

2型糖尿病合并非酒精性脂肪性肝病患者肝纤维化与胰岛素抵抗的关系

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摘要: **目的** 探讨2型糖尿病(T2DM)合并非酒精性脂肪性肝病(NAFLD)患者肝纤维化与胰岛素抵抗(IR)的关系。**方法** 收集2018年12月至2020年1月就诊于兰州大学第二医院的T2DM患者298例,依据腹部超声检查结果,分为单纯T2DM组($n=81$)及T2DM合并NAFLD组($n=217$)。收集两组病史资料及馒头餐糖耐量试验结果,计算稳态模型胰岛素抵抗指数(HOMA-IR)、胰岛素动态分泌敏感性评估指数(ISImatsuda)及胰岛素敏感指数(ISI)。依据NAFLD肝纤维化评分(NFS)将T2DM合并NAFLD患者分为排除纤维化亚组($n=69$)、不确定亚组($n=86$)及纤维化亚组($n=62$),比较各组间IR程度。应用Logistic回归分析影响肝纤维化发展的因素。ROC曲线分析HOMA-IR、ISImatsuda对患者肝纤维化的诊断价值。**结果** 相比于单纯T2DM组,合并NAFLD组患者的HOMA-IR升高,ISImatsuda、ISI则下降(P 均 <0.01);合并NAFLD患者中,肝纤维化亚组HOMA-IR(11.96 ± 4.66)高于不确定亚组(9.74 ± 4.16)和排除纤维化亚组(6.21 ± 2.99),ISImatsuda、ISI低于其他两组,差异均有统计学意义(P 均 <0.01)。Logistic回归分析显示,高HOMA-IR是影响T2DM合并NAFLD患者肝纤维化的危险因素($P < 0.01$),而高ISImatsuda为延缓肝纤维化的保护性因素($P < 0.05$)。ROC曲线分析提示HOMA-IR取最佳截断值为9.895时,诊断T2DM合并NAFLD患者发生肝纤维化的敏感度为75.8%,特异度为71.6%,ROC曲线下面积为0.738。**结论** IR是促进肝纤维化进展的危险因素,改善胰岛素敏感性可能是延缓肝纤维化的治疗靶标。

关键词: 2型糖尿病; 非酒精性脂肪性肝病; 肝纤维化; 胰岛素抵抗

中图分类号: R575.5 文献标识码: A 文章编号: 1674-8182(2021)04-0443-06

Relationship between liver fibrosis and insulin resistance in patients with type 2 diabetes and nonalcoholic fatty liver disease

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Abstract: Objective To explore the relationship between liver fibrosis and insulin resistance (IR) in patients with type 2 diabetes mellitus (T2DM) combined with nonalcoholic fatty liver disease (NAFLD). **Methods** A total of 298 patients with T2DM admitted to the Second Hospital of Lanzhou University from December 2018 to January 2020 were selected and divided into simple T2DM group (T2DM group, $n=81$) and T2DM combined with NAFLD group (T2DM plus NAFLD group, $n=217$) according to the results of abdominal ultrasound examination. The medical history data and the results of steamed bread meal sugar-tolerance test were collected to analyze Homeostasis model assessment-insulin resistance index (HOMA-IR), insulin dynamic secretion index (ISImatsuda) and insulin sensitivity index (ISI). According to NAFLD fibrosis score (NFS), T2DM patients with NAFLD were divided into fibrosis excluded subgroup ($n=69$), uncertainty fibrosis subgroup ($n=86$) and fibrosis subgroup ($n=62$). The degree of IR was compared among the groups. Logistic regression analysis was used to explore the influencing factors of liver fibrosis progression. Receiver operation curve (ROC) analysis was used to define the diagnostic value of HOMA-IR and ISImatsuda in liver fibrosis. **Results** Compared with T2DM group, HOMA-IR increased, while ISImatsuda and ISI decreased in T2DM plus NAFLD group (all $P < 0.01$). In the T2DM patients with NAFLD, HOMA-IR in liver fibrosis subgroup (11.96 ± 4.66) was higher than those in uncertain subgroup (9.74 ± 4.16) and fibrosis exclusion subgroup (6.21 ± 2.99), and ISImatsuda and ISI were statistically lower than

those in uncertain fibrosis subgroup and fibrosis excluded subgroup (all $P < 0.05$). Logistic regression analysis showed that high HOMA-IR was an independent risk factor of liver fibrosis in patients with T2DM and NAFLD ($P < 0.01$), while high ISImatsuda had a protective effect on delaying liver fibrosis ($P < 0.05$). ROC curve suggested that when the best cut-off value of HOMA-IR was 9.895, the sensitivity for diagnosing liver fibrosis in patients with T2DM and NAFLD was 75.8%, the specificity was 71.6%, and the area under ROC curve was 0.738. **Conclusion** IR is a risk factor for the progression of liver fibrosis, and improving insulin sensitivity may be a therapeutic target for delaying liver fibrosis.

