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• 临床研究 •

2 型糖尿病患者代谢清除率与血清游离脂肪酸的相关性 *

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摘要 目的:探讨 2 型糖尿病(type 2 diabetes mellitus, T2DM)患者代谢清除率(metabolic clearance rate, MCR)与血清游离脂肪酸(nonesterified fatty acid, NEFA)、甘油三酯(triglyceride, TG)和胆固醇的相关性。**方法:**选择 2014 年 10 月至 2016 年 12 月我院收治的 127 例 T2DM 患者,测量患者身高、体重,并计算身体质量指数(BMI),进行口服糖耐量试验、胰岛素释放试验,检测血清脂质的水平。将 T2DM 患者按 MCR 值分为低 MCR 组(63 例)、高 MCR 组(64 例),比较两组间临床指标的差异,评价 MCR、HOMA-IR 与变量间的相关性。**结果:**T2DM 患者 BMI、TG、空腹血糖和糖化血红蛋白(HbA1C)均高于参考值;T2DM 患者低 MCR 组 HbA1C、空腹血糖、总胆固醇(total cholesterol, TC)、TG、低密度脂蛋白胆固醇(LDL-C)和 NEFA 明显升高($P<0.05$),高密度脂蛋白胆固醇(HDL-C)明显降低($P<0.05$);相关分析显示:MCR 与 HDL-C 呈显著正相关($P<0.05$, $r=0.215$),与 TC、TG、LDL-C、HbA1C、NEFA 均呈显著负相关($P<0.05$; $r=-0.191, -0.380, -0.216, -0.587, -0.356$)。**结论:**2 型糖尿病患者 MCR 降低,与 HbA1C 与血清 NEFA 水平呈负相关。MCR 不仅能评价胰岛素抵抗,而且能反映机体糖脂代谢水平。

关键词:2 型糖尿病;代谢清除率;游离脂肪酸

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Correlation of Metabolic Clearance Rate with Serum Nonesterified Fatty Acid Level of Type 2 Diabetes Patients *

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ABSTRACT Objective: To investigate the correlation of metabolic clearance rate (MCR) with serum nonesterified fatty acid (NEFA), triglyceride (TG) and cholesterol of patients with type 2 diabetes mellitus (T2DM). **Methods:** The body mass index (BMI), oral glucose tolerance, insulin release, and fasting serum lipids were determined in 127 cases of T2DM patients from October, 2014 to December, 2016. T2DM patients were divided into the low-MCR group ($n=63$) and the high-MCR group ($n=64$) according to MCR median. The clinical characteristics were compared between two groups and the correlations of MCR, HOMA-IR and variables were evaluated. **Results:** Our data suggested that BMI, TG, fasting glucose and HbA1C of T2DM patients were higher than the upper limit of corresponding reference interval. Low-MCR group showed decreased high density lipoprotein cholesterol (HDL-C) and increased fasting glucose, HbA1C, total cholesterol (TC), TG, low density lipoprotein cholesterol (LDL-C) and NEFA ($P<0.05$). MCR was positively correlated with HDL-C ($P<0.05$, $r=0.215$) and negatively correlated with TC, TG, LDL-C, HbA1C, NEFA ($P<0.05$; $r=-0.191, -0.380, -0.216, -0.587, -0.356$). **Conclusions:** The MCR of T2DM patients was decreased and negatively correlated with HbA1C and serum NEFA levels. MCR can not only evaluate the insulin resistance, but also reflect the level of glucose and lipid metabolism.

Key words: Type 2 diabetes mellitus; Metabolic clearance rate; Nonesterified fatty acid**Chinese Library Classification(CLC):** R587.1 **Document code:** A**Article ID:** 1673-6273(2018)13-2465-04

前言

2 型糖尿病(type 2 diabetes mellitus, T2DM)是一种以胰岛β

细胞功能障碍或胰岛素抵抗为主要特征的复杂代谢性疾病^[1],由遗传和环境多因素共同作用所致,临床表现为慢性高血糖和脂代谢紊乱。血清 NEFA(nonesterified fatty acid, NEFA)主要来

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源于甘油三酯(triglyceride, TG)的水解,可以一定程度地反映机体脂代谢的情况^[2],且极易受到糖代谢的影响^[3]。近年研究认为持续高 NEFA 的脂毒性是造成胰岛 β 细胞功能障碍的关键因素^[4]。

代谢清除率(metabolic clearance rate, MCR)被定义为葡萄糖输注速率除以葡萄糖浓度,能在各种葡萄糖浓度下作为可靠标志物^[5]评估健康人群、高血糖、高胰岛素血症及糖耐量受损人群的胰岛素抵抗^[6]。然而, MCR 用于脂代谢情况的价值目前并不清楚。因此,本研究主要分析了 T2DM 患者的 MCR 与血脂水平的相关性,旨在评估 MCR 能否反映脂代谢。

