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不同亚型脂联素与非酒精性脂肪性肝病的关系 *

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摘要 目的：探究总脂联素(total adiponectin，total APN)和高分子量脂联素(high-molecular-weight adiponectin，HMW APN)与非酒精性脂肪性肝病(Nonalcoholic Fatty Liver Disease，NAFLD)的关系。**方法：**连续纳入 50 名男性健康男性及 50 名非酒精性脂肪性肝病男性患者，收集患者临床资料及其他临床生化数据，通过 ELISA 法检测总脂联素、支链氨基酸及可溶性晚期糖基化终末产物含量，Western blot 法测定高分子量、中分子量和低分子量脂联素水平，进一步分析其相关性。**结果：**与对照组的健康受试者相比，NAFLD 患者的总脂联素和三种不同形式的脂联素水平均显著降低。在 NAFLD 患者中，总脂联素与身高(R=-0.270, *P*=0.032)和羧甲基赖氨酸(R=-0.259, *P*=0.040)显著负相关；高分子量脂联素与空腹血糖(R=0.350, *P*=0.016)显著正相关，与丙氨酸氨基转移酶(R=-0.321, *P*=0.029)和天门冬氨酸氨基转移酶(R=-0.295, *P*=0.045)显著负相关。**结论：**总脂联素和三种不同形式的脂联素水平均与 NAFLD 呈显著负相关。

关键词：非酒精性脂肪性肝病；高分子量脂联素；中分子量脂联素；低分子量脂联素

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The Correlation between Different Adiponectin Isoforms with Nonalcoholic Fatty Liver Disease*

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ABSTRACT Objective: To investigate the correlation between total adiponectin (total APN) and high-molecular-weight adiponectin (HMW APN) with nonalcoholic fatty liver disease (NAFLD). **Methods:** A total of 50 healthy males and 50 male patients with NAFLD were included in the study. Their clinical biochemical characteristics were measured and collected. Total adiponectin, branched chain amino acid (BCAAs) and soluble receptor for advanced glycation end product (sRAGE) were measured by ELISA. The variation of high-molecular-weight, medium-molecular-weight and low-molecular-weight adiponectin levels were determined by Western blot in NAFLD patients. Then, the correlation among the characteristics was further analyzed. **Results:** When compared with healthy subjects in control group, significantly decreased levels of total adiponectin and three adiponectin isoforms were found in NAFLD patients. In NAFLD patients, height (R=-0.270, *P*=0.032) and N-epsilon carboxymethyl lysine (CML) (R=-0.259, *P*=0.040) were significantly negatively correlated with total adiponectin; HMW adiponectin was significantly positively associated with fasting plasma glucose (FPG) (R=0.350, *P*=0.016), and negatively associated with ALT (R=-0.321, *P*=0.029) and AST (R=-0.295, *P*=0.045) respectively. **Conclusions:** The levels of total adiponectin and three adiponectin isoforms are in significantly negative correlation with NAFLD.

Key words: Nonalcoholic fatty liver disease (NAFLD); High-molecular-weight adiponectin (HMW APN); Medium-molecular-weight adiponectin (MMW APN); Low-molecular-weight adiponectin (LMW APN)

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前言

非酒精性脂肪性肝病 (nonalcoholic fatty liver disease，NAFLD)代表了一系列从单纯性脂肪变性到非酒精性脂肪性肝炎、肝纤维化和肝硬化的进行性肝病[1]。NAFLD 的特征是肝脏脂肪累积≥ 5 %，其临床病理特征为肝脂肪变性，有或无其他病理特征，并且无脂肪肝的其他特定病因[2,3]。流行病学调查显示全球 NAFLD 患病数高达 10 亿[2]，欧洲与北美的发病率分别

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为 23.7 %和 24.1 %[4],亚洲约为 25 %[5]。近年来研究认为导致 NAFLD 的病因除基因遗传学因素外,还与代谢综合征、胰岛素抵抗、脂肪组织分泌的脂联素等细胞因子的内分泌功能紊乱相关。

