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载脂蛋白亚型与糖尿病合并冠心病的相关性研究*

王玉晶 闫爽[△] 郎宁 张瑛琦 周伟或 刘思颖

(哈尔滨医科大学附属第四医院 黑龙江 哈尔滨 150001)

摘要 目的:探讨载脂蛋白亚型与糖尿病合并冠脉病变严重程度相关性,为预防及治疗糖尿病伴发的动脉粥样硬化性疾病提供新的依据。**方法:**选取 440 名心内科患者,根据冠脉造影有无冠脉狭窄及是否合并糖尿病分为四组:冠脉内膜光滑组 94 人(A 组);单纯冠脉狭窄组 108 人(B 组);糖尿病合并冠脉狭窄组共 184 人(C 组);糖尿病冠脉无狭窄组 44 人(D 组),记录患者空腹血糖、餐后血糖、传统血脂脂谱、载脂蛋白 A(apoA)、载脂蛋白 B(apoB)及两者的比值(apoB/apoA);采用 Gensini 评分比较传统血脂、apoA、apoB 及与 Gensini 积分值的相关性。**结果:**与正常对照组比较,糖尿病冠脉无狭窄组 apoB、apoB/apoA、LDL 和 TG 升高,apoA 和 HDL 降低,B 组和 C 组 apoA 与 Gensini 积分值存在负相关($P=0.0157<0.05$);apoB;apoB/apoA 与 Gensini 积分值存在正相关($P<0.0001$);两组中,apoB 与 Gensini 积分值相关系数最大($r=0.85795, 0.85941$),且 apoB 与 Gensini 积分值的相关性都强于 LDL 与积分值的相关性。**结论:**在糖尿病患者预测心血管风险上,apoB, apoA, apoB/apoA 的测定可能优于传统的血脂指标。

关键词:2 型糖尿病;冠心病;载脂蛋白亚型;apoB/apoA 比值;Gensini 评分

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Correlative Research of Apolipoprotein Isoforms and Diabetic with Coronary Heart Disease*

WANG Yu-jing, YAN Shuang[△], LANG Ning, ZHANG Ying-qi, ZHOU Wei-yu, LIU Si-ying

(The Fourth Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, 150001, China)

ABSTRACT Objective: To investigate the relationship between the apolipoprotein isoforms and severity of diabetes with coronary heart disease, and to provide new evidences for early diagnosis and prevention of diabetes combined with coronary atherosclerosis. **Methods:** 440 patients from department of cardiology were selected and randomly divided into four groups according to the coronary angiography with and without coronary artery stenosis and whether combined with diabetes mellitus: A group (normal control group, $n=94$), B group (coronary heart disease, $n=108$), C group (coronary heart disease with diabetes mellitus, $n=184$). D group (diabetes mellitus without coronary heart disease, $n=44$). Fasting blood glucose, postprandial blood glucose, apoB, apoA, apoB/apoA ratio were measured. The degree of coronary stenosis was evaluated by calculating Gensini's score. The correlation between the Gensini's score and the level of apoA, apoB and apoA/apoB was compared. **Results:** Compared with coronary heart disease combined type 2 diabetes group, ApoA and Gensini score value was negatively related. ApoB level and apoB/apoA ratio were positively correlated with Gensini score value. Comparing coronary heart disease combined type 2 diabetes group with simple stenosis of coronary disease groups and type 2 diabetes without coronary heart disease, ApoB with Gensini score value correlation coefficient ($r = 0.85795, 0.85941$), the largest and the correlation between apoB and Gensini score value was stronger than LDL and the integral value of correlation. **Conclusion:** On the prediction of cardiovascular risk in diabetes patients, apoB, apoA, and apoB/apoA determination may be superior to the traditional lipid indexes.

