

• 临床研究 •

血红蛋白糖化指数与2型糖尿病患者颈动脉内膜中层厚度的相关性研究

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[摘要] 目的: 探讨血红蛋白糖化指数(hemoglobin glycation index, HGI)与2型糖尿病(type 2 diabetes mellitus, T2DM)患者颈动脉内膜中层厚度(carotid intima-media thickness, cIMT)的关系。方法: 选取在扬州大学医学院附属盐城市妇幼保健院住院的T2DM患者302例, 检测患者cIMT、空腹血糖(fasting plasma glucose, FPG)、糖化血红蛋白(glycated hemoglobin A1c, HbA1c)水平。根据HbA1c和FPG计算HGI, 高HGI定义为HGI \geq 0, 低HGI定义为HGI $<$ 0。观察患者cIMT与HGI的关系。结果: 302例T2DM患者中cIMT增厚者140例(46.4%)。cIMT增厚组高HGI比例较cIMT正常组高(36.4% vs. 22.8%, $P < 0.05$), 病程、吸烟比例、高血压比例、收缩压(systolic blood pressure, SBP)、舒张压(diastolic blood pressure, DBP)、HbA1c、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)均较cIMT正常组高($P < 0.05$), 估算的肾小球滤过率(estimated glomerular filtration rate, eGFR)低于cIMT正常组($P < 0.05$)。HbA1c、HGI与cIMT呈正相关($r=0.257, 0.399, P < 0.05$), Logistic回归分析显示HGI及HbA1c均增加cIMT增厚的风险[OR=1.511(95%CI: 1.237~1.846), OR=1.287(95%CI: 1.053~1.571)]。结论: T2DM患者动脉粥样硬化患病率较高, HGI可能是HbA1c以外的T2DM患者动脉粥样硬化风险的新指标。

[关键词] 2型糖尿病; 血红蛋白糖化指数; 糖化血红蛋白; 颈动脉内膜中层厚度; 动脉粥样硬化

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Study on the correlation between hemoglobin glycation index and carotid intima-media thickness in patients with type 2 diabetes

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[Abstract] **Objective:** To explore the relationship between hemoglobin glycation index (HGI) and carotid intima-media thickness (cIMT) in patients with type 2 diabetes mellitus (T2DM). **Methods:** A total of 302 T2DM patients admitted to the Affiliated Yancheng Maternity and Child Health Hospital of Yangzhou University Medical School were enrolled. The clinical parameters including cIMT, fasting plasma glucose (FPG), and glycated hemoglobin A1c (HbA1c) were measured. HGI was calculated based on HbA1c and FPG, with high HGI defined as HGI \geq 0 and low HGI defined as HGI $<$ 0. The relationship between cIMT and HGI was observed. **Results:** Among the 302 patients with T2DM, 140 cases (46.4%) had thickened cIMT. The proportion of high HGI in the cIMT thickening group was higher than that in the normal cIMT group (36.4% vs. 22.8%, $P < 0.05$). The cIMT thickening group also had longer duration of diabetes, higher smoking rate, hypertension rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), HbA1c, and low-density lipoprotein cholesterol (LDL-C) levels compared to the normal cIMT group ($P < 0.05$). The estimated glomerular filtration rate (eGFR) was lower in the cIMT thickening group ($P < 0.05$). HbA1c and HGI were positively correlated with cIMT ($r=0.257, 0.399$,

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$P < 0.05$). Logistic regression analysis showed that both HGI and HbA1c increased the risk of cIMT thickening [OR = 1.511 (95% CI: 1.237-1.846), OR = 1.287 (95% CI: 1.053-1.571)]. **Conclusion:** The prevalence of atherosclerosis is high in patients with T2DM, and HGI may be a new indicator of atherosclerosis risk in T2DM patients, beyond HbA1c.