Keywords: Type 2 diabetes mellitus; Nonalcoholic fatty liver disease; Liver fibrosis; Insulin resistance

随着不良生活习惯及饮食结构的改变,如今2型糖尿病(type 2 diabetes mellitus, T2DM)和非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)患病率快速增长,成为常见的慢性疾病。NAFLD在T2DM患者中高度流行,T2DM是促进NAFLD和肝纤维化的最强预测因子^[1-2]。有研究统计约50%~75%的T2DM患者合并NAFLD^[3],其中17.7%显示出严重纤维化^[4]。而NAFLD和严重肝纤维化会增加T2DM患心血管疾病和慢性肾脏疾病的风险^[5-6]。因此早期识别T2DM患者发生NAFLD及NAFLD肝纤维化的危险因素对于降低NAFLD患病率、延缓肝纤维化发展、减轻糖尿病慢性并发症意义深远。胰岛素抵抗(insulin resistance, IR)被认为是NAFLD发病的一个环节,但目前关于其对肝纤维化的影响结论不统一,且既往该类研究均单一使用稳态模型胰岛素抵抗指数(HOMA-IR)评估IR程度,HOMA-IR仅涉及空腹血糖(fasting plasma glucose, FPG)和空腹胰岛素(fasting insulin, FINS),仅在一定程度上反映IR,具有局限性^[7]。本研究采用HOMA-IR联合胰岛素动态分泌敏感性评估指数(ISImatsuda)及胰岛素敏感指数(ISI)同时评估IR^[7-8],旨在分析不同IR评估指标对肝纤维化的影响和其作用的一致性,探讨IR与T2DM合并NAFLD患者肝纤维化的关系。

1 对象与方法

1.1 研究对象 连续性收集2018年12月至2020年1月就诊于兰州大学第二医院特需老年病科符合标准的T2DM患者298例。纳入标准:(1)T2DM诊断以《中国2型糖尿病防治指南(2017年版)》为标准^[9];(2)NAFLD的诊断则符合《非酒精性脂肪性肝病防治指南(2018年更新版)》^[10]。排除标准:(1)1型糖尿病、特殊类型糖尿病及T2DM伴有急性并发症、妊娠及哺乳期妇女、风湿免疫性疾病患者;(2)嗜酒患者,乙醇摄入量男>20 g/d,女>10 g/d;(3)合并有病毒性肝炎、药物性肝损伤、胆汁淤积性肝损伤、肝豆状核变性及药物依赖患者;(4)近期服用影响血

脂、肝功能的药物患者。

1.2 资料采集 依据纳入排除标准,采集所有符合标准患者病史资料如性别、年龄、T2DM病程,测量体重、身高,计算BMI,由经验丰富的超声科医师行腹部彩超检查,抽取空腹8 h以上静脉血,测FPG、FINS、空腹C肽(fasting C-peptide, FCP)、糖化血红蛋白(HbA1c)、AST、ALT、AST/ALT、TG、CHO、HDL-C、LDL-C、白蛋白(ALB)、尿酸(sUA)、PLT;行标准馒头餐^[11](100 g面粉做成的馒头,进食第1口计时,分别测餐后30、60、120和180 min的血糖、胰岛素、C肽水平);测量静息30 min后的收缩压、舒张压;计算NAFLD纤维化评分^[12](NAFLD fibrosis score, NFS)。

计算公式:(1) $NFS = -1.675 + 0.037 \times \text{年龄(岁)} + 0.094 \times \text{BMI (kg/m}^2) + 1.13 \times \text{糖耐量异常/糖尿病(是=1,否=0)} + 0.99 \times \text{AST/ALT} - 0.013 \times \text{PLT (10}^9/\text{L)} - 0.66 \times \text{ALB (g/dl)}$ 。

