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· 论著 ·

2 型糖尿病患者胰岛素抵抗与肺功能的相关性研究

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【摘要】 背景 近年来糖尿病导致的肺功能损伤开始引起人们的关注, 胰岛素抵抗 (IR) 是 2 型糖尿病 (T2DM) 的重要发病机制, 但其与肺功能的关系尚未明确。**目的** 分析 T2DM 患者 IR 与肺功能的相关性。**方法** 选取 2019 年 8—12 月在首都医科大学附属北京朝阳医院综合科及内分泌科住院的 260 例 T2DM 患者, 根据有无 IR 分为 IR 组 ($n=105$) 与无 IR 组 ($n=155$)。比较两组患者一般资料、实验室检查指标及肺功能指标, 采用 Spearman 秩相关分析及多元线性回归分析探讨 T2DM 患者胰岛素抵抗指数 (HOMA-IR) 的相关因素。**结果** IR 组患者年龄小于无 IR 组, 体质指数 (BMI) 大于无 IR 组, 糖化血红蛋白 (HbA_{1c})、空腹血糖 (FPG)、三酰甘油 (TG) 及超敏 C 反应蛋白 (hs-CRP) 高于无 IR 组, 高密度脂蛋白 (HDL) 低于无 IR 组 ($P < 0.05$)。IR 组患者用力肺活量占预计值的百分比 (FVC%pred)、第 1 秒用力呼气容积占预计值的百分比 (FEV₁%pred)、肺总量占预计值的百分比 (TLC%pred) 低于无 IR 组 ($P < 0.05$)。Spearman 秩相关分析结果显示, T2DM 患者 HOMA-IR 与 BMI、HbA_{1c}、FPG、TG、hs-CRP 呈正相关, 与 HDL、FVC%pred、FEV₁%pred、TLC%pred、肺一氧化碳弥散量占预计值的百分比 (DLCO%pred) 呈负相关 ($P < 0.05$)。多元线性回归分析结果显示, T2DM 患者 HOMA-IR 分别与 FVC%pred ($\beta = -0.610$)、FEV₁%pred ($\beta = -0.506$)、TLC%pred ($\beta = -0.511$)、DLCO%pred ($\beta = -0.583$) 独立相关 ($P < 0.05$)。**结论** 伴有 IR 的 T2DM 患者肺功能损伤主要表现为限制性通气功能及弥散功能下降, 且 HOMA-IR 越高则 T2DM 患者限制性通气功能及弥散功能下降越明显。

【关键词】 2 型糖尿病; 胰岛素抵抗; 肺功能**【中图分类号】** R 587.1 **【文献标识码】** A DOI: 10.12114/j.issn.1008-5971.2021.00.224

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Relationship between Insulin Resistance and Pulmonary Function in Patients with Type 2 Diabetes Mellitus HE

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【Abstract】 Background In recent years, pulmonary function injury caused by diabetes has attracted people's attention. Insulin resistance (IR) is an important pathogenesis of type 2 diabetes mellitus (T2DM). However, the relationship between IR and pulmonary function has not been clear. **Objective** To analyze the relationship between IR and pulmonary function in T2DM patients. **Methods** A total of 260 T2DM patients hospitalized in the Department of General Internal Medicine and Department of Endocrinology, Beijing Chao-yang Hospital, Capital Medical University from August to December in 2019 were selected. All patients were divided into IR group ($n=105$) and non-IR group ($n=155$) according to the presence or absence of IR. The general data, laboratory examination indicators and pulmonary function indexes were compared between the two groups. Spearman rank correlation analysis and multiple linear regression analysis were used to explore the related factors of homeostasis model-insulin resistance (HOMA-IR) in T2DM patients. **Results** The age in the IR group was younger than that in the non-IR group, body mass index (BMI) in the IR group was greater than that in the non-IR group, glycosylated hemoglobin (HbA_{1c}), fasting blood glucose (FPG), triglyceride (TG) and high-sensitivity C-reactive protein (hs-CRP) in the IR group were higher than those in the non-IR group, and high-density lipoprotein (HDL) in the IR group was lower than that in the non-IR group ($P < 0.05$). The percentage of forced vital capacity in predicted value (FVC%pred), percentage of forced expiratory volume in the first second in predicted value (FEV₁%pred) and percentage of total lung capacity in predicted value (TLC%pred) in the IR group were lower than those in the non-IR group ($P < 0.05$). Spearman rank correlation analysis showed that HOMA-IR was positively correlated with BMI, HbA_{1c} , FPG, TG and hs-CRP, and negatively correlated with HDL, FVC%pred, FEV₁%pred, TLC%pred and percentage of diffusion capacity for carbon monoxide of lung in predicted value (DLCO%pred) in T2DM patients ($P < 0.05$). Multiple linear regression analysis showed that HOMA-IR was independently correlated with FVC%pred ($\beta = -0.610$), FEV₁%pred ($\beta = -0.506$), TLC%pred ($\beta = -0.511$), DLCO%pred ($\beta = -0.583$) in T2DM patients, respectively ($P < 0.05$). **Conclusion** Pulmonary function injury in T2DM patients with IR is mainly characterized by the decline of restrictive ventilation function and diffusion function, and the higher HOMA-IR, the more obvious the decline of restrictive ventilation function and diffusion function in T2DM patients.