脂联素(adiponectin,APN)是由脂肪细胞分泌的一种细胞因子,其单体由 224 个氨基酸构成,分子量约为 30kDa。脂联素在血浆中以三种不同的基本寡聚复合物形式存在,分别为同源三聚体构成的低分子量脂联素(约 65kDa),六聚体构成的中分子量脂联素 (约 150kDa),12-18 多聚体构成的高分子量脂联素(大于 280kDa)[6,7]。脂联素可以在 NAFLD 的发展中发挥保护作用,并作为抗血管、抗炎、抗纤维化因子[8,9]。目前研究表明高分子量脂联素、总脂联素以及低分子量脂联素水平与总脂联素的比例与糖尿病、胰岛素抵抗、冠状动脉疾病和代谢综合征等疾病存在相关性[10,11]。有研究显示 NAFLD 患者人群的脂联素水平降低, 并且血清脂联素水平降低是 NAFLD 的独立危险因素[12,13]。还有研究显示在 2 型糖尿病患者中,NAFLD 患者人群的血清高分子量脂联素水平显著降低[14]。然而,不同脂联素亚型在 NAFLD 中发挥的生理作用仍然很不明确。本研究旨在探讨 NAFLD 患者中三种血清脂联素亚型变化特征及血清总脂联素、高分子量脂联素与其他临床生化指标的关系。

1 材料与方法

1.1 一般资料

连续纳入于西京医院健康检查中心接受常规健康检查的 50 名男性健康人群(年龄 42.53± 7.98 岁)作为对照组和 50 名男性 NAFLD 患者(年龄 43.3± 6.1 岁)作为实验组。所有受试者均接受血液采样和腹部超声检查。NAFLD 患者符合以下纳入标准:男性;年龄 30-70 岁;轻度非酒精性脂肪肝;无糖尿病、心血管疾病、外周动脉疾病、肺和肾脏疾病病史。排除标准:受试者患有未控制的高血压;携带乙型肝炎病毒和(或)丙型肝炎病毒感染的血清学标志物;患有自身免疫性肝病, 酒精性肝病;具有可能导致肝损伤,肝脂肪变性或肝纤维化的病因。

1.2 方法

1.2.1 生化资料收集 在禁食 8-12 h 后,抽取静脉血样,迅速分离血清样品并等分保存在 EP 管中,于 -80 ℃冷冻待检。按照试剂盒及检测仪器操作说明(R&D systems,USA),采用 ELISA 法对待检等分样品分别测定总脂联素、可溶性晚期糖基化终末产物受体 (soluble receptor for advanced glycation end product, sRAGE)、羧甲基赖氨酸、支链氨基酸。通过全自动生化分析仪(Beckman AU480)测定其他生化指标,如总胆固醇、高密度脂蛋白胆固醇,低密度脂蛋白胆固醇、甘油三酯、空腹血糖、天冬氨酸氨基转移酶、丙氨酸氨基转移酶等。以上生化指标检测均在血液采样后 48 h 内完成。

1.2.2 免疫印迹检测脂联素多聚体 在 SDS- 聚丙烯酰胺凝胶电泳后, 采用 Western blot 对脂联素多聚体进行分析。将稀释 10 倍的血清脂联素样本与不添加还原剂的 5× Laemmli 缓冲液混合。在 4 %-15 %标准预制 10 孔凝胶(Bio-Rad, USA)中加入 15 μL 样品并开始电泳。用硝酸纤维素膜(PALL, USA)对样品进行免疫印迹分析。使用人 / 小鼠 Acrp30 / 脂联素单克隆抗体 (R&D Systems, USA) 和山羊抗大鼠 IgG 辣根过氧化物酶(Santa Cruz Biotechnology, USA)进行蛋白质印迹检测,并使用 ECL-Plus 化学发光试剂盒(Amersham Bioscience, USA)以及 U-VP Bio-Imaging Systems 显色。采用 Vision Works LS 采集和分析软件对印迹密度进行分析。