1 材料和方法

1.1 研究对象

收集 2014 年 10 月至 2016 年 12 月在武汉大学中南医院确诊为 T2DM 的住院患者 127 例,其中男 78 例,女 49 例,年龄范围 26-83 岁,平均(55.7 $\pm$ 12.7)岁。纳入标准:按 2014 年美国糖尿病指南糖尿病诊疗标准诊断的 T2DM 患者,且有完善的临床资料和实验室检查结果。排除标准:T2DM 合并恶性肿瘤或肿瘤标志物异常, T2DM 合并其它内分泌系统疾病, T2DM 合并感染性疾病,糖尿病肾病,重复入院患者。

1.2 标本采集与检测

所有受检者禁食 12 小时以上,抽取清晨空腹静脉血。促凝胶分离血清用于检测总胆固醇(total cholesterol, TC)和 TG(AU Chemistry System, BECKMAN COULTER, 苏州), 高密度脂蛋白胆固醇(HDL-C)、低密度脂蛋白胆固醇(LDL-C)、NEFA(SEK-ISUI, 积水); EDTA-K2 抗凝血糖专用管分离血浆用于检测血糖(AU Chemistry System, BECKMAN COULTER, 苏州); EDTA-K2 抗凝全血用于检测 HbA1C(ARKRAY, JAPAN)。血糖和血脂用贝克曼奥林巴斯 5800 全自动生化分析仪检测, HbA1C 用 ADAMS HA-8160 糖化分析仪检测。

口服糖耐量试验和胰岛素释放试验:嘱受试者清晨抽取空

腹静脉血后,口服 75 g 葡萄糖,于 30、60、120、180 min 抽取静脉血检测葡萄糖^[7]和胰岛素,其中葡萄糖采用贝克曼奥林巴斯 5800 全自动生化分析仪检测,胰岛素采用中佳光电 GC-1200 放射免疫计数器检测。

1.3 胰岛素抵抗评价

本研究采用 MCR 和经典 HOMA-IR 指数评价胰岛素抵抗^[5,8]; MCR 指数 = $18.8 - (0.271 \times \text{BMI}) - (0.0052 \times \text{insulin}_{120}) - (0.27 \times \text{glyc}_{120})$ ^[9]; HOMA-IR 指数 = $\text{glyc}_0 \times \text{insulin}_0 / 22.5$ ^[10]。其中, BMI 指数 = 体重 / 身高²(kg/m²), glyc₀ 是空腹血糖, glyc₁₂₀ 是 120 min 血糖, insulin₀ 是空腹胰岛素, insulin₁₂₀ 是 120 min 胰岛素。

1.4 统计学分析

用 SPSS 23.0 软件进行数据分析。K-S 检验评价数据是否呈正态分布,正态分布数据以均数 $\pm$ 标准差表示,偏态分布数据以中位数(四分位数间距)表示。组间比较,正态分布数据使用两独立样本 t 检验,非正态分布数据使用秩和检验曼-惠特尼检验,以 $P < 0.05$ 表示差异有统计学意义。相关性分析采用 Spearman 相关分析,以 $P < 0.05$ 表示相关性显著, r 为正数即正相关,反之为负相关。用多元逐步回归分析各变量对 MCR 和 HOMA-IR 的作用,以 $P < 0.05$ 表示回归方程有统计学意义。

2 结果

2.1 一般临床资料

127 例 T2DM 患者 BMI 为 24.54 (22.14, 27.25), 一般临床资料见表 1。T2DM 患者的 BMI 指数、HbA1C、Glyc₀、TG 均高于参考范围。

2.2 MCR 对糖脂水平的影响

为探讨 MCR 对糖脂水平的影响,以中位数 6.56 将 T2DM 患者分为 "高 MCR" 和 "低 MCR" 两组,比较两组间临床指标差异,结果显示低 MCR 组除 HDL-C 外,其余指标显著高于高 MCR 组。