【Key words】 Type 2 diabetes mellitus; Insulin resistance; Pulmonary function

2型糖尿病(type 2 diabetes mellitus, T2DM)是由多种病因导致的胰岛素分泌不足或胰岛素抵抗,从而引起血糖持续升高的慢性代谢性疾病。在高血糖的长期刺激下,机体的肾脏、视网膜、心血管等大血管及微血管均会发生病变。肺脏尚不是糖尿病的主要靶器官,但肺脏含有丰富的肺泡毛细血管网及结缔组织,且近年越来越多的学者开始关注糖尿病肺损伤^[1]。既往研究发现,糖尿病甚至糖尿病前期患者就已出现肺功能下降,而肺功能损伤又会加剧糖尿病病情进展^[2-3]。研究表明,肺功能损伤程度与眼底病变、尿微量白蛋白等糖尿病靶器官损伤密切相关^[4-5]。胰岛素抵抗(insulin resistance, IR)作为T2DM的重要发病机制,与肺功能的关系尚未明确。本研究旨在分析T2DM患者IR与肺功能的相关性,现报道如下。

1 对象与方法

1.1 研究对象 选取2019年8—12月在首都医科大

学附属北京朝阳医院综合科及内分泌科住院的260例T2DM患者,均符合1999年WHO制定的T2DM诊断标准。根据有无IR将所有患者分为IR组($n=105$)与无IR组($n=155$)。排除标准:既往有职业性粉尘接触史者;合并急/慢性肺疾病、心功能不全、急性冠脉综合征、急性脑血管疾病、胸廓畸形、结缔组织病、血液系统疾病、严重肝功能不全及其他原因引起的慢性肾功能不全者;伴有急性糖尿病酮症酸中毒者。本研究已通过首都医科大学附属北京朝阳医院伦理委员会审核批准(2017-科-136),所有患者对本研究知情并签署知情同意书。

1.2 观察指标

1.2.1 一般资料 收集所有患者的一般资料,包括性别、年龄、身高、体质量、糖尿病病程、吸烟指数、吸烟情况,计算体质指数(body mass index, BMI), BMI=体质量/身高²;吸烟指数=每天吸烟支数×吸烟年数;吸烟情况分为从不吸烟、戒烟(戒烟时间≥1年)及吸

烟(正在吸烟及戒烟时间 <1 年)。

1.2.2 实验室检查指标 收集所有患者的实验室检查指标,包括糖化血红蛋白(glycosylated hemoglobin, HbA_{1c})、空腹血糖(fasting plasma glucose, FPG)、空腹胰岛素(fasting insulin, FINS)、高密度脂蛋白(high density lipoprotein, HDL)、低密度脂蛋白(low density lipoprotein, LDL)、三酰甘油(triacylglycerol, TG)及超敏C反应蛋白(high-sensitivity C-reactive protein, hs-CRP)。根据胰岛素稳态模型法计算胰岛素抵抗指数(homeostasis model-insulin resistance, HOMA-IR), $HOMA-IR = FPG \times FINS / 22.5$, 以 $HOMA-IR > 2.69$ 定义为IR。