[**Key words**] type 2 diabetes mellitus; hemoglobin glycosylation index; glycosylated hemoglobin A1c; carotid intima-media thickness; atherosclerosis

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糖化血红蛋白(glycosylated hemoglobin A1c, HbA1c)是临床评估血糖控制的金标准^[1],反映近2~3个月的血糖平均控制水平。HbA1c升高与糖尿病慢性并发症如糖尿病肾病、糖尿病视网膜病变以及糖尿病大血管并发症均密切相关^[2-3]。但由于葡萄糖代谢和血红蛋白糖化率在个体间存在一定差异,会导致平均血糖水平相似的患者HbA1c数值存在变异,有研究发现平均血糖水平不能解释HbA1c约20%的变化^[4]。为克服这一问题,Hempe等^[5]提出应用血红蛋白糖化指数(hemoglobin glycation index, HGI)以量化HbA1c与平均血糖水平之间的差异。HGI反映了HbA1c实测值和预测值之间的差异,McCarter等^[6]发现高HGI患者视网膜病变和肾病风险成倍增加;但HGI水平和糖尿病大血管病相关性研究较少,Ahn等^[7]研究发现高HGI是心血管疾病的独立危险因素。颈动脉内膜中层厚度(carotid intima-media thickness, cIMT)可以反映早期全身性动脉粥样硬化的发生^[8],因此本研究通过分析HGI与cIMT之间关系,旨在为糖尿病患者血糖控制及并发症评估提供新的参考依据。

1 对象和方法

1.1 对象

回顾性收集2021年1月—2022年12月在扬州大学医学院附属盐城市妇幼保健院综合内科住院的2型糖尿病(type 2 diabetes mellitus, T2DM)患者302例(男113例,女189例),平均年龄(53.8±12.5)岁。依据《中国老年高血压管理指南》^[9]中的标准将cIMT≥0.9 mm诊断为内膜增厚,纳入cIMT增厚组,将cIMT<0.9 mm的患者纳入cIMT正常组。研究对象纳入标准:T2DM诊断依据《中国2型糖尿病防治指南(2020年版)》标准;排除标准:合并有糖尿病急性并发症如糖尿病酮症酸中毒、高血糖高渗综合征;严重肝肾功能不全;心力衰竭;血液系统疾病;与出血有关的消化道疾病;合并其他内分泌疾病如

甲状腺、垂体性疾病、库欣综合征等;既往有使用糖皮质激素史;合并感染。本研究经扬州大学医学院附属盐城市妇幼保健院医学伦理委员会批准(伦理号:2024-LW-011),并知情同意。

1.2 方法

所有患者均至少禁食8 h后清晨空腹测量身高、体重、收缩压(systolic blood pressure, SBP)、舒张压(diastolic blood pressure, DBP)。并抽取静脉血,采用上海惠中生物科技有限公司糖化血红蛋白测定试剂盒(高效液相色谱法)检测HbA1c。采用Roche Cobas c702生化分析仪检测空腹血糖(fasting plasma glucose, FPG)、总胆固醇(total cholesterol, TC)、甘油三酯(triglyceride, TG)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)和高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)、血清肌酐(creatinine, Cr)。cIMT测量:采用飞利浦EPIQ5彩超仪,探头频率为7.5 MHz,测量入选患者双侧颈动脉窦、颈总动脉远端距分叉处10 mm、颈内动脉起始端10 mm,共6处cIMT值,取其平均值^[10]。并根据MDRD简化公式计算估算的肾小球滤过率(estimated glomerular filtration rate, eGFR),计算公式: $186 \times \text{血Cr} - 1.154 \times \text{年龄} - 0.203 \times (0.742 \text{者为女性})$;体重指数(body mass index, BMI)计算公式如下: $\text{BMI} = \text{体重}(\text{kg}) / \text{身高}^2(\text{m}^2)$;参照《中国成人超重和肥胖症预防控制指南》的诊断标准,BMI≥28 kg/m²为肥胖^[11]。HGI计算方法^[12]:根据HbA1c和FPG做线性回归分析,建立回归方程:预测HbA1c=5.12+0.37×FPG, $R^2=0.52$, HGI=实际HbA1c-预测HbA1c,高HGI水平定义为HGI≥0,低HGI定义为HGI<0。

