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2 型糖尿病患者微血管病变与血清代谢学指标的关系 *

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摘要 目的:探讨 2 型糖尿病(T2DM)患者微血管病变与血清代谢学指标的关系。**方法:**选择我院于 2015 年 7 月~2016 年 7 月间收治的 T2DM 患者共 96 例,按是否存在微血管病变分为观察组($n=43$,存在微血管病变)及对照组($n=53$,无微血管病变)。检测并对比两组患者血清中三酰甘油(TG)、总胆固醇(TC)、高密度脂蛋白(HDL)、低密度脂蛋白(LDL)、空腹血糖(FBG)、糖化血红蛋白(HbA1C)、同型半胱氨酸(Hcy)、血清胱抑素 C(CysC)及血管内皮生长因子(VEGF)水平,并采用 logistic 回归分析 T2DM 微血管病变的危险因素。**结果:**观察组病程、吸烟率高于对照组,差异有统计学意义($P<0.05$);观察组 TG、LDL、HbA1C、CysC、Hcy、VEGF 水平均高于对照组,差异均有统计学意义($P<0.05$);两组 TC、HDL 水平比较,差异无统计学意义($P>0.05$);经 logistic 回归分析显示,病程、CysC、Hcy、VEGF 为微血管病变的危险因素($OR=1.975, 3.643, 4.054, 4.214, P<0.05$)。**结论:**CysC、Hcy、VEGF 为微血管病变的危险因素,对其水平的检测有助于早期 T2DM 微血管病变诊断及治疗。

关键词:2 型糖尿病;微血管病变;Hcy;CysC;VEGF

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Relationship between Microvascular Lesions and Serum Metabolic Parameters in Patients with Type 2 Diabetes Mellitus*

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ABSTRACT Objective: To investigate the relationship between microvascular lesions and serum metabolic parameters in patients with type 2 diabetes mellitus(T2DM). **Methods:** Selected 96 patients with T2DM in our hospital from July 2015 to July 2016, According to the presence of microvascular lesions were divided into observation group ($n=43$, with microvascular lesions)and control group($n=53$, without microvascular lesions). Detected the levels of triacylglycerol(TG), total cholesterol(TC), high density lipoprotein(HDL), low density lipoprotein (LDL), fasting blood glucose(FBG), glycosylated hemoglobin(HbA1C), homocysteine(Hcy)and serum cystatin C(CysC) and vascular endothelial growth factor (VEGF). Logistic regression analysis was used to analyze the risk factors of microvascular lesions. **Results:** Course of disease, smoking rate in observation group was higher than the control group, the difference was statistically significant ($P<0.05$); The levels of TG, LDL, HbA1C, CysC, Hcy, VEGF were higher than the control group, the differences were statistically significant($P<0.05$), but the TC and HDL levels in two groups had no significant difference($P>0.05$); Logistic regression analysis showed that the course of disease, CysC, Hcy, VEGF were the risk factors for microvascular lesions ($OR=1.975, 3.643, 4.054, 4.214, P<0.05$). **Conclusion:** CysC, Hcy, VEGF are the risk factors of the microvascular lesions, detecting these indexes is helpful to diagnosis and treatment of early T2DM with microvascular lesions.

Key words: Type 2 diabetes mellitus; Microvascular lesions; Hcy; CysC; VEGF

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前言

随着近些年人们生活习惯的改变,2 型糖尿病 (Type 2 diabetes mellitus, T2DM)的发病率呈逐年上升的趋势,严重的降低了患者的生活质量,已经是世界范围的健康问题^[1]。微血管病变为糖尿病患者最为常见的并发症,是以微血管的结构及功能改变为特征,主要表现为糖尿病性视网膜病变、心脏的微血管病变、糖尿病性肾病等^[2]。糖尿病性视网膜病变是 T2DM 患者致

盲的主要原因,糖尿病性肾病则是导致终末期肾病的主要原因,而大约有 8%的 T2DM 患者发展为终末期肾病,因此尽早的关注微血管病变并及时的干预对于 T2DM 患者的预后具有重要意义^[3,4]。本次研究中主要比较了 T2DM 患者血清中同型半胱氨酸(homocysteine, Hcy)、血清胱抑素 C(cystatin c, CysC)及血管内皮生长因子(vascular endothelial growth factor, VEGF)水平变化,旨在探讨血清代谢学指标与 T2DM 患者微血管病变的关系。现报道如下。