1.2.3 肺功能指标 严格按照中华医学会呼吸病学分会肺功能专业组制定的质控标准检测肺功能指标,包括用力肺活量占预计值的百分比(percentage of forced vital capacity in predicted value, FVC%pred)、第1秒用力呼气容积占预计值的百分比(percentage of forced expiratory volume in the first second in predicted value, FEV₁%pred)、用力肺活量与第1秒用力呼气容积比值(ratio of forced vital capacity to forced expiratory volume in the first second, FEV₁/FVC)、肺总量占预计值的百分比(percentage of total lung capacity in predicted value, TLC%pred)、肺一氧化碳弥散量占预计值的百分比(percentage of diffusion capacity for carbon monoxide of lung in predicted value, DLCO%pred)。

1.3 统计学方法 采用SPSS 22.0统计学软件进行数据处理。符合正态分布或近似正态分布的计量资料以($\bar{x} \pm s$)表示,组间比较采用成组 t 检验;偏态分布的计量资料以 $M(QR)$ 表示,组间比较采用Mann-Whitney U 检验;计数资料以相对数表示,组间比较采用 χ^2 检验;采用Spearman秩相关分析及多元线性回归分析探讨T2DM患者HOMA-IR的相关因素。以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 一般资料和实验室检查指标 两组患者性别、糖尿病病程、吸烟指数、吸烟情况及LDL比较,差异无统计学意义($P > 0.05$);IR组患者年龄小于无IR组, BMI大于无IR组, HbA_{1c}、FPG、TG及hs-CRP高于无IR组, HDL低于无IR组,差异有统计学意义($P < 0.05$),见表1。

2.2 肺功能指标 IR组患者FVC%pred、FEV₁%pred、TLC%pred低于无IR组,差异有统计学意义($P < 0.05$);两组患者FEV₁/FVC、DLCO%pred比较,差异无统计学意义($P > 0.05$),见表2。

2.3 Spearman秩相关分析 T2DM患者HOMA-IR为3.18(3.28)。Spearman秩相关分析结果显示, T2DM

患者HOMA-IR与BMI($r_s=0.268, P < 0.001$)、HbA_{1c}($r_s=0.334, P < 0.001$)、FPG($r_s=0.500, P < 0.001$)、TG($r_s=0.269, P < 0.001$)、hs-CRP($r_s=0.240, P=0.002$)呈正相关,与HDL($r_s=-0.250, P < 0.001$)、FVC%pred($r_s=-0.223, P < 0.001$)、FEV₁%pred($r_s=-0.177, P=0.004$)、TLC%pred($r_s=-0.230, P < 0.001$)、DLCO%pred($r_s=-0.150, P=0.015$)呈负相关。T2DM患者HOMA-IR与年龄($r_s=-0.121, P=0.051$)、FEV₁/FVC($r_s=0.073, P=0.239$)无直线相关关系。

2.4 多元线性回归分析 分别以FVC%pred、FEV₁%pred、TLC%pred、DLCO%pred为因变量,以可能影响肺功能的因素〔性别(赋值:男=0,女=1)、年龄(赋值:实测值)、BMI(赋值:实测值)、吸烟指数(赋值:实测值)及HOMA-IR(赋值:实测值)〕为自变量,进行多元线性回归分析,结果显示, T2DM患者HOMA-IR分别与FVC%pred、FEV₁%pred、TLC%pred、DLCO%pred独立相关($P < 0.05$),见表3~6。

3 讨论

T2DM可导致肾脏、视网膜、心脑血管及神经等全身多个系统损伤,其中糖尿病肺功能损伤易被人们所忽视。近年越来越多的研究表明, T2DM患者存在的肺功能损伤主要表现为限制性通气功能障碍和弥散功能障碍^[6-7]。有前瞻性研究证实,基线FVC%pred、FEV₁%pred降低与新发T2DM风险升高独立相关^[8-10]。肺功能与糖尿病相互影响,且机制复杂。研究表明,肺功能损伤可能与IR、全身性炎症反应、非酶糖基化反应、微血管病变等多种因素相关^[11]。既往有调查研究发现,IR与糖尿病患者肺功能损伤相关^[12],但目前IR与肺功能的关系尚未完全阐明。

