLD肝纤维化患者骨密度减低，两者具有相关性，进展性肝纤维化是骨量减少的危险因素。

[关键词]　2型糖尿病；非酒精性脂肪性肝病；肝纤维化；骨密度

Relationship between liver fibrosis and bone mineral density in type 2 diabetes with nonalcoholic fatty liver disease

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Abstract　**Objective:** To investigate the relationship between liver fibrosis and bone mineral density (BMD) in patients

收稿日期 (Date of reception)：2019–06–04

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基金项目 (Foundation item)：江苏省徐州市科技局计划项目 (KC14SH065)。This work was supported by Science and Technology Bureau Plan Project of Xuzhou City, China (KC14SH065).

with type 2 diabetes (T2DM) and nonalcoholic fatty liver disease (NAFLD). **Methods:** A total of 539 T2DM patients were divided into a T2DM group (*n*=234) and a T2DM+NAFLD group (*n*=305) according to abdominal ultrasonography, the T2DM+NAFLD group were further divided into a <−1.455 excluding fibrosis subgroup, a −1.455 to 0.676 suspicious fibrosis subgroup, and a >0.676 diagnosing fibrosis subgroup according to non-alcoholic fatty liver fibrosis score (NAFLDFS). BMD was examined and serological indexes such as fasting blood glucose (FBG), fasting C peptide (F-CP), fasting insulin (FINS), glycosylated hemoglobin (HbA1c), liver function,blood fat were determined. **Results:** BMD and T value of femoral neck, Ward's triangle, trochanter, femoral shaft and all femurs in the T2DM+NAFLD group were lower than those in the T2DM group (*P*<0.05). BMD and T value of femoral neck and Ward's triangle in the >0.676 subgroup were lower than those in the −1.455 to 0.676 subgroup and the <−1.455 subgroup (*P*<0.05). The incidence of osteopenia and osteoporosis was different between the T2DM and the T2DM+NAFLD group (48.29% vs 65.90%, *P*<0.01), and also different in the subgroups <−1.455, −1.455 to 0.676 and >0.676 (48.39% vs 67.98% vs 82.5%, *P*<0.01, for both comparisons). Relevance analysis showed NAFLDFS was positively correlated with BMD and T value of femoral neck and Ward's triangle (*P*<0.05). Logistic regression analysis showed that NAFLDFS was an independent risk factor for BMD after controlling for age, sex, BMI, course of disease, FBG, ALT, HDLC, HbA1C, APOB. The risk of bone loss increased in the −1.455 to 0.676 subgroup when compared with the <−1.455 subgroup (OR=2.235, 95%CI: 1.040–4.803, *P*<0.05), and increased in the >0.676 subgroup when compared with the <−1.455 subgroup (OR=4.463, 95%CI: 1.221–16.308, *P*<0.05). **Conclusion:** BMD is decreased in patients with hepatic fibrosis of T2DM combined with NAFLD. There is a correlation between them. Progressive hepatic fibrosis is a risk factor for bone loss.

Keywords type 2 diabetes; nonalcoholic fatty liver disease; liver fibrosis; bone mineral density

非酒精性脂肪性肝病(non-alcoholic fatty liver disease，NAFLD)包括非酒精性单纯性脂肪肝(non-alcoholic fatty liver，NAFL)、非酒精性脂肪性肝炎(non-alcoholic steatohepatitis，NASH)、肝硬化及肝癌。全球NAFLD患病率为25%[1]，NAFLD在2型糖尿病(type 2 diabetes mellitus，T2DM)人群中患病率高达80%[2]。伴NAFLD的T2DM患者的NASH及进展性纤维化的患病率分别为63%~87%和34%~60%[3]。伴有不同程度肝纤维化的患者，肝硬化及肝因性死亡增加[4-6]。胰岛素抵抗、代谢综合征(metabolic syndrome，MS)或T2DM以及PNPLA3或TM6SF2的遗传变异在NAFLD的发病机制中起作用[7]。同时，NAFLD增加了T2DM、心血管疾病及慢性肾病(chronic kidney disease，CKD)的风险[8]。国内外报道[9-12]NAFLD患者骨密度(bone mineral density，BMD)减低，罹患骨质疏松的风险增加。但目前尚无定论。Kim等[9]发现：显著肝纤维化是导致NAFLD患者骨量减少及骨质疏松的独立危险因素。非酒精性脂肪肝肝纤维化评分(non-alcoholic fatty liver disease fibrosis score，NAFLDFS)作为一种无创性评估肝纤维化的手段被美国胃肠病协会指南[4]推荐，有效地应用在T2DM合并NAFLD患者中[13]。本研究旨在利用NAFLDFS评分分析T2DM合并NAFLD肝纤维化与BMD的关系。