1.3 统计学分析

采用 SPSS 22.0 统计软件对实验数据进行统计学分析,连续变量以($\bar{x}$± SEM)表示,采用 Student's t 检验进行两组间平均值的比较, 采用 Pearson 相关系数检验各组数据的相关性,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组一般临床特征的比较

如表 1 所示, 与年龄匹配的健康对照组受试者相比,NAFLD 患者的一般临床与生化特征包括体重、身体质量指数、收缩压、舒张压、支链氨基酸、羧甲基赖氨酸、空腹血糖、总胆固醇、甘油三酯、低密度脂蛋白胆固醇水平均显著升高(P<0.01)。然而,NAFLD 患者可溶性晚期糖基化终末产物受体(sRAGE)水平(P<0.05)和脂联素水平(P<0.01)与对照组受试者相比显著降低。两组年龄、身高、天冬氨酸氨基转移酶、丙氨酸氨基转移酶比较均无明显差异(P>0.05)。

表 1 两组一般临床特征的比较($\bar{x}$± SEM)

Table 1 Comparison of the general characteristics between two groups($\bar{x}$± SEM)

Characteristics	Control Group(n=50)	NAFLD Group(n=50)	*P* value
Age (year)	42.53± 7.98	43.00± 6.10	0.7057
Height (m)	1.73± 0.06	1.74± 0.06	0.3390
Weight (Kg)	68.79± 8.29	79.08± 8.06	<0.0001
BMI (kg/m^2)	23.00± 2.28	26.19± 2.29	<0.0001
SBP (mmHg)	110.40± 12.23	117.06± 12.63	0.0024
DBP (mmHg)	72.10± 9.38	76.78± 9.39	0.0048
AST (IU/L)	21.47± 7.73	22.28± 5.68	0.4963
ALT (IU/L)	22.30± 10.14	24.43± 9.37	0.2122
Total APN (μg/mL)	5.85± 3.74	4.26± 2.71	0.0062
BCAA (μmol/L)	524.07± 101.78	672.51± 86.30	<0.0001

CML (pg/mL)	63.28± 24.78	78.42± 30.53	0.0020
sRAGE (pg/mL)	996.41± 440.85	844.04± 348.14	0.0299
FPG (mmol/mL)	4.70± 0.39	5.01± 0.54	0.0002
T.cho. (mmol/L)	4.10± 0.67	4.71± 0.78	<0.0001
TG (mmol/mL)	1.15± 0.41	1.62± 0.67	<0.0001
LDL (mmol/mL)	1.59± 0.49	1.83± 0.51	0.0065
HDL (mmol/mL)	1.30± 0.23	1.39± 0.28	0.0441

注:数据以 $\bar{x}$± SEM,表示。

NAFLD: nonalcoholic fatty liver disease; BMI: Body Mass Index; SBP: systolic blood pressure; DBP: Diastole pressure; AST: aspartate aminotransferase; ALT: alanine aminotransferase; APN: Adiponectin; CML: N-epsilon carboxymethyllysine; BCAA: branched chain amino acid; sRAGE: soluble receptor for advanced glycation end product; FPG: fasting plasma glucose; T. cho: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein; LDL: low-density lipoprotein.