本研究结果显示,IR组患者FVC%pred、FEV₁%pred、TLC%pred低于无IR组,提示伴有IR的T2DM患者肺功能损伤主要表现为限制性通气功能及弥散功能下降。IR引起肺限制性通气功能下降的原因较为复杂:(1)目前研究发现,IR可造成肌肉蛋白合成及分解失调,进而导致骨骼肌线粒体受损及肌力下降^[13-14]。肺泡Ⅱ型上皮细胞存在胰岛素受体^[15],而胰岛素受体可调节细胞对葡萄糖的摄取。当机体发生IR时,肺部表面活性物质受损,进而导致气道阻力增加。(2)此外,IR还可以通过上调转化生长因子表达而引起支气管和肺血管周围纤维化^[16]。(3)再者,IR还与全身慢性炎症反应相关^[17],慢性炎症的持续存在可导致肺脏慢性纤维化、肺顺应性降低,最终引起肺限制性通气障碍^[18]。本研究结果显示,IR组患者hs-CRP高于无IR组,提示伴有IR的T2DM患者存在全身慢性炎症。弥散功能下降是T2DM患者肺功能损伤的另外一种表现。崔静

表1 两组患者一般资料和实验室检查指标比较

Table 1 Comparison of general information and laboratory examination indicators between the two groups

组别	例数	性别 (男/女)	年龄 ($\bar{x} \pm s$, 岁)	BMI ($\bar{x} \pm s$, kg/m ²)	糖尿病病程 [$M(QR)$, 年]	吸烟指数 [$M(QR)$, 年支]	吸烟情况 [n (%)]		
							从不吸烟	戒烟	吸烟
无 IR 组	105	66/39	56.1 $\pm$ 10.6	25.91 $\pm$ 2.92	6 (10)	0 (400)	56 (53.3)	13 (12.4)	36 (34.3)
IR 组	155	97/58	52.4 $\pm$ 13.1	27.67 $\pm$ 4.39	6 (14)	0 (350)	87 (56.1)	11 (7.1)	57 (36.8)
检验统计量值		0.002 ^a	2.493 ^b	-3.903 ^b	-0.327 ^c	-0.582 ^c		2.091 ^a	
P 值		0.964	0.013	< 0.001	0.744	0.561		0.352	

组别	HbA _{1c} ($\bar{x} \pm s$, %)	FPG ($\bar{x} \pm s$, mmol/L)	HDL ($\bar{x} \pm s$, mmol/L)	LDL ($\bar{x} \pm s$, mmol/L)	TG ($\bar{x} \pm s$, mmol/L)	hs-CRP [$M(QR)$, mg/L]
无 IR 组	8.59 $\pm$ 2.07	6.21 $\pm$ 1.64	1.10 $\pm$ 0.26	2.80 $\pm$ 0.91	1.61 $\pm$ 1.06	0.94 (1.59)
IR 组	9.89 $\pm$ 2.10	8.32 $\pm$ 2.70	0.97 $\pm$ 0.21	2.83 $\pm$ 0.94	2.20 $\pm$ 1.28	1.62 (3.37)
检验统计量值	-4.878 ^b	-7.835 ^b	4.323 ^b	-0.305 ^b	-4.022 ^b	-3.112 ^c
P 值	< 0.001	< 0.001	< 0.001	0.761	< 0.001	0.002

注: IR= 胰岛素抵抗, BMI= 体质指数, HbA_{1c}= 糖化血红蛋白, FPG= 空腹血糖, HDL= 高密度脂蛋白, LDL= 低密度脂蛋白, TG= 三酰甘油, hs-CRP= 超敏 C 反应蛋白; ^a 表示 χ^2 值, ^b 表示 t 值, ^c 表示 Z 值

表2 两组患者肺功能指标比较 ($\bar{x} \pm s$, %)

Table 2 Comparison of pulmonary function indexes between the two groups

组别	例数	FVC%pred	FEV ₁ %pred	FEV ₁ /FVC	TLC%pred	DLCO%pred
无 IR 组	105	106.38 $\pm$ 15.18	101.31 $\pm$ 16.06	78.21 $\pm$ 5.98	95.96 $\pm$ 10.42	93.32 $\pm$ 14.21
IR 组	155	100.93 $\pm$ 13.74	96.94 $\pm$ 13.91	78.90 $\pm$ 5.21	91.71 $\pm$ 10.42	90.21 $\pm$ 12.68
t 值		3.011	2.332	-0.984	3.192	1.852
P 值		0.003	0.020	0.326	0.002	0.065