1.3 统计学方法

统计学处理采用SPSS 22.0软件,正态分布计量资料采用均数±标准差($\bar{x} \pm s$),两组间比较采用两独立样本t检验;计数资料以例数(构成比)[$n(\%)$]表示,采用 χ^2 检验。双变量采用Spearman相关性分析;采用二元Logistic回归分析cIMT增厚的影响因

素。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者一般临床资料和实验室指标的单因素比较

cIMT正常组162例(53.6%), cIMT增厚组140例(46.4%)。两组患者性别、年龄、BMI、肥胖比例、FPG、TC、TG、HDL-C水平差异无统计学意义($P > 0.05$); cIMT增厚组糖尿病病程、SBP、DBP、HbA1c、LDL-C较cIMT正常组高($P < 0.05$), eGFR较正常组低($P < 0.05$); cIMT增厚组中吸烟比例、高血压比例、高HGI比例均较cIMT正常组高($P < 0.05$, 表1)。

2.2 指标相关性分析

HbA1c与FPG的相关性分析结果显示, HbA1c

与FPG呈显著正相关($r=0.72, P < 0.01$), 根据HbA1c和FPG做线性回归分析, 得到回归方程: 预测HbA1c= $5.12+0.37 \times \text{FPG}$, $R^2=0.52$ 。

cIMT厚度与各临床指标的双变量相关性分析结果显示, cIMT厚度与糖尿病病程、高血压、SBP、HbA1c、高HGI呈正相关($P < 0.05$, 表2)。

2.3 cIMT增厚相关危险因素的二元Logistic分析

以cIMT是否增厚为因变量, 根据单因素分析结果, 以糖尿病病程、是否吸烟、是否伴有高血压、SBP、DBP、eGFR、HbA1c、HGI及LDL-C为自变量, 进行二元Logistic分析, 发现糖尿病病程长、患有高血压、高SBP、高HbA1c、高HGI增加cIMT增厚的风险; 其中, 高HGI相比HbA1c水平增高, 其出现cIMT增厚的相对风险更高[OR=1.511(95% CI: 1.237~1.846) vs. OR=1.287(95% CI: 1.053~1.571), 表3]。

表1 两组一般临床资料和实验室指标的比较

Table 1 Comparison of general clinical data and laboratory indexes between cIMT normal group and thickening group

Group	Number (Male/Female)	Age (years, $\bar{x} \pm s$)	Duration of diabetes (years, $\bar{x} \pm s$)	BMI ($\text{kg}/\text{m}^2, \bar{x} \pm s$)	Obesity [$n(\%)$]	Smoking [$n(\%)$]
Normal cIMT group	162(69/93)	52.8 \pm 10.8	8.2 \pm 1.9	22.9 \pm 5.3	44(27.2)	29(17.9)
Thickening cIMT group	140(44/96)	54.9 \pm 14.1	9.7 \pm 2.3*	23.8 \pm 4.9	32(22.9)	41(29.3)*
Group	Hypertension [$n(\%)$]	SBP (mmHg, $\bar{x} \pm s$)	DBP (mmHg, $\bar{x} \pm s$)	eGFR [$\text{mL}/(\text{min} \cdot 1.73\text{m}^2), \bar{x} \pm s$]	FPG (mmol/L, $\bar{x} \pm s$)	
Normal cIMT group	50(30.8)	138.9 \pm 11.3	81.3 \pm 8.8	108.5 \pm 12.9	8.2 \pm 2.8	
Thickening cIMT group	64(45.7)*	145.2 \pm 10.2**	84.2 \pm 15.2*	92.5 \pm 10.2**	8.6 \pm 3.3	
Group	HbA1c (%, $\bar{x} \pm s$)	High HGI [$n(\%)$]	TC (mmol/L, $\bar{x} \pm s$)	TG (mmol/L, $\bar{x} \pm s$)	LDL-C (mmol/L, $\bar{x} \pm s$)	HDL-C (mmol/L, $\bar{x} \pm s$)
Normal cIMT group	7.9 \pm 1.4	31(22.8)	4.46 \pm 1.24	1.69 \pm 0.66	3.12 \pm 0.84	1.23 \pm 0.22
Thickening cIMT group	8.4 \pm 2.7*	51(36.4)*	4.71 \pm 1.61	1.81 \pm 0.61	3.39 \pm 0.58**	1.28 \pm 0.38

Compared with the normal cIMT group, * $P < 0.05$, ** $P < 0.01$.