(2) $HOMA-IR = \text{FINS (mU/L)} \times \text{FPG (mmol/L)} / 22.5$ 。

(3) $ISImatsuda^{[8]} = 10\ 000 / [(\text{FPG} \times \text{FINS})^{1/2} \times (\text{G}_{\text{mean}} \times \text{I}_{\text{mean}})^{1/2}]$ (注: I_{mean} 、 G_{mean} 分别为馒头餐监测的5个时段胰岛素、血糖平均值)。

(4) $ISI^{[7]} = 1 / [\text{FINS (mU/L)} \times \text{FPG (mmol/L)}]$ 。

1.3 分组 根据腹部彩超检查结果有无NAFLD,将纳入研究对象分为单纯T2DM组81例,T2DM合并NAFLD组217例;将T2DM合并NAFLD组依据患者NFS评分再分亚组,即:NFS < -1.455分为排除肝纤维化亚组(T2DM + F0, 69例); $-1.455 \leq \text{NFS} < 0.676$ 分为不确定亚组(T2DM + F1, 86例); $\text{NFS} \geq 0.676$ 分为纤维化亚组(T2DM + F2, 62例)。

1.4 统计学方法 数据分析采用SPSS 22.0软件。计数资料以例表示,比较采用 χ^2 检验;符合正态分布计量资料以 $\bar{x} \pm s$ 表示,两组比较应用成组 t 检验,多组比较使用单因素方差分析;非正态分布资料以中位数(第25百分位数,第75百分位数)[$M(P_{25}, P_{75})$]表示,两组应用Mann-Whitney U 检验比较,多组使用Kruskal-Wallis H 检验;Pearson相关性分析和Logistic

回归分析 T2DM 患者发生 NAFLD 及肝纤维化的影响因素。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 影响 T2DM 合并 NAFLD 的单因素及多因素分析 对 T2DM 组与 T2DM 合并 NAFLD 组的一般资料和生化指标比较, T2DM 合并 NAFLD 患者 ISI_{Imatsuda}、ISI 较 T2DM 患者下降, 而 HOMA-IR、BMI、AST、ALT、HbA1c、FPG、FCP、FINS、sUA、TG、舒张压水平较 T2DM 组患者升高, 差异均有统计学意义 (P 均 < 0.01)。见表 1。

校正性别并且以 T2DM 是否合并 NAFLD 为因变量, 多因素 Logistic 回归分析显示, ISI_{Imatsuda}、ISI 水平增高是抑制 T2DM 患者发生 NAFLD 的保护性因素 (P 均 < 0.01), 而 HOMA-IR、FPG、FCP、FINS、sUA 水平增高为促进 T2DM 发生 NAFLD 的独立危险因素

(P 均 < 0.01)。见表 2。

2.2 影响 NAFLD 纤维化的单因素及多因素分析 为进一步了解影响 NAFLD 纤维化的因素, 以 NFS 评分为标准, 将 T2DM 合并 NAFLD 患者分为 3 个亚组, 对其病史资料及生化指标对比显示, 各亚组除 NFS 计算相关的年龄、BMI、AST/ALT 等指标差异有统计学意义外, 与 T2DM + F0、T2DM + F1 组相比, T2DM + F2 组的 HOMA-IR、FCP、FINS 显著升高, 而 ISI_{Imatsuda}、ISI 显著降低, 差异均有统计学意义 ($P < 0.05, P < 0.01$)。见表 3。

有序 Logistics 回归分析表明, HOMA-IR、FINS、FPG、FCP 随着肝纤维化严重等级逐步升高, 是促进 T2DM 合并 NAFLD 患者肝纤维化的危险因素 ($P < 0.05, P < 0.01$), 而高 ISI_{Imatsuda} 则是抑制肝纤维化的保护性因素 ($P < 0.05$)。见表 4。