注: FVC%pred= 用力肺活量占预计值的百分比, FEV₁%pred= 第 1 秒用力呼气容积占预计值的百分比, FEV₁/FVC= 第 1 秒用力呼气容积与用力肺活量的比值, TLC%pred= 肺总量占预计值的百分比, DLCO%pred= 肺一氧化氮弥散量占预计值的百分比

表3 T2DM 患者 FVC%pred 相关因素的多元线性回归分析

Table 3 Multiple linear regression analysis on related factors of FVC%pred in patients with T2DM

变量	β	SE	β'	t 值	P 值
性别	8.538	1.951	0.284	4.376	< 0.001
年龄	0.143	0.071	0.121	2.026	0.044
BMI	-0.188	0.217	-0.051	-0.870	0.385
吸烟指数	-0.005	0.002	-0.144	-2.257	0.025
HOMA-IR	-0.610	0.226	-0.155	-2.699	0.007

表4 T2DM 患者 FEV₁%pred 相关因素的多元线性回归分析Table 4 Multiple linear regression analysis on related factors of FEV₁%pred in patients with T2DM

变量	β	SE	β'	t 值	P 值
性别	5.378	2.030	0.174	2.649	0.009
年龄	0.168	0.074	0.138	2.288	0.023
BMI	-0.291	0.225	-0.077	-1.290	0.198
吸烟指数	-0.009	0.002	-0.229	-3.535	< 0.001
HOMA-IR	-0.506	0.235	-0.125	-2.154	0.032

表5 T2DM 患者 TLC%pred 相关因素的多元线性回归分析

Table 5 Multiple linear regression analysis on related factors of TLC%pred in patients with T2DM

变量	β	SE	β'	t 值	P 值
性别	4.887	1.537	0.221	3.179	0.002
年龄	-0.078	0.056	-0.089	-1.400	0.163
BMI	-0.201	0.171	-0.074	-1.181	0.239
吸烟指数	0.001	0.002	0.028	0.413	0.680
HOMA-IR	-0.511	0.178	-0.176	-2.868	0.004

表6 T2DM 患者 DLCO%pred 相关因素的多元线性回归分析

Table 6 Multiple linear regression analysis on related factors of DLCO%pred in patients with T2DM

变量	β	SE	β'	t 值	P 值
性别	-7.686	1.893	-0.278	-4.060	< 0.001
年龄	0.086	0.069	0.079	1.255	0.211
BMI	0.424	0.210	0.125	2.017	0.045
吸烟指数	-0.006	0.002	-0.181	-2.682	0.008
HOMA-IR	-0.583	0.219	-0.161	-2.661	0.008

等^[19]研究也证实, DLCO 与 T2DM 患者 HOMA-IR 呈负相关。

LEE 等^[20]对 2011—2013 年 1 922 名 19~40 岁的韩国成年人进行横断面调查, 结果显示, HOMA-IR 与 FVC%pred、FEV₁%pred、FEV₁/FVC 呈负相关。本研究结果显示, T2DM 患者 HOMA-IR 分别与 FVC%pred、FEV₁%pred、TLC%pred、DLCO%pred 独立相关, 提示 HOMA-IR 越高则 T2DM 患者限制性通气功能及弥散功能下降越明显。

综上所述, 伴有 IR 的 T2DM 患者肺功能损伤主要表现为限制性通气功能及弥散功能下降, 且 HOMA-IR

越高则 T2DM 患者限制性通气功能及弥散功能下降越明显。但本研究为回顾性研究,存在一定选择偏倚,且不能明确 T2DM 患者 IR 与肺功能损伤之间的因果关系;此外,本研究为单中心研究且样本量较小,所得结论仍有待扩大样本量、联合多个中心进一步研究证实。

作者贡献:何云云、王晓娟负责文章的设计与构思;何云云负责数据的整理、分析及撰写论文;陈哲、方向阳、常晶、逯勇负责数据的收集;王晓娟负责文章的质量控制及审校,并对文章整体负责、监督管理。

本文无利益冲突。

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