表2 cIMT与各指标间的双变量相关分析

Table 2 Bivariate correlation analysis between cIMT and each index

Item	Duration of diabetes	Smoking	Hypertension	SBP	DBP	eGFR	HbA1c	High HGI	LDL-C
r	0.223	0.346	0.389	0.297	0.305	0.329	0.257	0.399	0.291
P	<0.001	0.082	<0.001	<0.001	0.068	0.074	0.041	0.021	0.069

表3 cIMT增厚危险因素的多因素二元Logistic逐步回归分析

Table 3 Multivariable binary logistic stepwise regression analysis for the risk factors of cIMT thickening

Variable	β	SE	Wald χ^2	P	OR	95%CI
High HGI	0.413	0.200	16.395	<0.001	1.511	1.237-1.846
HbA1c	0.252	0.102	6.104	0.013	1.287	1.053-1.571
Hypertension	0.953	0.239	15.900	<0.001	2.593	1.623-4.143
SBP	0.198	0.032	38.258	<0.001	1.219	1.145-1.298
Duration of diabetes	0.418	0.194	4.643	0.031	1.519	1.034-2.222

3 讨论

动脉粥样硬化是T2DM患者心脑血管及周围血管硬化的共同病理基础,T2DM患者动脉粥样硬化的患病率较非糖尿病人群显著增高。本研究302例T2DM患者中140例cIMT增厚,提示接近半数患者有动脉粥样硬化。虽然HbA1c控制水平与糖尿病患者动脉粥样硬化发生发展的相关性已得到公认,但在Advance研究中,以HbA1c<6.5%为控制目标的T2DM患者主要心血管事件并无显著改善^[13],而Ziemann等^[14]研究也发现,HbA1c的控制水平与老年患者发生动脉硬化及心室僵硬度无关。此外一些临床研究也显示,部分患者HbA1c的水平可持续高于或低于其空腹血糖、平均血糖或连续血糖监测的水平^[15-17]。因此HbA1c作为平均血糖的标志物,其与实际平均血糖的差异及其用于糖尿病慢性并发症的预测存在一定局限性。

HbA1c并非血糖的直接测量,而是反映葡萄糖与血红蛋白结合的比例,其受到血糖浓度、红细胞膜通透性、遗传学、影响红细胞寿命的相关疾病及个体间异质性等多因素影响^[18]。本研究发现FPG仅能解释52%的HbA1c,提示尚有血糖浓度以外的因素可影响HbA1c,与陈晓正等^[19]研究相仿。然而有关HbA1c与实际血糖水平的差异尚无统一衡量标准,且这种差异与T2DM患者大血管并发症相关性的观察结果也不一致。Cosson等^[20]应用果糖胺通过回归方程计算HbA1c,并分析其与实测HbA1c之间的差异,称之为糖化间隙,但仅观察到高糖化间隙增加T2DM患者大量白蛋白尿的风险,而与大血管病变风险无关。而由HGI所评估出HbA1c的变异性,是个体对糖化的不同敏感性的体现^[21]。目前HGI与T2DM大血管并发症已有研究报道,且即使在非糖尿病人群中观察到HGI水平升高增加cIMT增厚的风险^[22]。本研究发现,高HGI是T2DM患者cIMT增厚的独立危险因素,且相对危险度高于HbA1c,提示高HGI增加T2DM患者动脉粥样硬化风险。台湾学者Cheng等^[12]发现高HGI可3倍增加T2DM患者发生冠状动脉多支血管病变的风险。Steen等^[23]研究结果亦显示HGI每增加1%,心血管死亡风险增加16%。虽然有研究发现糖化间隙和HGI在反映HbA1c与实际平均血糖之间的差异方面表现出高度一致性^[24-25],但两者与T2DM患者大血管病变之间相关性的研究结果却不一致。果糖胺是细胞外蛋白质与葡萄糖发生非酶促反应的产物,