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1 资料与方法

1.1 一般资料

选择我院于 2015 年 7 月~2016 年 7 月间收治的 T2DM 患者共 96 例。纳入标准:T2DM 诊断均符合 1999 年 WHO 提出的糖尿病诊断标准^[9]。排除标准:并发心脑血管疾病患者;1 型糖尿病、妊娠糖尿病患者;两周内服用过胰岛素治疗患者;心、肝器官严重功能不全者;并发恶性肿瘤疾病者。按是否存在微血管病变情况分为观察组 (n=43, 存在微血管病变) 及对照组 (n=53, 无微血管病变)。观察组中糖尿病性肾病 27 例, 糖尿病性视网膜病变 16 例。患者均知情同意本次研究且签署《知情同意书》, 本次研究经医院伦理委员会批准。

1.2 研究方法

所有患者均对以下指标进行检测: 三酰甘油 (triacylglycerol, TG)、总胆固醇 (total cholesterol, TC)、高密度脂蛋白 (High density lipoprotein, HDL)、低密度脂蛋白 (Low density lipoprotein, LDL)、空腹血糖 (Fasting blood glucose, FBG)、糖化血红蛋白 (HbA1C)、CysC、Hcy、VEGF。于清晨采集患者静脉血 5 mL, 采用离心机以 3000 r/min 的转速离心 10 min, 取血清液于 2 h 内进行检测。HbA1c 水平经由全自动糖化血红蛋白分析仪 (日

本 TOSOH 公司制造)测定。HDL、LDL、TC、TG 水平经由 ADVIA2400 全自动生化分析仪 (德国西门子股份公司)测定。Hcy 经循环酶法检测, 试剂盒购自深圳奥萨医药有限公司。CysC 经免疫比浊法检测, 试剂盒购自汉明德生物科技股份有限公司, VEGF 经酶联免疫吸附法 (ELISA) 检测, 试剂盒购自美国 Assay Designs。检测步骤均严格按试剂盒说明进行操作, 为避免实验偶然误差, 本次研究均由一名检验科经验丰富的医师进行检测。

1.3 统计学方法

采用 SPSS20.0 软件对数据进行处理, 计数资料以 n(%) 表示, 两组数据比较采用 χ^2 检验, 计量资料以 ($\bar{x} \pm s$) 表示, 两组比较采用 t 检验; T2DM 微血管病变的危险因素采用 logistic 回归分析。P<0.05 代表差异有统计学意义。

2 结果

2.1 两组患者一般资料情况比较

观察组病程、吸烟率高于对照组, 差异有统计学意义 (P<0.05)。两组患者年龄、性别、身体质量指数 (Body Mass Index, BMI) 比较差异无统计学意义 (P>0.05)。详见表 1。

表 1 两组一般资料比较

Table 1 Comparison of general information in the two groups

Groups	n	Age (year)	Gender (male/female)	Course of disease (month)	BMI (kg/m ²)	Smoking rate (%)
Observation group	43	54.78± 9.74	26/17	76.43± 19.91	24.25± 3.42	24(55.81)
Control group	53	55.32± 9.21	31/22	29.09± 11.83	25.42± 3.52	18(33.96)
t/ χ^2	-	0.278	0.038	14.457	1.640	4.606
P	-	0.781	0.845	0.000	0.104	0.031

2.2 两组患者血清代谢学指标比较

观察组 TG、LDL、HbA1C、CysC、Hcy、VEGF 水平均高于

对照组, 差异均有统计学意义 (P<0.05); 两组 TC、HDL 水平比较, 差异无统计学意义 (P>0.05)。详见表 2。

表 2 两组患者血清代谢学指标比较

Table 2 Comparison of serum metabolic indexes in the two groups

Groups	n	TG (mmol/L)	TC (mmol/L)	HDL (mmol/L)	LDL (mmol/L)	HbA1C (%)	CysC (mg/L)	Hcy (μ mol/L)	VEGF (ng/L)
Observation group	43	2.13± 0.76	5.25± 1.87	1.16± 0.46	3.20± 0.99	7.93± 1.81	2.80± 0.79	24.13± 6.04	325.23± 40.12
Control group	53	1.76± 0.63	4.99± 1.63	1.21± 0.39	2.79± 0.85	6.67± 1.59	1.39± 0.45	13.46± 3.02	230.24± 47.12
t	-	2.608	0.727	0.576	2.182	3.628	10.988	11.252	10.487
P	-	0.010	0.468	0.565	0.031	0.000	0.000	0.000	0.000

2.3 微血管病变与血清代谢指标的相关性分析

将微血管病变作为因变量, 将病程、吸烟率、TG、LDL、HbA1C、CysC、Hcy、VEGF 作为自变量, 经 logistic 回归分析, 结

果显示, 病程、CysC、Hcy、VEGF 为微血管病变的危险因素 (P<0.05)。详见表 3。

表 3 微血管病变的 logistic 回归分析

Table 3 Logistic regression analysis of microvascular lesions

Indexes	β	SE	Wald	P	OR (95%CI)
Course of disease	2.083	0.346	5.215	0.000	1.975 (1.533~10.832)
CysC	1.294	0.525	6.183	0.000	3.643 (1.312~10.093)
Hcy	1.445	0.345	16.725	0.000	4.054 (1.113~8.384)
VEGF	1.433	0.345	17.433	0.000	4.214 (2.144~8.292)