2.2 三种不同脂联素亚型特征

本研究进一步分析了健康受试者和 NAFLD 患者的脂联素亚型在血浆中的表达,图 1 显示了两组受试者的不同脂联素亚型表达情况;图 2 统计结果显示与对照组相比,NAFLD 患者血清高分子量、中分子量和低分子量脂联素水平均显著降低(P<0.01)。

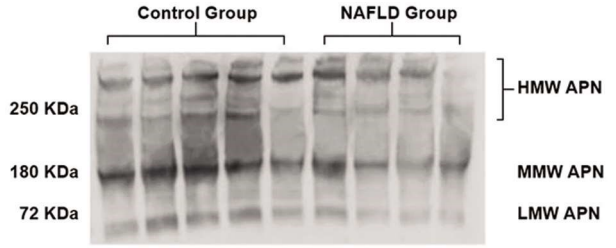

图 1 Western blot 实验中对照组与 NAFLD 组的不同脂联素亚型典型图

Fig.1 Representative photograph of different adiponectin isoforms' expression via western blot assay in control and NAFLD groups

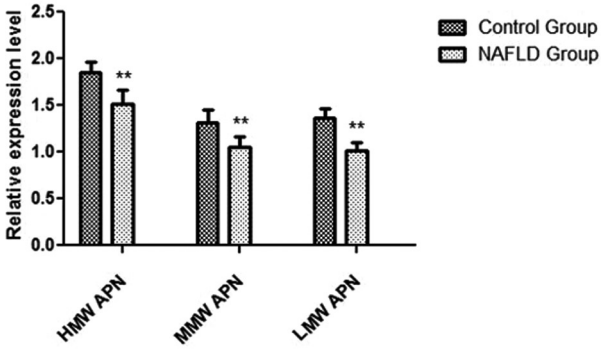

图 2 对照组与 NAFLD 患者的不同脂联素亚型的相对表达水平的统计分析(** 表示 P<0.01)

Fig.2 The corresponding statistical analysis of relative expression of different adiponectin isoforms in control and NAFLD groups

2.3 血清总脂联素、高分子量脂联素与 NAFLD 相关临床生化指标的相关性分析

为探究 NAFLD 患者血清总脂联素、高分子量脂联素亚型水平与其他 NAFLD 相关指标之间的关系,本研究分别将两组受试者的血清总脂联素、高分子量脂联素亚型与其他 NAFLD 相关的临床生化指标进行相关性分析,结果见表 2、表 3。如表 2 所示,在对照组中,总脂联素水平与年龄呈显著正相关(R=0.243,P=0.042),与甘油三酯(R=-0.250,P=0.037)、低密度脂蛋白(R=-0.264,P=0.027)呈显著负相关;在 NAFLD 患者中,总脂联素水平与身高 (R=-0.270,P=0.032), 羧甲基赖氨酸(R=-0.259,P=0.040)呈显著负相关。如表 3 所示,在对照组中,身体质量指数(R=0.430,P=0.011),舒张压(R=0.370,P=0.031)与高分子量脂联素水平呈显著正相关; 在 NAFLD 患者中, 空腹血糖(R=0.350,P=0.016) 也与高分子量脂联素水平呈显著正相关;在 NAFLD 患者中,丙氨酸氨基转移酶(R=-0.321,P=0.029)和天冬氨酸氨基转移酶(R=-0.295,P=0.045)均与高分子量脂联素呈显著负相关。

表 2 血浆总脂联素水平有关因素的相关性($\bar{x}$± SEM)

Table 2 Correlation of the factors associated with plasma total adiponectin levels($\bar{x}$± SEM)

Characteristics[a]	Control Group(n=50) R(P value)	NAFLD Group(n=50) R(P value)
Age (year)	0.243(p=0.042)	-0.045(p=0.724)
Height (m)	-0.102(p=0.401)	-0.270(p=0.032)
Weight (Kg)	-0.107(p=0.379)	-0.127(p=0.323)
BMI (kg/m^2)	-0.055(p=0.654)	-0.143(p=0.262)
SBP (mmHg)	0.231(p=0.054)	0.064(p=0.618)
DBP (mmHg)	0.175(p=0.148)	