Key words: Type 2 diabetes; Coronary heart disease; Apolipoprotein isoforms; Gensini's score

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前言

随着人类饮食结构及生活方式的改变和来自各方面压力的增加,2 型糖尿病发病率持续增长,但住院率及对此疾病的重视程度却不成比例。因此,随着糖尿病病程延长并发症发生越来越多,越来越重,给患者本身、家庭乃至国家增加了很大负

担,这不仅仅是经济方面的威胁,糖尿病会给患者造成肉体和精神上的痛苦,加之糖尿病发展的最终趋势多会引起其它重要脏器组织(如肾、心、血管等)的并发症,不少患者由此常会背负沉重的精神压力而产生负性情绪可引起人体交感神经活动增强,儿茶酚胺过量分泌,脂类代谢紊乱等,不仅使血糖升高,治疗的依从性下降,还可加速并发症发生,对病情和预后都有不

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作者简介:王玉晶(1982-),女,硕士研究生,住院医师,主要研究方向:糖尿病与血脂代谢异常

电话:13904819554, E-mail: ruixin198208@163.com

[△] 通讯作者:闫爽,女,博士研究生,主任医师,主要研究方向:糖尿病及慢性并发症、甲亢、骨质疏松,

E-mail: qingmei0724@163.com

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良影响。反过来,血糖控制不佳,病情加重,又会导致病人精神痛苦、悲观等,严重时导致自杀,危害社会等严重后果。因此我们要寻求糖尿病慢性并发症的危险因素,只有这样我们才能尽可能减缓慢性并发症发展,引起患者死亡的首要病因为心肌梗死。目前很多研究结果显示^[1-5],糖尿病相关的核心代谢紊乱如:糖、脂质代谢紊乱、胰岛素抵抗、高凝状态、亚临床症状等损伤血管内皮功能,加速动脉粥样硬化的进程。而脂肪代谢紊乱为糖尿病患者动脉粥样硬化发病机制中重要物质基础。传统的血脂参数评估包括胆固醇(TCHO)、甘油三酯(TG)、低密度脂蛋白胆固醇(LDL-C)、非高密度脂蛋白胆固醇(非HDL-C)以及高密度脂蛋白胆固醇(HDL-C)。大量的研究表明,血浆LDL-C、HDL-C和甘油三酯是心血管疾病独立的预测因子,1996年,Lamarche^[2]等人在Quebec Cardiovascular Study中通过对2155名男性5年随访研究首次提出了apoB优于其它常规血脂参数在预测心血管危险方面,随后一长期前瞻性和回顾性研究^[3-7]显示,apoB、apoA以及apoB/apoA比值较传统的血脂参数能更准确的反应心血管发生的风险。本研究通过检测经冠状动脉造影证实的冠心病患者的血浆脂质成分,探讨载脂蛋白亚型与糖尿病合并冠心病时冠状动脉狭窄严重程度的关系。

1 材料与方法

1.1 一般资料

入选的试验对象共440名患者,分为四组:(1)冠脉造影内膜光滑作为正常对照组(A组)94名,男50名(53%),女44名(47%),年龄32-77岁,平均(53.3±12.5)岁。(2)单纯冠脉狭窄组(B组)108名,男78名(72%),女30名(28%),年龄

34-77岁,平均(56.3±12.5)岁。(3)糖尿病合并冠脉狭窄(C组)184名,男100名(54.3%),女84名(45.7%),年龄38-80岁,平均(57.8±12.5)岁,病程0-10年。(4)糖尿病冠脉造影为内膜光滑者为糖尿病冠脉无狭窄组(D组)44名,男22名,女22名,年龄35-80岁,糖尿病病程0-10年。

1.2 入选标准

糖尿病及冠脉狭窄组根据以下标准:(1)根据1999年WHO糖尿病诊断标准确诊为糖尿病;(2)有糖尿病病史;(3)冠脉造影结果示至少一支冠状动脉管腔直径狭窄 $\geq 50\%$,诊断冠心病;(4)临床上除其它器质性心脏病;(5)Gensini评分积分值为 ≥ 1 分。