3 讨论

糖尿病是目前较为常见且无法治愈的终身性疾病,给社会带来了沉重的负担,严重的威胁着人类的健康。根据 WHO 统计显示,2011 年糖尿病患者约有 3.66 亿,预计到 2030 年糖尿病患者将增至 5.52 亿,而其中约有 48% 的患者将分布于中国与印度^[6,7],并且 T2DM 的发病正趋于低龄化。近年来的研究表明,儿童 T2DM 的发病率呈上升趋势^[8]。各种并发症是导致 T2DM 患者死亡的主要原因,其中微血管病变所引起的疾病占死亡人数的 20%~50%^[9,10]。因此研究糖尿病微血管病变的进展机制,尽早的诊断及预防 T2DM 患者并发症的发生具有极大的社会和经济效益。

微血管遍布人体全身各处,因此 T2DM 对人体的危害几乎累及各个组织器官,在临床中糖尿病微血管病变多见于糖尿病性视网膜病变及糖尿病性肾病,其发病机制与细胞因子、基化终末产物及氧化应激等因素相关^[11,12]。本次研究中对我院 T2DM 患者一般资料及血清代谢学指标进行分析,结果显示,观察组病程、吸烟率高于对照组,差异有统计学意义($P<0.05$)。这与之前的研究相似,该研究表明,有吸烟史的 T2DM 患者的发生糖尿病微血管病变的风险率为无吸烟史 T2DM 患者的 2 倍^[13]。烟草中所产生的尼古丁及一氧化碳可使血管收缩,导致血小板聚集进而产生血栓,致使眼部组织缺氧,因此戒烟对延缓糖尿病病情的进展十分重要。观察组 TG、LDL、HbA1C、CysC、Hcy、VEGF 水平均高于对照组,差异均有统计学意义($P<0.05$)。以上结果提示,高血脂、高血糖对于糖尿病微血管病变具有促进作用。强化降糖可以有效的减少糖尿病微血管病变,HbA1C 每减少 1%,糖尿病微血管病变率则降低 25%,国外常常将 HbA1C 作为糖尿病的诊断及管理参考指标^[14]。经 logistic 回归分析,结果显示,病程、CysC、Hcy、VEGF 为微血管病变的危险因素($P<0.05$)。以上结果表明,尽早的对糖尿病患者的病情进行控制,有助于降低或延缓微血管病变情况的发生,这与之前的报道相似^[15]。同时通过检测 T2DM 患者 CysC、Hcy、VEGF 水平,可以准确的对微血管病变情况进行评估。CysC 为半胱氨酸蛋白酶抑制剂,其分子量较低,能自由的穿过肾小球,因此肾脏是唯一能清除 CysC 的器官。近年来研究发现,CysC 可较早的反映糖尿病肾病的进展程度^[16]。传统的肾功能检测项目通常为肌酐、尿素氮,但由于肾脏较强的代偿能力,因此在肾小球受损初期,血清中肌酐、尿素氮仍然能够保持在正常水平,只有当肾小球严重受损时,肌酐、尿素氮才会明显升高。而 CysC 则随着肾小球滤过率的改变而改变,有文献报道显示,在诊断糖尿病微血管病变中,CysC 的灵敏度明显高于肌酐、尿素氮^[17]。Hcy 是甲硫氨酸代谢产物,是目前公认的导致心血管疾病的独立危险因素,其影响机制是多方面的:血清中 Hcy 升高可促进微血管平滑肌细胞增殖,导致血管硬化;血清中 Hcy 升高后,导致血液中产生过氧化物、羟自由基等,损伤血管内皮细胞,导致血管出现栓塞;高浓度 Hcy 可抑制细胞产生对血管具有保护作用的谷胱甘肽;从而加速了对血管的破坏^[18,19]。VEGF 又称为血管调理素,可增强血管通透性,肾组织中的 VEGF 经肾小球产生,低水平的 VEGF 具有促进血管形成以及促进内皮生长的能力^[20]。本次研究结果显示,VEGF 为微血管病变的危险

因素,提示 VEGF 参与了微血管病变的发病过程,因此降低 T2DM 患者中 VEGF 水平的表达有助于预防及抑制糖尿病微血管病变的进展。

综上所述,T2DM 微血管病变患者的 TG、LDL、HbA1C、CysC、Hcy、VEGF 的水平相对更高,病程、CysC、Hcy、VEGF 为微血管病变的危险因素,对其水平的检测有助于早期 T2DM 微血管病变诊断及治疗。但 CysC、Hcy、VEGF 三个因素之间是否存在协同作用尚不明确,还需进一步研究。

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