而HbA1c是红细胞内蛋白与葡萄糖发生非酶促反应的产物,研究表明细胞内蛋白质更高程度的非酶糖化可能在与高血糖相关的大血管并发症中发挥更重要的致病作用。因此细胞内外蛋白质分子水平间的差异可能是导致糖化间隙和HGI与大血管并发症相关性研究结果不一致的原因之一。此外,越来越多的证据表明,晚期糖基化终末产物(advanced glycation end product, AGE)普遍存在于糖尿病患者的循环系统中,通过多种机制促进动脉粥样硬化的发生发展^[26]。而高水平的HGI被认为是一种糖代谢表型,其特征是对蛋白糖基化的敏感性增加,它和AGE的浓度呈正相关,可反映AGE组织积累水平^[27],因此能更直接反映AGE对糖尿病患者靶器官的损害风险。

目前研究已发现HGI与T2DM周围血管病变、心血管病变及心血管死亡风险的相关性,本研究也观察到高HGI与cIMT增厚的相关性,因此推测HbA1c与实际血糖的差异可能参与了T2DM大血管病变的发生发展,且与HbA1c相比,高HGI与大血管病变风险的相关性更强。Rhee等^[28]研究显示无论基线HbA1c水平如何,HGI升高超过4年,会显著加重发生冠状动脉钙化的风险。另有研究发现,HGI是T2DM合并冠心病(coronary heart disease, CHD)发生的独立危险因素,其对T2DM患者合并CHD的预测敏感度为68.09%,特异度为89.8%,相比HbA1c,HGI在评估T2DM患者合并CHD风险方面具有良好的诊断效能^[29]。还有研究发现,即使患者通过HbA1c评估的血糖水平相似,但患者之间发生大血管并发症的风险也不同,可以推测,高HGI与不依赖高血糖的全身动脉硬化的发生有关^[30]。

综上所述,导致动脉粥样硬化的危险因素众多,而T2DM是最为重要的病因之一。HbA1c作为评估T2DM患者血糖控制水平及慢性并发症风险的重要指标,有一定的局限性;而HGI可能亦是预测T2DM大血管病变的重要指标,是对HbA1c的进一步补充,对HGI更加全面的评估有利于T2DM大血管病变的早期预防和诊治。本研究作为横断面研究,也有一些不足之处,首先样本量较少,且系回顾性研究,研究结论尚需前瞻性研究进一步证实。其次,本研究未分析治疗方案可能对动脉粥样硬化的影响,尤其是他汀类降脂药和抗凝药物以及GLP-1受体激动剂或SGLT-2抑制剂使用的情况,在后续研究中也需进一步分析以更好验证本研究的结果。

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Conflict of Interests:

The authors declare no competing interests.

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张成洲负责文章整体构思与设计,主导资料收集与分析,论文初稿的撰写,论文的审阅和修订。陈健、任明慧、李雅洁负责调查研究,资料搜集与分析,论文的审阅和修订,为本文提供了丰富的基础数据支持。李文和、徐宽枫负责文章整理结构设计、数据管理和维护,数据的统计和分析,论文的审阅和修订。孟民负责文章整体构思与设计,研究方法制定,监督和指导,确保研究的准确性和深度。崔岱负责文章整体构思与设计,提供资源,对研究过程监督和指导,论文的审阅和修订,促进团队成员之间的沟通与协作。

Author's Contributions:

ZHANG Chengzhou was responsible for conceptualization, data curation, formal analysis, writing-original draft, writing-review and editing. CHEN Jian, REN Minghui, LI Yajie were responsible for investigation, data curation, writing-review and editing. LI Wenhe, XU Kuanfeng were responsible for conceptualization, data curation, formal analysis, writing-review and editing. MENG Min was responsible for conceptualization, methodology, supervision. CUI Dai was responsible for conceptualization, resources, supervision, writing-review and editing, communication and collaboration.

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