AST (IU/L)	-0.114(p=0.346)	-0.059(p=0.645)
ALT (IU/L)	0.035(p=0.773)	-0.094(p=0.465)
BCAA (μmol/L)	0.035(p=0.829)	-0.170(p=0.195)
CML (pg/mL)	-0.175(p=0.148)	-0.259(p=0.040)
sRAGE (pg/mL)	0.104(p=0.390)	0.022(p=0.862)
FPG (mmol/mL)	-0.006(p=0.963)	-0.082(p=0.520)
T.cho. (mmol/mL)	0.079(p=0.517)	0.133(p=0.300)
TG (mmol/mL)	-0.250(p=0.037)	-0.064(p=0.618)
LDL (mmol/mL)	-0.264(p=0.027)	0.036(p=0.778)
HDL (mmol/mL)	0.046(p=0.707)	0.114(p=0.375)

注：a 通过 Pearson 相关性将数据与 BCAAs 进行比较。

Note: a data was compared with the BCAAs via Pearson correlation.

表 3 血浆高分子量脂联素水平有关因素的相关性($\bar{x}$± SEM)

Table 3 Correlation of the factors associated with plasma HMW adiponectin levels($\bar{x}$± SEM)

Characteristics[a]	Control Group(n=50) R(P value)	NAFLD Group(n=50) R(P value)
Age (year)	0.020(p=0.912)	0.122(p=0.412)
Height (m)	-0.027(p=0.878)	-0.137(p=0.358)
Weight (Kg)	0.311(p=0.074)	-0.002(p=0.990)
BMI (kg/m^2)	0.430(p=0.011)	0.114(p=0.446)
SBP (mmHg)	0.244(p=0.165)	0.187(p=0.208)
DBP (mmHg)	0.370(p=0.031)	0.179(p=0.228)
AST (IU/L)	-0.188(p=0.287)	-0.295(p=0.045)
ALT (IU/L)	0.136(p=0.444)	-0.321(p=0.029)
BCAA (μmol/L)	0.167(p=0.345)	-0.223(p=0.132)
CML (pg/mL)	0.176(p=0.320)	0.015(p=0.923)
sRAGE (pg/mL)	0.103(p=0.563)	-0.033(p=0.827)
FPG (mmol/mL)	-0.068(p=0.703)	0.350(p=0.016)
T.cho. (mmol/mL)	-0.231(p=0.188)	0.050(p=0.739)
TG(mmol/mL)	-0.028(p=0.875)	-0.179(p=0.229)
LDL (mmol/mL)	-0.184(p=0.298)	-0.0033(p=0.823)
HDL(mmol/mL)	-0.161(p=0.363)	0.000(p=0.998)

注：a 通过 Pearson 相关性将数据与 BCAAs 进行比较。

Note: a data was compared with the BCAAs via Pearson correlation.

3 讨论

脂联素的不同亚型具有不同的生物学特性并能够激活生物体中不同的信号传导通路。人体中三种不同脂联素亚型的水平和变化受多种因素影响。本研究发现 NAFLD 患者的总脂联素水平显著降低，与 Neuman MG[12]等人的研究结论相符。同时，与 Neuman[12]等人的研究结果一致，我们也得出 NAFLD 患者的身体质量指数、羧甲基赖氨酸、空腹血糖、总胆固醇、甘油三酯、低密度脂蛋白呈显著升高的趋势。Sunny[15]与 Cheng[16]的研究还表明 NAFLD 患者的血浆支链氨基酸水平存在显著增加。与 Zelber-Sagi[17]Palma-Duran SA[18]等人对 NAFLD 患者的研究结果相一致，我们也发现可溶性晚期糖基化终末产物受体(sRAGE)水平在 NAFLD 患者中显著减少。虽然已有研究得出 NAFLD 患者的高密度脂蛋白水平较低 [12]，但是本实验得出 NAFLD 患者的高密度脂蛋白水平呈显著升高。同时，甘油三酯 / 高密度脂蛋白的平均比率(TG / HDL)从对照组受试者(0.885)到 NAFLD 患者呈现(1.165)增高的趋势。较高的脂质比率表明晚期 NAFLD 患者的风险显著增加[19]。同样，总脂联素水平的降低以及其他临床参数的异常变化也提示 NAFLD 患者的风险不断增加。