表 1 T2DM 组与 T2DM 合并 NAFLD 组一般资料、生化指标比较

一般资料和生化指标	T2DM 组 ($n=81$)	T2DM 合并 NAFLD 组 ($n=217$)	$t/z/\chi^2$ 值	P 值
男/女(例)	43/38	113/104	$\chi^2 = 0.628$	0.428
年龄(岁, $\bar{x} \pm s$)	50.98 \pm 3.93	50.20 \pm 11.01	$t = 0.855$	0.393
T2DM 病程[年, $M(P_{25}, P_{75})$]	4.00(1.00, 9.50)	5.00(5.00, 10.00)	$z = 0.160$	0.873
BMI($\bar{x} \pm s$)	24.16 \pm 2.73	26.99 \pm 3.68	$t = 6.291$	< 0.001
AST[U/L, $M(P_{25}, P_{75})$]	19.00(15.50, 24.00)	23.00(18.00, 31.00)	$z = 4.192$	< 0.001
ALT[U/L, $M(P_{25}, P_{75})$]	24.00(16.50, 32.50)	31.00(21.00, 50.05)	$z = 3.700$	0.001
AST/ALT [$M(P_{25}, P_{75})$]	0.80(0.63, 1.07)	0.75(0.62, 0.95)	$z = 1.047$	0.295
FPG(mmol/L, $\bar{x} \pm s$)	9.12 \pm 3.70	12.03 \pm 4.44	$t = 5.721$	< 0.001
ALB(g/L, $\bar{x} \pm s$)	45.21 \pm 5.04	45.30 \pm 4.74	$t = 0.150$	0.881
PLT($\times 10^9/L, \bar{x} \pm s$)	189.35 \pm 61.57	188.75 \pm 65.60	$t = 0.071$	0.944
HbA1c(% , $\bar{x} \pm s$)	8.49 \pm 2.07	9.31 \pm 2.20	$t = 2.911$	0.004
FCP[ng/ml, $M(P_{25}, P_{75})$]	1.01(0.61, 1.80)	2.31(1.57, 3.22)	$z = 7.787$	< 0.001
FINS[mU/L, $M(P_{25}, P_{75})$]	7.12(2.93, 12.04)	17.09(12.06, 23.89)	$z = 8.039$	< 0.001
HOMA-IR [$M(P_{25}, P_{75})$]	2.52(1.30, 4.91)	9.08(5.84, 12.09)	$z = 8.895$	< 0.001
ISI _{Imatsuda} [$M(P_{25}, P_{75})$]	89.31(59.11, 160.56)	32.07(23.97, 45.86)	$z = 9.312$	< 0.001
ISI [$M(P_{25}, P_{75})$]	0.0177(0.0090, 0.0341)	0.0049(0.0037, 0.0076)	$z = 8.898$	< 0.001
sUA($\mu\text{mol/L}, \bar{x} \pm s$)	299.64 \pm 91.35	346.88 \pm 101.72	$t = 3.663$	< 0.001
CHO(mmol/L, $\bar{x} \pm s$)	4.41 \pm 0.86	4.63 \pm 1.23	$t = 1.752$	0.081
TG[mmol/L, $M(P_{25}, P_{75})$]	1.63(1.34, 3.00)	2.26(1.54, 3.36)	$z = 2.655$	0.008
HDL-C(mmol/L, $\bar{x} \pm s$)	1.07 \pm 0.28	1.09 \pm 0.32	$t = 0.537$	0.592
LDL-C(mmol/L, $\bar{x} \pm s$)	2.70 \pm 0.77	2.77 \pm 1.07	$t = 0.628$	0.531
收缩压(mm Hg, $\bar{x} \pm s$)	130.23 \pm 22.38	135.65 \pm 21.43	$t = 1.919$	0.656
舒张压(mm Hg, $\bar{x} \pm s$)	79.09 \pm 11.96	84.93 \pm 11.84	$t = 3.781$	< 0.001

表 2 T2DM 患者发生 NAFLD 的影响因素

因素	β 值	SE	$Z(\chi^2)$	OR(95% CI)	P 值
HOMA-IR	0.246	0.038	41.209	1.279(1.186 ~ 1.379)	< 0.001
ISI	-0.546	12.692	23.481	0.579(0.045 ~ 0.732)	< 0.001
ISI _{Imatsuda}	-0.018	0.003	31.501	0.982(0.976 ~ 0.988)	< 0.001
FPG(mmol/L)	0.263	0.050	27.458	1.300(1.179 ~ 1.435)	< 0.001
FCP(ng/ml)	0.865	0.197	19.316	2.375(1.615 ~ 3.491)	< 0.001
FINS(mU/L)	0.068	0.022	9.394	1.071(1.025 ~ 1.119)	0.002
sUA($\mu\text{mol/L}$)	0.005	0.002	6.980	1.005(1.001 ~ 1.008)	0.008