1 对象与方法

1.1 对象

选取2017年4月至2019年4月于徐州医科大学第二附属医院内分泌科住院的T2DM患者539例，全部符合1999年WHO诊断标准。由同一名经验丰富的超声科医生根据指南[14]筛选出脂肪肝患者，再利用NAFLDFS诊断阈值初步评估是否存在肝纤维化。将研究人群分为T2DM组(*n*=234)，T2DM合并NAFLD组(*n*=305，评分<−1.455亚组，NAFLDFS评分−1.455~0.676亚组，评分>0.676亚组)。排除标准[14]：女性未绝经，过去12个月每周饮用酒精男性≥210 g、女性≥140 g，病毒性肝炎，药物性肝病，全胃肠外营养，肝豆状核变性，自身免疫性肝病等可能导致脂肪肝的特定疾病及服用过影响骨代谢的药物，既往有腰椎及髋部骨折、腰椎术后异物、腰椎严重退行性变、脊椎侧弯、髋关节置换、严重骨性关节炎以及患有可影响骨代谢的疾病。本

研究获得徐州医科大学第二附属医院医学伦理委员会批准。

1.2 方法

询问既往病史、饮酒史及长期服药史等。由同一名测量者清晨测量并登记患者身高、体重、腰围(waist circumference，WC)、腰臀比(waist hip ratio，WHR)、收缩压(systolic blood pressure，SBP)等。空腹8 h以上，于次日清晨抽取静脉血测定谷草转氨酶(glutamic oxaloacetic transaminase，AST)、谷丙转氨酶(alanine aminotransferase，ALT)、三酰甘油(triglyceride，TG)、胆固醇(cholesterol，CHOL)、低密度脂蛋白(low-density lipoprotein，LDLC)、极低密度脂蛋白(very low-density lipoprotein，VLDL)、空腹血糖(fasting blood glucose ，FBG)、空腹C肽(fasting C-peptide，F-CP)(放射免疫法)、空腹胰岛素(fasting insulin，FINS)(放射免疫法)、糖化血红蛋白(glycosylated hemoglobin，HbA1c)、载脂蛋白B(apolipoprotein b，APOB)、载脂蛋白E(apolipoprotein E，APOE)、总蛋白(total protein，TP)、白蛋白(albumin，ALB)、球蛋白(globulin，GLB)、前白蛋白(prealbumin，PA)、血尿酸(serum uric acid，SUA)、谷氨酰转移酶(glutamyl transferase，GGT)、胆碱酯酶(cholinesterase，CHE)等血清学指标(日立7600全自动生化分析仪)。用稳态模型评估胰岛素抵抗指数(HOME-IR)= FINS*FBG/22.5。行消化系彩超(深圳迈瑞公司DC-6C彩超诊断仪)检查及使用双能X线骨密度仪(DXA，购于美国GE公司)测定股骨颈、Ward's三角、大粗隆、股骨干及全部股骨BMD，结果用BMD(g/cm^2)和T值表示。参照WHO推荐的诊断标准，T值≥−1诊断为骨量正常，−2.5<T值<−1诊断为骨量减少，T值≤−2.5诊断为骨质疏松[15]。NAFLDFS=−1.675+0.037×年龄+0.094×BMI+1.13×空腹血糖调节受损或者糖尿病(是=1，否=0)+0.99×AST/ALT − 0.013×PLT(×10^9/L)−0.66×ALB(g/dL)。NAFLDFS<−1.455可排除纤维化，>0.676可诊断纤维化。

1.3 统计学处理

采用SASS 19.0软件进行数据分析，正态分布资料用均数±标准差($\bar{x}\pm s$)表示，两组间比较采用独立样本t检验，多组间比较采用单因素ANOVA分析，非正态分布资料用中位数及四分位数间距[M (Q_L, Q_U)]表示，两组间比较采用Mann-Whitney U检验，多组间比较采用Kruskal Wallis H检验。分类资料采用χ^2检验。Spearman分析NAFLDFS与各指标相关性。Logistic回归分析NAFLDFS对骨量变化的影响。P<0.05为差异有统计学意义。

