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2 型糖尿病足溃疡合并营养不良患者血清 Tol 样受体 9、糖化血红蛋白、25 羟维生素 D 检测的临床意义 *

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摘要 目的:检测 2 型糖尿病足溃疡合并营养不良患者血清 Tol 样受体 9(TLR9)、糖化血红蛋白(HbA1c)、25 羟维生素 D[25-(OH)D₃]的水平,并分析其临床意义。**方法:**选择 2018 年 3 月~2019 年 3 月我院收治的 2 型糖尿病足溃疡患者 81 例,根据预后营养指数(PNI)对患者营养状况进行评估并分组,PNI≤ 50 患者作为营养不良组 27 例,PNI>50 患者作为营养正常组 54 例,检测并比较两组营养指标、体重指数(BMI)、PNI 值、血糖、血脂、TLR9、HbA1c、25-(OH)D₃。**结果:**营养不良组患者 PNI 值、BMI、血清总蛋白(TP)、血清白蛋白(ALB)、血清前白蛋白(PA)显著低于营养正常组($P<0.05$),而营养不良组患者空腹血糖(FBG)、餐后 2 h 血糖(PBG)显著高于营养正常组($P<0.05$)。两组患者总胆固醇(TC)、三酰甘油(TG)水平无显著差异($P>0.05$),营养不良组患者血清 TLR9、HbA1c 水平显著高于营养正常组($P<0.05$),而 25-(OH)D₃ 水平显著低于营养正常组($P<0.05$)。血清 TLR9、HbA1c 与 PNI 值、BMI、TP、ALB、PA 均呈显著负相关关系($P<0.05$),而与 FBG、PBG 呈显著正相关关系($P<0.05$);血清 25-(OH)D₃ 与 PNI 值、BMI、TP、ALB、PA 均呈显著正相关关系($P<0.05$),而与 FBG、PBG 呈显著负相关关系($P<0.05$)。**结论:**2 型糖尿病足溃疡合并营养不良患者血清 TLR9、HbA1c 及 25-(OH)D₃ 水平与机体营养状况及血糖控制密切相关,有望成为患者疾病监测及营养风险评估的潜在指标。

关键词:2 型糖尿病足溃疡;营养不良;Tol 样受体 9;糖化血红蛋白;25 羟维生素 D

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Clinical Significance of Serum Tol Receptor 9, Glycosylated Hemoglobin and 25 Hydroxyvitamin D in Patients with Type 2 Diabetic Foot Ulcer Complicated with Malnutrition*

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ABSTRACT Objective: To detect the tol receptor 9 (TLR9), glycosylated hemoglobin (HbA1c) and 25 hydroxyvitamin D [25-(OH)D₃] levels in patients with type 2 diabetic foot ulcer complicated with malnutrition, and to analyze their clinical significance. **Methods:** 81 patients with type 2 diabetic foot ulcer who were admitted to our hospital from March 2018 to March 2019 were selected. The nutritional status of the patients was evaluated and grouped according to the prognostic nutritional index (PNI). 27 patients with PNI≤ 50 were treated as malnutrition group, and 54 patients with PNI>50 were treated as normal nutrition group. Nutritional indicators, body mass index (BMI), PNI, blood glucose, blood lipids, TLR9, HbA1c, 25-(OH)D₃ were measured and compared between the two groups. **Results:** PNI value, BMI, serum total protein (TP), serum albumin (ALB) and serum prealbumin (PA) in the malnutrition group were significantly lower than those in the normal nutrition group ($P<0.05$). Fasting blood glucose (FBG) and 2 h postprandial blood glucose (PBG) in the malnutrition group were significantly higher than those in the normal nutrition group ($P<0.05$). There were no significant differences in total cholesterol (TC) and triacylglycerol (TG) levels between the two groups ($P>0.05$). Serum TLR9 and HbA1c levels in the malnutrition group were significantly higher than those in the normal nutrition group ($P<0.05$), while the 25-(OH)D₃ level was significantly lower than that in the normal nutrition group ($P<0.05$). Serum TLR9 and HbA1c were significantly negatively correlated with PNI, BMI, TP, ALB and PA ($P<0.05$), while serum FBG and PBG were significantly positively correlated ($P<0.05$). Serum 25-(OH)D₃ was significantly positively correlated with PNI, BMI, TP, ALB and PA ($P<0.05$), while significantly negatively correlated with FBG and PBG ($P<0.05$). **Conclusion:** Serum TLR9, HbA1c and 25-(OH)D₃ levels in patients with type 2 diabetic foot ulcer complicated with malnutrition are closely related to nutritional status and blood glucose control, and which are expected to be potential indicators for disease monitoring and nutritional risk assessment in patients.