表3 T2DM 合并 NAFLD 各纤维化亚组资料比较

项目	T2DM + F0 组 (n = 69)	T2DM + F1 组 (n = 86)	T2DM + F2 组 (n = 62)	$\chi^2/F/H$ 值	P 值
男/女 (例)	37/32	44/42	32/30	$\chi^2 = 0.100$	0.951
年龄 (岁, $\bar{x} \pm s$)	43.30 \pm 9.54	51.88 \pm 9.84 ^a	55.66 \pm 10.28 ^{ab}	$F = 27.610$	<0.001
T2DM 病程 [年, $M(P_{25}, P_{75})$]	4.00 (1.00, 7.00)	4.00 (0.46, 10.00)	6.00 (2.75, 12.25)	$H = 5.918$	0.052
BMI ($\bar{x} \pm s$)	25.93 \pm 3.17	26.63 \pm 3.04	28.67 \pm 4.42 ^{ab}	$F = 10.648$	<0.001
AST [U/L, $M(P_{25}, P_{75})$]	23.00 (17.00, 30.00)	23.50 (19.00, 37.00)	23.00 (19.00, 29.00)	$H = 1.439$	0.487
ALT [U/L, $M(P_{25}, P_{75})$]	34.00 (23.00, 51.00)	36.00 (23.00, 56.00)	24.50 (14.00, 38.25) ^{ab}	$H = 13.042$	0.001
AST/ALT ($\bar{x} \pm s$)	0.71 \pm 0.19	0.76 \pm 0.21 ^a	1.24 \pm 1.12	$F = 14.843$	<0.001
FPG [mmol/L, $M(P_{25}, P_{75})$]	9.98 (8.07, 12.93)	12.62 (10.29, 14.64) ^a	9.99 (7.81, 17.78)	$H = 11.286$	0.004
ALB (g/L, $\bar{x} \pm s$)	47.54 \pm 4.07	45.38 \pm 4.35 ^a	42.70 \pm 4.73 ^{ab}	$F = 19.957$	<0.001
PLT ($\times 10^9/L$, $\bar{x} \pm s$)	252.64 \pm 51.00	179.14 \pm 41.83 ^a	130.98 \pm 41.99 ^{ab}	$F = 122.645$	<0.001
HbA1c (% , $\bar{x} \pm s$)	9.17 \pm 2.11	9.49 \pm 2.06	9.21 \pm 2.49	$F = 0.486$	0.616
FCP [ng/ml, $M(P_{25}, P_{75})$]	1.98 (1.07, 2.97)	1.89 (1.56, 2.77)	3.15 (2.43, 3.88) ^{ab}	$H = 34.788$	<0.001
FINS [mU/L, $M(P_{25}, P_{75})$]	13.48 (9.07, 17.15)	17.15 (12.99, 20.58) ^a	25.54 (17.77, 32.95) ^{ab}	$H = 50.573$	<0.001
HOMA-IR ($\bar{x} \pm s$)	6.21 \pm 2.99	9.74 \pm 4.16 ^a	11.96 \pm 4.66 ^{ab}	$F = 34.980$	<0.001
ISImatsuda [$M(P_{25}, P_{75})$]	45.61 (32.55, 68.60)	29.59 (22.31, 38.11) ^a	27.33 (22.32, 36.85) ^a	$H = 43.997$	<0.001
ISI [$M(P_{25}, P_{75})$]	0.007 (0.005, 0.12)	0.005 (0.004, 0.006) ^a	0.004 (0.003, 0.005) ^{ab}	$H = 57.328$	<0.001
sUA ($\mu\text{mol/L}$, $\bar{x} \pm s$)	352.19 \pm 87.57	335.15 \pm 100.40	357.23 \pm 117.09	$F = 0.986$	0.375
CHO (mmol/L, $\bar{x} \pm s$)	4.66 \pm 1.10	4.77 \pm 1.39	4.41 \pm 1.11	$F = 1.577$	0.209
TG [mmol/L, $M(P_{25}, P_{75})$]	2.12 (1.46, 3.35)	2.31 (1.58, 3.53)	2.25 (1.72, 3.57)	$H = 1.489$	0.475
HDL-C (mmol/L, $\bar{x} \pm s$)	1.06 \pm 0.30	1.16 \pm 0.35	1.06 \pm 0.30	$F = 2.585$	0.078
LDL-C (mmol/L, $\bar{x} \pm s$)	2.78 \pm 0.84	2.84 \pm 1.24	2.67 \pm 1.05	$F = 0.445$	0.641
收缩压 (mm Hg, $\bar{x} \pm s$)	131.77 \pm 17.71	135.94 \pm 17.67	139.58 \pm 28.42	$F = 2.208$	0.112
舒张压 (mm Hg, $\bar{x} \pm s$)	85.94 \pm 11.87	84.73 \pm 10.63	84.08 \pm 13.41	$F = 0.421$	0.657