2 结果

2.1 各组临床资料、生化指标、BMD及T值比较

与T2DM组比较，NAFLD+T2DM组具有更高的BMI，WC，SBP，FINS，F-CP，HOME-IR，ALT，AST，GGT，CHE，SUA，TG，CHOL，LDLC，VLDL，APOB，APOE及更短的T2DM病程，APTT，AST/ALT，HDLC，差异均有统计学意义(P<0.05)。两组性别，年龄，FBG，HbA1c等其他指标差异无统计学意义(表1)。与T2DM组比较，NAFLD+T2DM组股骨颈，Ward's三角，大粗隆，股骨干及全部股骨的BMD及T值下降，差异有统计学意义(P<0.05，表2)。

与<−1.455亚组比较，−1.455~0.676亚组具有较高的年龄，BMI，WC，AST/ALT和更低的ALT，CHE，WBC，PLT，TP，ALB，PA；与<−1.455亚组比较，>0.676亚组具有更高的年龄，病程，BMI，WC，WHR，PT，AST/ALT，冠心病和高血压患病率和更低的ALT，GGT，CHE，WBC，PLT，TG，CHOL，LDLC，VLDL，APOB，TP，ALB，GLB，PA。>0.676亚组的年龄，BMI，WC，WHR，AST/ALT，冠心病和高血压患病率显著高于−1.455~0.676亚组，而ALT，CHE，WBC，PLT，TG，CHOL，LDLC，VLDL，APOB，TP，ALB，GLB，PA显著低于−1.455~0.676亚组(P<0.05)。3组在性别，FBG，FINS，F-CP，HOME-IR，HbA1C等其他指标上差异无统计学意义(P>0.05，表3)。>0.676亚组较<−1.455组，−1.455~0.676组股骨颈，Ward's三角BMD及T值降低，差异具有统计学意义(P<0.05，表4)。

2.2 NAFLDFS，BMD与其他指标的相关性

NAFLDFS除公式中的指标外，与病程，SCr，SUA，WC呈正相关，与WBC，TP，肝酶(GGT，ALP，CHE)，血脂(TG，CHOL，VLDL，APOB，LDLC)，股骨颈，Ward's三角的BMD及T值呈负相关(P<0.05)。相关性分析示：股骨BMD与性别(男=0，女=1)、年龄、病程、ALT呈负相关，与BMI呈正相关(r=−0.402，−0.323，−0.149，−0.135，0.261，P<0.05，表5)。

表1 各组临床资料，生化指标的比较

Table 1 Comparison of clinical data and biochemical indexes in each group

组别	性别(男/女)	年龄/岁	病程/年	BMI/(kg·m^{-2})	WC/cm	SBP/mmHg
T2DM	234(111/123)	63.83 ± 9.59	10(2~19)	24.12 ± 3.07	89.71 ± 9.05	132.59 ± 19.26
T2DM+NAFLD	305(122/183)	63.35 ± 9.66	8(1~12)	26.55 ± 3.48	94.41 ± 10.43	138.12 ± 18.32
P	>0.05	>0.05	<0.01	<0.01	<0.01	<0.01
组别	FBG/(mmol·L^{-1})	FINS/(μIU·mL^{-1})	F-CP/(ng·mL^{-1})	HOME-IR	APTT/s	ALT/(U·L^{-1})
T2DM	8.77 ± 3.81	7.66 ± 4.46	1.85 ± 0.82	2.25(1.53~3.22)	30.77 ± 3.38	17(13~24)
T2DM+NAFLD	9.33 ± 3.25	12.20 ± 7.89	2.64 ± 1.19	3.82(2.38~5.31)	29.41 ± 2.77	21(16~33)
P	>0.05	<0.01	<0.01	<0.01	<0.01	<0.01
组别	AST/(U·L^{-1})	AST/ALT	GGT/(U·L^{-1})	CHE/(U·L^{-1})	SUA/(μmol·L^{-1})	TG/(mmol·L^{-1})
T2DM	18(15~21)	1.04(0.81~1.31)	21(17~27)	8.10 ± 1.69	293.48 ± 85.85	1.26(0.93~1.75)
T2DM+NAFLD	18(15~25)	0.88(0.71~1.10)	29(22~44)	8.97 ± 1.88	311.76 ± 85.53	1.99(1.43~2.92)
P	<0.05	<0.01	<0.01	<0.01	<0.05	<0.01
组别	HDLC/(mmol·L^{-1})	LDLC/(mmol·L^{-1})	VLDL/(mmol·L^{-1})	APOB/(g·L^{-1})	CHOL/(mmol·L^{-1})	APOE/(mg·L^{-1})
T2DM	1.25 ± 0.33	3.06 ± 0.99	0.57(0.42~0.80)	0.98 ± 0.29	4.79 ± 1.29	38.89 ± 13.42
T2DM+NAFLD	1.15 ± 0.31	3.33 ± 0.92	0.90(0.64~1.30)	1.07 ± 0.27	5.11 ± 1.15	45.50 ± 14.78
P	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