本研究分析了正常对照组人群和 NAFLD 患者人群中总脂联素及高分子量脂联素亚型各自的临床生化相关因素。对于对照组受试者，总脂联素水平与年龄呈正相关，而总脂联素水平与甘油三酯，低密度脂蛋白呈负相关。但也有研究指出总脂联素水平在高年龄人群中与年龄增加无显著关系[20]。对于健康对照者，总脂联素与年龄、甘油三酯、低密度脂蛋白的相关性可能存在以下几种原因：1)与总脂联素呈负相关的雄激素浓度在 40 岁后随年龄增加而降低[21]。2)在 50-70 岁时，甘油三酯和低密度脂蛋白水平增长最多[22]。另外，对照组受试者的高分子量脂联素水平与身体质量指数和舒张压呈正相关。已有研究表明，肥胖或存在颈动脉动脉粥样硬化斑块的人群将显示出相对较低的高分子量脂联素水平[23,24]。

而对于 NAFLD 患者而言，总脂联素与身高和羧甲基赖氨酸呈显著负相关。但是到目前为止，尚无相关研究表明 NAFLD 和身高的相关性。已有研究表明羧甲基赖氨酸是一种重要的脂质过氧化产物，能够通过氧化应激对肝脏产生损伤[25]，其血浆水平与总脂联素水平呈负相关。在 NAFLD 患者中，高分子量脂联素水平较低且其与天冬氨酸氨基转移酶，丙氨酸氨基转移酶和空腹血糖的相关性更高，存在统计学意义。有研究指出成人哮喘患者、类风湿性关节炎患者和 NAFLD 患者的高分子量脂联素水平降低[26-28]。在 NAFLD 患者中，与其他临床生化指标相比，高分子量脂联素与丙氨酸氨基转移酶和天冬氨酸氨基转移酶的相关性呈更为显著的负相关。已有研究表明即使在正常范围内，糖尿病患者[29]、肥胖儿童[30]或 BMI <25 kg/m^2[31]的 NAFLD 患者丙氨酸氨基转移酶和高分子量脂联素之间也呈独立的负相关，这与我们的研究结果相似，但是我们的发现进一步证明在无糖尿病和肥胖的 NAFLD 患者中，天冬氨酸氨基转移酶与高分子量脂联素之间存在较为显著的负相关。因此，高分子量脂联素的变化与肝功能的关联在三种不同脂联素亚型中更加紧密。同时，也有研究证实高分子量脂联素在糖尿病患者或代谢异常受试者的脂质代谢中发挥重要作用[32,33]。

虽然本实验测定了 NAFLD 患者中的三种脂联素亚型的变化和其与多种 NAFLD 相关的生化指标的相关性分析，但是我们的研究依旧存在一些局限性。一方面，本实验纳入的研究人群相对较少；另一方面，研究参与者是来自于同一地区的中国人群，且仅纳入了男性人群。同时，由于本实验是针对 NAFLD 患者和健康人群进行的横断面研究，仅能得出不同分子量脂联素亚型与其他 NAFLD 相关生化指标的相关程度，尚不能确定其因果关系。因此，今后应在更大样本量的 NAFLD 人群中采取队列研究从而深入细致地分析不同脂联素亚型与 NAFLD 相关生化指标的相关性及其因果关系。

总之，本研究结果表明总脂联素和三种不同形式的脂联素水平均与 NAFLD 呈显著负相关。且在 NAFLD 患者中，身高和羧甲基赖氨酸与总脂联素呈显著负相关；高分子量脂联素与空腹血糖呈显著正相关，与氨基转移酶水平呈显著负相关。

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