1.3 观察指标

清晨空腹抽取静脉血,检测空腹血糖、餐后血糖、糖化血红蛋白比值、总胆固醇(TCHO)、甘油三酯(TG)、低密度脂蛋白胆固醇(LDL)、高密度脂蛋白胆固醇(HDL)、载脂蛋白B(apoB)、载脂蛋白A(apoA)、apoB/apoA比值。

1.4 评估冠脉病变程度的方法

Gensini评分法:首先,将冠脉分成14段,根据病变血管的不同节段制定不同的权重系数(表1);其次,根据冠脉管腔狭窄程度分别给以不同的权重系数。冠脉狭窄程度权重系数:冠脉狭窄25%的权重系数为1,冠脉狭窄50%的权重系数为2,冠脉狭窄75%的权重系数为4,冠脉狭窄90%的权重系数为8,冠脉狭窄99%的权重系数为16,冠脉狭窄100%的权重系数为32;评分方法为冠脉管腔狭窄程度权重系数乘以各病变血管的权重系数,最后总评分(即积分值)为各分支血管评分之和。

表1 Gensini评分法中冠状动脉不同节段权重系数

Table 1 Gensini score of weight coefficients of coronary artery in different segments

different segmentsweight coefficientdegree of stenosisweightcoefficient	
Proximal segment of right coronary artery 1	1%~25%1
Middle segment of right coronary artery	1
Distal segment of right coronary artery 1	26%~50%2
Posterior descending branch	1
Posterolateral branch of left ventricle 1	51%~75%4
Left main coronary trunk	5
Proximal segment of anterior descending branch 2.5	76%~90%8
Middle segment of anterior descending branch	1.5
Distal segment of descending branch 1	91%~99%16
The first diagonal branch	1
The second diagonal branch	0.5 100% 32
Proximal segment of the left circumflex branch	2.5
Distal segment of the left circumflex branch	1
Obtuse marginal branch	1

1.5 统计学处理

采用SAS9.0软件包进行数据的统计学处理,对于正态分布的计量资料数据以均数 $\pm$ 标准差表示,三组间比较采用协方差分析,两两比较用的SNK-q检验、秩检验,积分值与TC、TG、HDL、LDL、apoB、apoA、apoB/apoA比值的相关关系采用直线相关分析。以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 四组的血脂比较

B组、D组TG、LDL、apoB水平和apoB/apoA比值显著高于A组,差异具有统计学意义($P<0.05$);D组apoA、HDL显著低于A组,差异具有统计学意义($P<0.05$);C组的apoA、HDL

水平低于 A、D 组, 差异具有统计学意义 ($P<0.05$); C 组 TG, 有统计学意义 ($P<0.05$); 从中反映了糖尿病患者更应给予降脂治疗, 以预防及延缓冠心病的发生及发展。见表 2。

表 2 四组血脂水平比较

Table 2 Comparison of lipid level among the four groups

Variable	A group	B group	C group	D group
N	106	116	209	44
Age(y)	53.3± 8.7	56.3± 9.0 *	57.8± 9.3*	56.4± 9.0*
TC(mmol/L)	4.9± 1.0	5.2± 0.8*	5.3± 0.9*#	4.7± 0.6
TG(mmol/L)	1.5± 0.8	1.9± 1.3	2.4± 1.7 **	2.1± 1.4*
HDL(mmol/L)	1.4± 0.4	1.3± 0.3*	1.1± 0.3*▲#	1.2± 0.2*
LDL (mmol/L)	3.0± 1.0	3.9± 1.1 *	4.3± 1.0 *▲#	4.0± 0.7*
ApoA(g/L)	1.4± 0.3	1.3± 0.3 *	1.1± 0.2 *▲#	1.2± 0.2*
ApoB (g/L)	0.8± 0.1	1.0± 0.2*	1.2± 0.3 *▲#	0.9± 0.1*
ApoB/apoA	0.6± 0.2	0.8± 0.3*	1.0± 0.3 *▲#	0.9± 0.1*

注: B 组, C 组与 A 组比较, *: ($P<0.05$); ▲ $P<0.05$; C 组 vs B 组; # $P<0.05$, C 组 vs D 组。

Note: * $P<0.05$, compared with A group; ▲ $P<0.05$, compared with B group; # $P<0.05$, compared with D group.