表2 各组各部位BMD及T值的比较

Table 2 Comparison of BMD and T value of various sites in each group

组别	股骨颈		Ward's 三角		大粗隆		股骨干	全部股骨	
	BMD	T 值	BMD	T 值	BMD	T 值	BMD	BMD	T 值
T2DM	0.92 ± 0.15	−0.28 ± 1.13	0.75 ± 0.19	−0.82 ± 1.19	0.80 ± 0.15	0.08 ± 1.11	1.17 ± 0.19	0.98 ± 0.16	0.00 ± 1.18
T2DM+NAFLD	0.86 ± 0.14	−0.69 ± 1.11	0.68 ± 0.17	−1.33 ± 1.14	0.77 ± 0.14	−0.11 ± 1.12	1.12 ± 0.18	0.94 ± 0.15	−0.29 ± 1.11
P	<0.01	<0.01	<0.01	<0.01	<0.05	<0.05	<0.01	<0.01	<0.01

2.3 各组及各亚组骨量异常情况比较

T2DM组骨量正常(T≥−1)121例，骨量异常(T<−1)113例，T2DM+NAFLD组骨量正常104例，骨量异常201例，两组在骨量异常发生率上存在差异(48.29% vs 65.90%，*P*<0.01)；<−1.455组亚组骨量正常32例，骨量异常30例，−1.455~0.676组亚组骨量正常65例，骨量异常138例，>0.676组亚组骨量正常7例，骨量异常33例，三组骨量异常发生率差异有统计学意义(48.39% vs 67.98% vs 82.5%，均*P*<0.01)。

2.4 Logistic 回归分析 T2DM 合并 NAFLD 患者 NAFLDFS 评分对骨量减少的影响

以是否存在骨量异常(骨量减少和骨质疏松)为因变量，NAFLDFS评分等级为自变量，logistic回归分析示：NAFLDFS评分是骨量减少的影响因素。−1.455~0.676亚组相对于<−1.455亚组相比，骨量减少的风险增加(OR=2.265，95%CI 1.269~4.040，*P*=0.006)；>0.676亚组相对于<−1.455亚组相比，骨量减少的风险增加(OR=5.029，95%CI 1.934~13.076，*P*=0.001)。控制年龄，性别，BMI，病程，ALT后，NAFLDFS评分仍是骨量减少的影响因素。

在上述基础上进一步控制可能对BMD造成影响的FBG，HDLC，HbA1C，APOB后，NAFLDFS评分仍是骨量减少的影响因素(−1.455~0.676亚组 vs <−1.455亚组：OR=2.235，95%CI 1.040~4.803，*P*=0.039；>0.676亚组vs <−1.455亚组：OR=4.463，95%CI 1.221~16.308，*P*=0.024；表6)。