注:与 T2DM + F0 组相比, ^a $P < 0.05$;与 T2DM + F1 组相比, ^b $P < 0.05$ 。

表4 T2DM 合并 NAFLD 肝纤维化的影响因素

因素	β 值	SE	$Z(\chi^2)$	OR(95% CI)	P 值
HOMA-IR	0.236	0.034	48.636	1.266 (1.184 ~ 1.353)	<0.001
ISImatsuda	-0.008	0.004	3.942	0.992 (0.984 ~ 0.999)	0.047
FPG (mmol/L)	0.060	0.029	4.395	1.062 (1.003 ~ 1.124)	0.036
FINS (mu/L)	0.119	0.017	49.489	1.126 (1.089 ~ 1.164)	<0.001
FCP (ng/ml)	0.679	0.125	29.613	1.972 (1.543 ~ 2.519)	<0.001

表5 HOMA-IR 及 ISImatsuda 对肝纤维化诊断价值的

ROC 曲线

项目	最佳截断值	约登指数	灵敏度	特异度	P 值	ROC 曲线下面积
HOMA-IR	9.895	0.474	0.758	0.716	<0.001	0.738
ISImatsuda	24.214	0.248	0.435	0.813	0.001	0.642

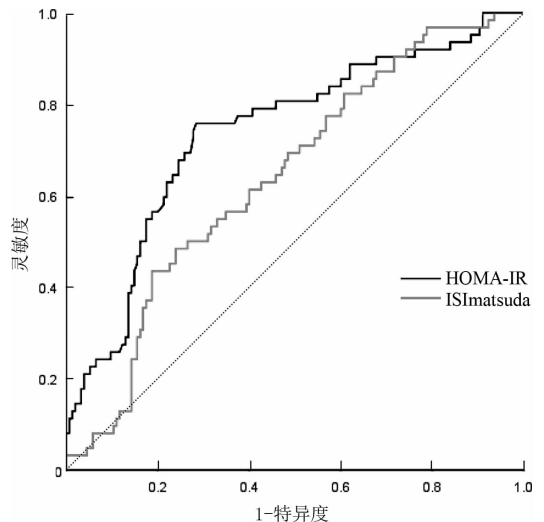


图1 HOMA-IR 和 ISImatsuda 对肝纤维化诊断价值的 ROC 曲线

2.3 HOMA-IR 及 ISImatsuda 对肝纤维化诊断价值的 ROC 曲线分析 经分析 ROC 曲线图, HOMA-IR 水平可较好的用以预测 T2DM 合并 NAFLD 患者肝纤维化的风险 (ROC 下曲线面积 0.738), 且当 HOMA-IR = 9.895 时, 灵敏度及特异度均高于 70%。

3 讨论

NAFLD 是以肝细胞内脂肪过度堆积为病理特征

的疾病, 包含非酒精性脂肪肝 (NAFL, 无肝细胞损伤的脂肪变性)、脂肪性肝炎 (NASH, 脂肪变性伴肝细胞气球样变性、有或无纤维化) 和肝硬化^[10], 全球患病率为 30%, 我国患病率为 29.2%, 且以 0.594% 的发展速度快速增长^[13], 逐渐成为导致肝功能不全、原发性肝癌和原位肝移植的主要疾病之一^[14]。其发病涉及炎症反应、氧化应激、免疫紊乱等多种机制, 被认为是代谢综合征在肝脏的表现^[3]。在 T2DM 患者中, NAFLD 发病率高达 50% ~ 75%, 且表现出更高的 NASH 率和明显的纤维化^[5,15]。T2DM 影响 NAFL 向

纤维化的发展速度,决定 NAFLD 的严重程度^[16-17]。本研究以 Angulo 等建立的具有高度敏感性及特异性的无创肝纤维化程度评分 NFS 为标准,纳入 81 例单纯 T2DM 及 217 例 T2DM 合并 NAFLD 患者,发现约 28.58% (62/217) 的 T2DM 合并 NAFLD 患者存在肝纤维化,与此前学者研究结果相符合^[4,18],这一数据支持 T2DM 患者为晚期肝硬化的高危人群,凸显出早期筛查 NAFLD、评估推进肝纤维化发展的危险因素的深远价值。