表 1 患者的一般临床资料及 MCR 分组比较结果

Table 1 Clinical characteristics and MCR analysis

	Low-MCR group (n=63)	High-MCR group (n=64)	T2DM patients (n=127)	P-value*
HbA1C, %	9.86 $\pm$ 2.03	7.60 $\pm$ 1.61	8.74 $\pm$ 2.13	0.000
Glyc ₀ , mmol/L	10.21(8.17, 12.40)	6.92(5.52, 7.85)	7.94(6.48, 11.01)	0.000
TC, mmol/L	4.73 $\pm$ 0.85	4.41 $\pm$ 0.93	4.55 $\pm$ 0.90	0.047
TG, mmol/L	2.04(1.42, 3.07)	1.36(0.96, 2.03)	1.80(1.21, 2.52)	0.001
HDL-C, mmol/L	1.14(0.99, 1.26)	1.22(1.06, 1.54)	1.20(1.02, 1.33)	0.016
LDL-C, mmol/L	3.06 $\pm$ 0.85	2.73 $\pm$ 0.85	2.88 $\pm$ 0.86	0.032
Log ₂ NEFA	9.20(8.84, 9.67)	9.01(8.71, 9.34)	9.13(8.71, 9.46)	0.021

* P-values refer to the results of the comparisons between the low-MCR group and the high-MCR group.

2.3 MCR 和 HOMA-IR 与糖脂水平的相关性

用 Spearman 相关分析评价 MCR、HOMA-IR 与糖脂水平的相关性,结果见表 2。MCR 与 HDL-C 呈显著正相关,与 TC、TG、LDL-C、HbA1C、NEFA 均呈显著负相关; HOMA-IR 仅与 TG 呈显著正相关。为排除糖脂代谢之间的相互影响,进一步用

多元逐步回归分析,结果显示对 MCR 起主要作用的是 HbA1C 和 Log₂NEFA(MCR = $16.499 - 0.479 \times \text{HbA1C} - 0.256 \times \text{Log}_2\text{NEFA}$, 调整后 $R^2 = 0.305$, $P < 0.01$), 没有变量明显影响 HOMA-IR。

3 讨论

表 2 MCR 和 HOMA-IR 与 2 型糖尿病患者糖脂水平的相关性

Table 2 Correlations of MCR, HOMA-IR with glucose, lipids levels of T2DM patients

		HbA1C, %	TC, mmol/L	TG, mmol/L	HDL-C, mmol/L	LDL-C, mmol/L	Log ₂ NEFA
MCR	r	-0.587	-0.191	-0.380	0.215	-0.216	-0.356
	P	0.000	0.031	0.000	0.016	0.015	0.000
HOMA-IR	r	0.127	0.013	0.215	- 0.127	0.058	0.173
P		0.156	0.887	0.016	0.158	0.515	0.051

2 型糖尿病是由遗传因素和环境因素共同作用引起的复杂性代谢性疾病,以遗传因素为主导,运动缺乏、肥胖、老龄化等都是其易感因素^[11-13]。由于严重肥胖患者的激增,全人类已经处于糖尿病灾难性流行的边缘^[14]。根据国际糖尿病联盟(international diabetes federation, IDF)报道,目前全球糖尿病成年患者已达到 4.15 亿,预计 2040 年将超过 6 亿^[15]。截至 2015 年统计显示,糖尿病已经在全球致残病因中排名第六位,给个人和社会乃至全球带来重大的健康隐患和经济负担,估算治疗费用达 82.5 亿美元^[15],成为全球持续增长的经济负担。因此,临床迫切需要能有效降低 T2DM 的发病风险的新策略新方法,增加疾病的警醒预防,实现 T2DM 早期诊断以及个性化治疗以减轻并发症发生风险和死亡率^[16]。

T2DM 是一种慢性代谢性疾病,胰岛素抵抗和减弱的胰岛素分泌是发病的关键病理过程^[12,17],慢性高血糖和脂代谢紊乱是其明显的临床特征^[18]。NEFA 是存在于人体的主要脂类物质之一,是中性脂肪的分解产物,能为机体提供能源,也可导致氧化应激^[19]。正常水平下的 NEFA 能增强基础状态和葡萄糖刺激后的胰岛素分泌量^[20],是胰岛β 细胞刺激分泌偶联的必需物质^[21],高 NEFA 通过启动氧化应激机制产生活性分子,这些活性分子既可直接氧化和损伤核酸、蛋白质、脂类,又可作为分子信号,激活体内应激敏感信号通路,导致β 细胞功能受损,加重胰岛素抵抗^[22]。血清中游离脂肪酸浓度与血糖代谢、脂类代谢、内分泌功能等有关,高血糖和高浓度的 NEFA 可通过多种途径影响葡萄糖的摄取、氧化及糖异生^[23,24],并可干扰胰岛素的分泌和信号转导。胰岛素抵抗是指胰岛素细胞对糖刺激的效应减弱,胰岛素对葡萄糖的摄取和利用率下降,机体对胰岛素药物治疗的敏感性降低,是多种代谢性疾病如肥胖、高血糖、脂代谢紊乱等的发病基础^[25,26]。