表3 各亚组临床资料和生化指标的比较

Table 3 Comparison of clinical data and biochemical indexes in each sub-group

组别	性别(男/女)	年龄/岁	病程/年	BMI/(kg·m^{-2})	WC/cm	WHR
<−1.455	62 (20/42)	56.63 ± 9.29	3 (5~10)	24.95 ± 3.27	90.85 ± 9.90	0.93 ± 0.08
−1.455~0.676	203 (88/115)	63.62 ± 8.30*	8 (1~13)	26.55 ± 3.28*	94.12 ± 8.77*	0.94 ± 0.06
>0.676	40 (14/26)	72.40 ± 8.91*#	10 (6~20)*	29.08 ± 3.42*#	101.49 ± 15.04*#	0.98 ± 0.14*#
组别	FBG/(mmol·L^{-1})	FINS/(μU·mL^{-1})	F-CP/(ng·mL^{-1})	HOME-IR	PT/s	ALT/(U·L^{-1})
<−1.455	9.46 ± 3.06	10.96 ± 6.49	2.43 ± 1.03	3.66 (2.24~5.15)	10.47 ± 0.80	25 (19~41)
−1.455~0.676	9.32 ± 3.38	12.45 ± 8.22	2.69 ± 1.23	3.80 (2.43~5.40)	10.73 ± 1.14	21 (15~32)*
>0.676	9.18 ± 2.91	13.32 ± 8.63	2.78 ± 1.27	4.72 (2.48~5.86)	11.10 ± 0.82*	16 (10~25)*#
组别	HbA1C/%	AST/ALT	GGT/(U·L^{-1})	CHE/(U·L^{-1})	WBC/(10^9·L^{-1})	TG/(mmol·L^{-1})
<−1.455	8.36 ± 1.77	0.80 (0.62~0.94)	33 (26~48)	9.66 ± 1.81	7.06 ± 1.70	2.07 (1.62~3.03)
−1.455~0.676	8.58 ± 2.14	0.89 (0.71~1.10)*	29 (22~43)	8.97 ± 1.82*	6.55 ± 1.67*	2.02 (1.44~3.02)
>0.676	8.56 ± 1.78	1.16 (0.85~1.41)*#	25 (19~36)*	7.90 ± 1.79*#	5.69 ± 1.54*#	1.56 (1.19~2.28)*#
组别	PLT/(10^9·L^{-1})	LDLC/(mmol·L^{-1})	VLDL/(mmol·L^{-1})	APOB/(g·L^{-1})	CHOL/(mmol·L^{-1})	患高血压/%
<−1.455	284.62 ± 48.82	3.52 ± 0.98	0.94 (0.74~1.38)	1.14 ± 0.30	5.43 ± 1.27	46.77
−1.455~0.676	214.20 ± 43.54*	3.34 ± 0.87	0.90 (0.65~1.35)	1.07 ± 0.26	5.11 ± 1.97	49.26
>0.676	169.23 ± 56.26*#	2.98 ± 1.00*#	0.71 (0.54~0.71)*#	0.96 ± 0.30*#	4.59 ± 1.16*#	72.50*#
组别	患冠心病/%	TP/(g·L^{-1})	ALB/(g·L^{-1})	GLB/(g·L^{-1})	PA/(mg·L^{-1})	
<−1.455	8.06	72.48 ± 5.46	45.31 ± 2.74	27.23 ± 4.58	318.52 ± 86.93	
−1.455~0.676	10.89	70.59 ± 6.28*	43.44 ± 3.50*	27.16 ± 4.69	296.01 ± 75.39*	
>0.676	30.00*#	67.34 ± 6.33*#	42.16 ± 2.86*#	25.20 ± 5.13*#	247.43 ± 60.72*#	

与<−1.455组比较，*P<0.05；与−1.455~0.676组比较，#P<0.05。

Compared with <−1.455 subgroup, *P<0.05; Compared with −1.455–0.676 subgroup, #P<0.05.

表4 各亚组各部位BMD及T值的比较

Table 4 Comparison of BMD and T value of various sites in each sub-group

组别	股骨颈		Ward's三角		大粗隆		股骨干	全部股骨	
	BMD	T值	BMD	T值	BMD	T值	BMD	BMD	T值
<−1.455	0.90 ± 0.13	−0.41 ± 0.99	0.72 ± 0.16	−1.06 ± 1.10	0.79 ± 0.13	0.03 ± 1.05	1.34 ± 0.18	0.96 ± 0.14	−0.15 ± 1.03
−1.455~0.676	0.86 ± 0.15	−0.69 ± 1.15	0.68 ± 0.18	−1.32 ± 1.17	0.77 ± 0.15	−0.14 ± 1.18	1.21 ± 0.19	0.94 ± 0.15	−0.30 ± 1.15
>0.676	0.81 ± 0.12*#	−1.10 ± 0.96*#	0.62 ± 0.14*#	−1.74 ± 0.94*#	0.76 ± 0.12	−0.21 ± 0.92	1.11 ± 0.18	0.92 ± 0.13	−0.46 ± 1.00

与<−1.455组比较，*P<0.05；与−1.455~0.676组比较，#P<0.05。

Compared with <−1.455 subgroup, *P<0.05; Compared with −1.455–0.676 subgroup, #P<0.05.