Key words: Type 2 diabetic foot ulcer; Malnutrition; Tol receptor 9; Glycosylated hemoglobin; 25 hydroxyvitamin D

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前言

糖尿病足是2型糖尿病患者慢性并发症之一,它是导致患者截肢的主要原因,不仅给患者身心健康带来严重影响,同时也给个人家庭以及社会带来了沉重的经济负担^[1-3]。糖尿病足形成的主要原因为糖尿病血管病变、神经病变以及感染,加上2型糖尿病患者机体的高糖环境,导致某些细胞因子以及生长因子水平的改变,而这种改变严重影响伤口的愈合^[4,5]。此外,2型糖尿病患者免疫系统以及机体代谢系统的紊乱,且多合并营养不良等,导致伤口处炎症期的延长以及伤口感染不能得到有效的控制而长期无法愈合,最终形成糖尿病足^[6]。血清 Tol 样受体9(TLR9)属于I型跨膜受体,可诱导趋化因子、促炎细胞因子的分泌,而TLR9的促炎症性质与糖尿病足疾病发展有关^[7]。糖化血红蛋白(HbA1c)是反映血糖控制的有效指标,而长期的高血糖易增加糖尿病足的发生风险^[8]。25羟维生素D[25-(OH)D₃]是维生素D在肝脏中经过羟基化作用转化而成,参与着糖尿病足的发病过程,并可调控机体氧化损伤、炎症等基因的表达^[9]。故本研究探讨2型糖尿病足溃疡合并营养不良患者血清TLR9、HbA1c、[25-(OH)D₃]检测的临床意义,为该患者的营养风险评估提供一定的参考依据,现报道如下:

1 资料与方法

1.1 临床资料

选择2018年3月~2019年3月我院收治的2型糖尿病足溃疡患者81例作为研究对象,其中男性患者57例、女性患者24例,年龄43~68岁,平均年龄(55.83±7.21)岁;Wagner分级2级51例、3级30例;平均溃疡面积(14.38±3.13)cm²,平均溃疡深度(3.16±1.10)cm。纳入标准:①所有患者均符合WHO制定的有关糖尿病的诊断标准^[10],足部溃疡符合"中国2型糖尿病防治指南(十三)--糖尿病足的诊治"的有关规定^[11];②因2

型糖尿病引发的慢性病理性足部皮肤溃疡;③溃疡部位有充分血液供应[踝肱指数(ABI)为0.8~1.2];④Wagner分级标准2~3级;⑤年龄39~71岁。排除标准:①皮肤溃疡或溃疡处出现恶性病变者;②近期接受激素、免疫抑制剂、放射性治疗等患者;③合并心肝肾功能严重异常者。根据预后营养指数(PNI)^[12]对患者营养状况进行评估并分组,PNI=ALB(g/L)+5×TLC(10⁹/L),其中ALB为血清白蛋白值,TLC为外周血淋巴细胞总数。将PNI≤50患者作为营养不良组,PNI>50患者作为营养正常组,其中营养不良组患者27例,营养正常组患者54例。

1.2 方法

测定患者清晨排便后体重及身高,并计算患者体重指数(BMI);抽取患者清晨空腹静脉,分别检测患者血清总蛋白(TP)、ALB、前白蛋白(PA),同时检测患者空腹血糖(FBG)、餐后2h血糖(PBG)、总胆固醇(TC)、三酰甘油(TG)。采用酶联免疫吸附法(ELISA)检测患者血清TLR9浓度,采用伯乐VARIANT II糖化血红蛋白测定仪及其配套试剂检测患者血清HbA1c水平,采用罗氏Cobas e170电化学发光免疫分析仪及其配套试剂检测血清25-(OH)D₃水平。

1.3 统计学分析

采用统计学软件SPSS 22.0,计量资料以($\bar{x} \pm s$)表示并应用t检验;计数资料以百分数形式表示并采用 χ^2 检验,采用Pearson相关性分析各指标之间的相关性,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组临床资料比较