NAFLD 的存在与机体代谢失调相关,既往有学者就 T2DM 患者 NAFLD 肝纤维化与 IR 的关系行临床研究,但评估标准单一使用 HOMA-IR,且结果存在争议,部分认为 IR 为肝纤维化的影响因素^[19],也有结果表明仅内源性胰岛素分泌是肝纤维化的危险因素,而与 IR 无关^[20-21]。为避免进餐后胰岛素分泌及 HOMA-IR 的局限性,本研究联合 HOMA-IR、ISI_{Matsuda} 及 ISI 共同评估胰岛素敏感性,并分析不同 IR 指标对肝纤维化影响的一致性。ISI_{Matsuda} 是可以全程反映葡萄糖耐量实验过程中 IR 的合理的全身胰岛素敏感性评估指标,其值越小,抵抗越严重^[8];ISI 是评价餐后胰岛素敏感性的有效指标,与正常血糖钳夹技术一致性高,也可以较好体现 IR 程度。通过数据比较,发现 T2DM 合并 NAFLD 组患者 HOMA-IR 高于而 ISI_{Matsuda}、ISI 则低于单纯 T2DM 组;为进一步评估 IR 对肝纤维化的影响,依据 NFS 对肝纤维化分层,发现纤维化亚组 HOMA-IR 高于排除纤维化亚组和不确定亚组,而 ISI_{Matsuda}、ISI 则低于其他两组,提示胰岛素敏感性随着纤维化程度加重而降低,回归分析表明 HOMA-IR、ISI_{Matsuda} 是促进肝纤维化的独立影响因素,与既往部分结果一致^[19]。此外通过 ROC 分析发现,HOMA-IR 对肝纤维化具有一定诊断价值,ROC 曲线下面积为 0.738,且当 HOMA-IR 最佳截断值为 9.895 时,特异度为 71.6%,而灵敏度达 75.8%,因此监测胰岛功能、评估胰岛素敏感性,对于评估肝纤维化风险、预防 NAFLD 的发生和发展,有积极意义。

IR 是指外周组织对循环中胰岛素的敏感性或代谢作用反应性下降,当机体处于 IR 状态,胰岛素对外周脂肪组织脂解的抑制作用减弱,大量游离脂肪酸异位沉积于肝脏^[22],若大于 5% 肝细胞脂肪变性,则可诊断 NAFLD。而 IR 促进肝纤维化机制与炎症级联激活的介导有关,IR 的细胞机制可以刺激巨噬细胞活化,释放炎症因子,产生 TNF- α 及 IL-6, TNF- α 可激活细胞内信号分子传导,介导肝巨噬细胞、肝星

形细胞关联,促进星形细胞活化,产生高密度细胞外基质,使胶原蛋白沉积在肝脏腺泡区,发展为肝纤维化和肝癌^[23];而 IL-6 作为炎症介质,抑制白色脂肪组织中胰岛素介导的脂解作用,增加游离脂肪酸向肝脏的传递及糖原异生蛋白转录,调节促炎性细胞因子的产生、核分裂和细胞凋亡,推动肝纤维化进程^[24]。既然 IR 可以促进 NAFLD 形成,推动肝纤维化发展,改善胰岛素敏感性可能是 T2DM 合并 NAFLD 患者潜在治疗方向。目前已有胰岛素增敏剂罗格列酮改善 NASH、缓解肝纤维化病理特征^[25-26]、二甲双胍延长 NASH 肝硬化患者生存期,降低 T2DM 患者肝癌的发病率^[27-28]等研究成果,并且均与 IR 逆转有关^[29],这也从侧面表明 IR 对 NAFLD 组织学改变的影响。

综上所述,IR 与 T2DM 合并 NAFLD 患者肝纤维化关系密切,改善胰岛素敏感性或许是这类患者的治疗方向,临床工作中对于存在 IR 的 T2DM 合并 NAFLD 患者,应尽早筛查肝纤维化,并进行合理分期,以改善肝脏和心血管疾病的结局为目标,遵循个体化原则,给予合理饮食运动指导,以降低糖尿病慢性并发症及肝硬化、肝癌等相关并发症风险。

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收稿日期: 2020-10-22 修回日期: 2020-11-30 编辑: 王国品