表5 NAFLDFS与其他指标的相关性

Table 5 Relevance between NAFLDFS and other indicators

参数	病程	WBC	TP	GGT	ALP	CHE
r	0.225	−0.320	−0.241	−0.142	−0.139	−0.310
P	<0.001	<0.001	<0.001	0.013	0.015	<0.001
项目	Scr	SUA	TG	CHOL	LDLC	VLDL
r	0.149	0.120	−0.223	−0.184	−0.159	−0.023
P	0.010	0.037	<0.001	0.001	0.005	<0.001
参数	APOB	WC	股骨颈BMD	股骨颈T值	Ward's三角BMD	Ward's三角T值
r	−0.159	0.221	−0.113	−0.129	−0.131	−0.132
P	0.005	0.001	0.049	0.024	0.022	0.021

表6 T2DM合并NAFLD患者NAFLDFS评分对骨量减少的影响

Table 6 Effect of NAFLDFS score on bone loss in patients with type 2 diabetes complicated with non-alcoholic fatty liver disease

变量	B	SE	Wald	*P*	OR	95%CI
MODEL1						
NAFLDFS			13.031	0.001		
NAFLDFS(1)	0.817	0.295	7.661	0.006	2.265	1.269~4.040
NAFLDFS(2)	1.615	0.488	10.973	0.001	5.029	1.934~13.076
MODEL2						
NAFLDFS			7.395	0.025		
NAFLDFS(1)	0.891	0.357	6.239	0.012	2.438	1.211~4.904
NAFLDFS(2)	1.420	0.612	5.385	0.020	4.137	1.247~13.727
MODEL3						
NAFLDFS			5.971	0.052		
NAFLDFS(1)	0.804	0.390	4.247	0.039	2.235	1.040~4.803
NAFLDFS(2)	1.496	0.661	5.118	0.024	4.463	1.221~16.308

NAFLDFS(1)：−1.455~0.676亚组 vs <−1.455亚组；NAFLDFS(2)：>0.676亚组 vs <−1.455亚组比较。MODEL1：未控制。MODEL2：控制年龄，性别，BMI，病程，ALT。MODEL3：控制年龄，性别，BMI，病程，FBG，ALT，HDLC，HbA1C，APOB。

NAFLDFS (1): −1.455–0.676 subgroup vs <−1.455 subgroup; NAFLDFS (2): >0.676 subgroup vs <−1.455 subgroup. MODEL1: Uncontrolled. MODEL2: Control age, sex, BMI, course of disease, ALT. MODEL3: Control age, sex, BMI, course of disease, FBG, ALT, HDLC, HbA1C, APOB.

3 讨论

NAFLD是一种代谢应激性肝病，慢性肝损伤引发炎症、星状细胞活化和进行性纤维化[16]。肝活检是确定NAFLD患者是否存在NASH及纤维化的可靠方法，但其受成本、抽样误差和相关并发症的限制。Angulo等[13]以733例肝穿刺患者作为研究对象，发现除NAFLDFS<−1.455外，进展性肝纤维化的阴性预测值在估计组和验证组分别为93%和88%；NAFLDFS>0.676时诊断进展性肝纤维化的阳性预测值分别高达90%和82%。另有一项Meta分析[17]指出：NAFLDFS在13项研究共3 064例患者中