本研究显示 T2DM 患者的 BMI、Glyc0、TG 和 HbA1C 均高于参考范围,表明 T2DM 患者普遍存在超重和糖脂代谢异常的情况。低 MCR 组的 T2DM 患者 HDL-C 水平明显低于高 MCR 组,而 HbA1C、Glyc0、TC、TG、LDL-C、NEFA 水平明显高于高 MCR 组。HDL 在机体内的生理作用是运载周围组织中的胆固醇到肝脏,再转化为胆汁酸或直接通过胆汁从肠道排出,从而促进胆固醇的代谢,减少游离胆固醇在肝外组织细胞中的沉积^[27,28]。影像学检查结果显示 HDL-C 的含量与动脉管腔狭窄程度呈显著负相关,表明 HDL 是一种具有抗动脉粥样硬化作用的血浆脂蛋白,是冠心病的保护因子^[29]。血清 HDL-C 含量与代谢清除率有相同的变化趋势,进一步证实 HDL-C 对心血管疾病的保护作用。HbA1C 主要反映机体近两个月内的血糖变

化情况,不受检测当天血糖波动、运动和饮食的影响,是衡量血糖控制的金标准,也在糖尿病的诊疗和管理中起非常重要的评价作用^[30]。HbA1C 越高,说明最近一段时间的血糖水平越高,或患者近期对血糖的控制情况越差,机体的代谢清除率也越低。相关性分析显示 MCR 与糖脂指标均相关,HOMA-IR 仅与 TG 呈正相关。MCR 与 HbA1C 及血清 TC、TG、LDL-C、NEFA 的显著负相关表明,当机体代谢清除率低的时候,血糖及血脂多项指标均有不同程度的升高,不仅证实了糖脂代谢的关联,还说明 MCR 的降低伴随着体内多种代谢物质的堆积。TC 是血液中所有脂蛋白所含胆固醇的总和,TG 是脂质的组成成分,在体内起供给和储存能源的作用,LDL 是运输内源性胆固醇的主要载体,上述三种脂代谢产物与动脉粥样硬化、脑卒中、冠心病等心血管疾病关系密切,是冠心病发生的危险因素^[31,32]。

临床研究表明 T2DM 患者随着病程的进展,伴发并发症的可能性越来越高,且糖尿病脂代谢紊乱导致的心血管疾病是 T2DM 患者主要死因。因此,一个能综合反映多种糖脂代谢水平的评价指标对 T2DM 患者的血糖波动、疗效监测以及并发症的预防和控制都具有临床指导意义。多元逐步回归分析进一步表明 MCR 不仅能够反映血糖(HbA1C)代谢,而且能反映血脂(NEFA)代谢。一方面,T2DM 患者糖代谢障碍,表现为 MCR 降低,长期血糖控制不良导致 HbA1C 升高。另一方面,T2DM 患者因糖利用不足而通过加强脂肪分解获取机体所需能量,TG 分解可引起 NEFA 的升高。既往研究表明血清 NEFA 有很强的细胞毒性,可损害细胞膜、线粒体和溶酶体膜等,且能增强细胞因子毒性,造成胰岛β 细胞功能损害和胰岛素抵抗,在 2 型糖尿病代谢异常的发生发展中起了重要作用^[33]。这一过程中,NEFA 参与血糖的升高,引起胰岛素的代偿分泌和胰岛素抵抗,导致 NEFA 进一步升高,随着代谢失衡加剧,高浓度 NEFA 的细胞毒性又加重胰岛素抵抗,形成恶性循环。

HOMA(Homeostasis model assessment,稳态模式评估法)是由牛津大学 Turner 小组于 1985 年提出的,目前已广泛应用于临床的反映糖尿病患者胰岛素情况的经典指标,主要包括:用于评价机体胰岛素抵抗 HOMA-IR,用于评价机体胰岛素敏感性的 HOMA-IS 以及用于评价机体胰岛素β 细胞功能的 HOMA-β。本实验未能成功建立 HOMA-IR 与血清糖脂指标的回归方程,说明 HOMA-IR 作为评价胰岛素抵抗的传统指标,对糖脂代谢的评价作用存在局限性。HOMA-IR 与 HbA1C 也不存在明显的相关性,提示该指标仅能反映机体实时胰岛素抵抗,而无法体现患者近一段时间的血糖控制情况。

综上所述,NEFA 在 T2DM 的发生、发展中有重要作用,

MCR 的降低与 T2DM 患者的糖脂代谢密切相关, 尤其是 NEFA 与 HbA1C。MCR 不仅能反映胰岛素抵抗, 而且能综合评价 T2DM 患者的糖脂代谢, 对 T2DM 的病情进展和疗效监测具有一定的临床意义。

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