2.2 两组的血脂参数与积分值相关分析

在 B 组和 C 组中, 积分值与 TC, LDL, apoB, apoB/apoA 正相关, $P<0.05$; 积分值与 apoA, HDL 负相关, $P<0.05$; 比较各相关系数, apoB 与积分值的相关系数最大 ($r=0.85795, 0.85941$),

两组中 apoB 与积分值的相关性都强于 LDL 与积分值的相关性。说明了代表动脉硬化颗粒浓度的 apoB 与冠脉病变程度关系密切, 联系比较强。见表 3。

表 3 B 组和 C 组的积分值与各血脂相关性分析

Table 3 Correlation analysis of Gensini score and lipid level between simple stenosis of coronary artery stenosis and diabetic with coronary heart disease

Indicators	B group		C group	
	r	P	r	P
LDL	0.64607	<0.0001	0.72539	<0.0001
ApoB	0.85795	<0.0001	0.85941	<0.0001
ApoB/apoA	0.71919	<0.0001	0.72979	<0.0001
ApoA	-0.16234	<0.0001	-0.22388	<0.0001
TG	-----	insignificance	-----	insignificance
HDL	-0.14513	<0.0001	-0.19472	<0.0001

3 讨论

糖尿病伴发血脂异常是导致并加速冠心病和其它动脉粥样硬化病变发生发展的关键因素^[2,5,6]。以往评估冠心病风险的血脂参数包括 TC、TG、LDL 和 HDL, 近年来, 大型临床试验 (如 AMORIS 试验^[1,7]、AFCAPS / TexCAPS 试验^[3,8]) 研究提示, apoB、apoA 及 apoB / apoA 在预测冠心病风险及冠脉狭窄程度方面具有更大优势^[9]。apoA 是 HDL 的主要蛋白质成分, Belalcazar^[10,11]等人研究结果提示载脂蛋白 A 长期稳定表达能够延缓动脉硬化进展, 并使斑块重塑, 形成稳定表型。另外, 载脂蛋白 A 还可以通过抗炎、抗栓和内皮功能保护等多种作用抑制动脉粥样硬化的发生、发展。apoB 是 LDL、IDL 和 VLDL 的运载蛋白参与动脉硬化发生、发展^[12]。Smith EB 等人测定 apoB 浓度发现 apoB 结合的蛋白多糖颗粒存在于内皮细胞和斑块外基质中可以直接作用于血管壁, 与动脉粥样硬化形成密切相关^[13]。apoB 的数量决定了富含胆固醇的脂蛋白颗粒进入斑块并黏附于斑块的数目^[14,15], apoB 数量越多, 动脉粥样硬化

越严重。另外, 评估冠脉病变的 LDL、HDL 在病理状态下易受食物、药物影响, 而 apoA、apoB^[16,17]则不然。Garfagnini 等人早在 1995 年发现, 心梗患者冠脉造影显示两支或多支动脉病变与单纯单支病变相比 apoA 水平降低, apoB/apoA 比值升高, apoB 优于其它常规血脂参数^[18]。本研究发现与 A 组比较, B 组 apoB、apoB/apoA 水平升高, 有显著的统计学意义, 与上述文献报道一致^[19]。糖尿病患者慢性高血糖致糖基化作用增强, apoB 糖化后其结构和功能发生改变, 不能被受体识别而被清道夫细胞吞噬转而形成泡沫细胞, 为动脉粥样硬化形成奠定病理基础^[20,21]。研究发现, 与 A 组比较, D 组 apoB、apoB/apoA、LDL 和 TG 升高, apoA 和 HDL 降低, 提示了糖尿病患者血清中的抗动脉粥样硬化因子降低, 而致病因子升高, 说明这些患者体内已经具备了引发动脉粥样硬化心血管疾病的生物化学基础。同时本研究也发现, 与 A 组和 D 组相比, C 组 apoB、apoB/apoA、LDL 和 TG 升高, apoA 和 HDL 降低, 三组相比有显著的统计学意义。提示了 apoB 升高、apoA 降低可能参与糖尿病冠脉病变发生、发展的过程。因此, 在对糖尿病患者的诊治过程中, 采取降低