受试者工作特征曲线下面积为0.85(0.81~0.90)。

本研究结果发现：NAFLDFS除与BMD负相关外，也与TP，肝酶(GGT，ALP，CHE)，血脂(TG，CHOL，VLDL，APOB，LDLC)呈负相关。人体70%~80%的TG由肝内源性合成，CHOL主要在肝和脂肪组织中合成，总蛋白和血脂减少反映肝合成能力的降低。同时肝细胞存活数量减少，肝酶降低。Mendes等[18]研究发现：28.2%的患者在最初诊断为NAFLD时已存在门脉高压，门静脉高压及亚临床脾功能亢进可能解释了本研究患者WBC及PLT减少的原因。NASH患者较非NASH患者，异常蛋白尿和CKD的患病率增加，进展性纤维化的严重程度与降低的eGFR独立相关[19-20]。肾功能不全导致UA，Scr升高。本研究结果表明：肝纤维化患者高血压，冠心病患病率高，糖尿病病程长，同时肥胖特征明显，这与MS诊断一致。Marceau等[21]研究551例重度肥胖患者肝活检资料发现：代谢综合征4个组分中每增加1个，脂肪变性的风险从1倍增加到99倍，而糖尿病或糖耐量受损患者的纤维化风险增加了7倍。

既往研究[22-23]示：T2DM群体中BMD变化定论不一，可降低，正常，甚至高于正常，而骨折风险增加。有研究[22]发现，与健康人群相比，T2DM患者股骨颈和腰椎BMD升高，而骨折风险却增加69%。另有研究[23]发现：T2DM患者较非T2DM患者的BMD减低。肝纤维化与BMD关系的研究较少。Kim等[9]报道显著纤维化导致NAFLD患者骨量减少及骨质疏松。另有研究[10]报道：NASH患者存在低BMD，且与增高的CRP和ALT有关。患NASH儿童的BMD低于没有NASH的NAFLD儿童[11]。NAFLD与BMD关系也存在争议。一项Meta分析[12]表明：男性NAFLD与低BMD显著相关。与此同时，有研究[24]表明：T2DM合并NAFLD患者的BMD无下降。本研究发现：T2DM合并NAFLD肝纤维化患者BMD减低，两者具有相关性，进展性肝纤维化是骨量减少的危险因素。实际上，当NAFLDFS>−1.455时，即有骨量减少风险增加，因此建议T2DM合并NAFLD患者应早期关注低BMD的风险。

T2DM合并NAFLD肝纤维化患者BMD减低可能的机制：一方面，合并NAFLD的T2DM患者胰岛素抵抗显著，胰岛素抵抗与高风险骨质疏松及骨量减少有关[25]。胰岛素本身能促进成骨细胞的增殖和分化，并能产生代谢信号，促进骨胶原合成，影响骨的微结构[26]。同时，胰岛素敏感性下降导致肾1a-羟化酶的活性下降，尿钙排出量升高，导致钙、磷吸收量减少，破骨细胞活性增强，骨更新率和钙化下降。肝纤维化患者肝功能下降，合成IGF-1能力下降。IGF-1是骨胶原蛋白和成骨细胞刺激因子，刺激葡萄糖摄取，有利于胰岛素信号转导，这也减轻胰岛素抵抗对BMD影响[27]。另一方面，全身炎症促使NAFLD进展为NASH[28]。一些炎症因子如IL-1，IL-6家族及TNF-α，TNF可溶性受体(TNFR-55)等均可增加破骨细胞数量，促进骨吸收[29]。再者，氧化应激产生大量活性氧，过多的氧自由基使得细胞呈缺氧状态，诱导破骨细胞生成，影响骨细胞代谢。本研究存在一些局限性，如经DXA诊断的骨质疏松患者部分已服用药物治疗，排除此部分患者后患者资料较少，故将骨质疏松纳入骨量减少分析，有待日后进一步完善患者资料，扩大样本量。

综上所述，T2DM合并NAFLD肝纤维化患者BMD减低，两者具有相关性，进展性肝纤维化是骨量减少的危险因素。

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本文引用： 徐雅倩, 樊宽鲁, 蔡可英. 2型糖尿病合并非酒精性脂肪性肝病肝纤维化与骨密度的相关性[J]. 临床与病理杂志, 2020, 40(3): 674-681. doi: 10.3978/j.issn.2095-6959.2020.03.022
Cite this article as: XU Yaqian, FAN Kuanlu, CAI Keying. Relationship between liver fibrosis and bone mineral density in type 2 diabetes with nonalcoholic fatty liver disease[J]. Journal of Clinical and Pathological Research, 2020, 40(3): 674-681. doi: 10.3978/j.issn.2095-6959.2020.03.022