apoB、LDL 水平和(或)升高 apoA、HDL 治疗,以消除或降低引起心血管合并症的危险因素,这样有助于进一步延长糖尿病患者的生存时间。

冠状动脉病变程度与冠心病的发生、发展有密切关系。当今冠脉造影被人们视为诊断冠心病的金标准。为了更好的、较全面的反映冠心病患者病情的严重程度。本实验使用 Gensini 评分。Gensini 评分对冠状动脉病变程度的评估是一种非常有效、量化的方法,它既考虑冠脉病变的范围,也考虑了冠脉病变的严重程度^[22,23]。Gensini 评分法对患者的心脏功能性作出了更为精确的分层,在冠脉病变的评价上更详细,在评价冠脉病变的严重程度更敏感。据文献报道^[23],冠状动脉病变越严重, Gensini 评分越高。胡良喈^[23]等人通过使用 Gensini 评分对每支血管病变程度进行定量评定得出,冠状动脉病变程度与 apoB 相关性最强。因此,本实验根据冠脉造影结果有无狭窄和有无糖尿病分为四组,联合使用 Gensini 评分得出总的评分既积分值,深入的评估冠脉狭窄程度,使用直线相关分析对四组血脂及积分值进行相关性的统计分析最后得出, apoB、LDL、apoB/apoA 分别与 B 组、C 组的积分值正相关 $P < 0.05$, 并且 C 组 apoB、LDL、apoB/apoA 相关系数最大($r = 0.85941, 0.72539, 0.72979$); apoA 与积分值负相关, $P < 0.05$, 并且 C 组 apoA 相关系数最大($r = -0.22388$); 积分值与 TG、HDL 不相关, $P > 0.05$ 。本实验结果提示 apoB、LDL、apoB/apoA、apoA 与糖尿病伴发的冠脉病变程度最相关,随着 apoB、LDL、apoB/apoA 升高, apoA 降低,冠状动脉狭窄程度加重。本实验研究结果与胡良喈报道^[23]基本相似,不同的是本实验增加糖尿病合并冠脉狭窄组,得出 apoB 与积分值具有相关性,提示糖尿病患者血浆脂质成分中的 apoB 可能为冠脉病变发生和发展危险因素之一。

最近的 ADA 和美国心脏病学院建议在治疗心肌代谢性疾病时应该把 apoB 考虑进去^[24]。本实验通过使用 Gensini 评分论述 apoA、apoB 和 apoB/apoA 比值与糖尿病合并冠脉病变狭窄程度相关性,进一步证实先前关于 apoB 文献报道,同时提供了 apoB 可能优于 LDL 在糖尿病合并冠心病风险上证据,建议糖尿病患者在监测血糖的同时,应定期监测血脂及载脂蛋白的变化,及时使用降脂药物,降低 TC、LDL、apoB 等致病因子在血中的含量,以便及早防治其并发症。在糖尿病冠脉存在狭窄病变时,代表致动脉粥样硬化因子 TG、LDL、apoB 与抗动脉粥样硬化因子 HDL、apoA 间失衡表现的更为突出,同时载脂蛋白 apoB 与冠脉狭窄程度的积分值有显著相关性并强于优于传统的血脂指标 LDL。因此可把 apoB 及 apoB/apoA 作为糖尿病合并冠脉狭窄衡量的新指标,对以后的降脂所达到的理想目标提供指导^[24,25]。

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