营养不良组与营养正常组患者性别、年龄、Wagner分级、溃疡面积以及溃疡深度比较,差异均无统计学意义($P>0.05$),见表1。

表1 两组患者临床资料比较

Table 1 Comparison of clinical data between the two groups

Groups	n	Gender		Age(years)	Wagner classification		Ulcer area (cm ²)	Ulcer depth (cm)
		Male	Female		2 grade	3 grade		
Malnutrition group	27	20	7	56.32±8.31	15	12	15.13±3.52	3.31±1.25
Normal nutrition group	54	37	17	54.89±7.03	36	18	14.01±2.97	3.04±0.98
t/ χ^2	-	0.266		0.812	0.953		1.503	1.064
P	-	0.606		0.420	0.329		0.137	0.291

2.2 两组患者营养指标、BMI和PNI值比较

正常组($P<0.05$),见表2。

营养不良组患者PNI值、BMI、TP、ALB、PA显著低于营养

表2 两组患者营养指标、BMI和PNI值比较($\bar{x} \pm s$)

Table 2 Comparison of nutritional indicators, BMI and PNI value between the two groups($\bar{x} \pm s$)

Groups	n	PNI value	BMI(kg/m ²)	TP(g/L)	ALB(g/L)	PA(mg/L)
Malnutrition group	27	43.72±5.33	21.84±2.17	59.81±5.48	30.19±4.88	181.93±12.84
Normal nutrition group	54	57.73±7.04	23.61±1.98	67.90±6.29	34.70±4.16	193.41±13.65
t	-	7.807	3.673	5.687	4.339	3.638
P	-	0.000	0.000	0.000	0.000	0.000

2.3 两组患者血糖、血脂指标比较

营养不良组患者 FBG、PBG 显著高于营养正常组 ($P<0.05$), 两组患者 TC、TG 水平无显著差异 ($P>0.05$), 见表 3。

表 3 两组患者血糖、血脂指标比较($\bar{x} \pm s$)

Table 3 Comparison of blood glucose and blood lipid indicators between the two groups($\bar{x} \pm s$)

Groups	n	FBG(mmol/L)	PBG(mmol/L)	TC(mmol/L)	TG(mmol/L)
Malnutrition group	27	8.71± 1.33	16.72± 2.26	4.81± 1.02	1.83± 0.79
Normal nutrition group	54	7.90± 1.54	15.17± 2.10	4.68± 1.21	1.76± 0.85
t	-	2.331	3.053	0.479	0.358
P	-	0.022	0.003	0.633	0.722

2.4 两组患者血清 TLR9、HbA1c、25-(OH)D₃ 水平比较

营养不良组患者血清 TLR9、HbA1c 水平显著高于营养正

常组 ($P<0.05$), 而 25-(OH)D₃ 水平显著低于营养正常组 ($P<0.05$), 见表 4。

表 4 两组患者血清 TLR9、HbA1c、25-(OH)D₃ 水平比较($\bar{x} \pm s$)

Table 4 Comparison of serum TLR9, HbA1c, 25- (OH) D₃ levels between the two groups($\bar{x} \pm s$)

Groups	n	TLR9(ng/mL)	HbA1c(%)	25-(OH)D ₃ ng/mL)
Malnutrition group	27	5.74± 1.21	9.57± 1.14	8.96± 2.01
Normal nutrition group	54	4.28± 1.03	8.39± 0.93	14.63± 1.78
t	-	5.670	4.987	12.941
P	-	0.000	0.000	0.000

2.5 相关性分析

血清 TLR9、HbA1c 与 PNI 值、BMI、TP、ALB、PA 均呈显著负相关关系 ($P<0.05$), 而与 FBG、PBG 呈显著正相关关系 ($P<0.05$); 血清 25-(OH)D₃ 与 PNI 值、BMI、TP、ALB、PA 均呈

显著正相关关系 ($P<0.05$), 而与 FBG、PBG 呈显著负相关关系 ($P<0.05$), 血清 TLR9、HbA1c、25-(OH)D₃ 与 TC、TG 未见相关性 ($P>0.05$), 见表 5。

表 5 血清 TLR9、HbA1c、25-(OH)D₃ 与营养指标、PNI 值、BMI、血糖、血脂水平的相关性分析

Table 5 Correlation Analysis of serum TLR9, HbA1c, 25 - (OH) D₃ and nutritional indicators, PNI value, BMI, blood glucose, blood lipid levels

Indicators	TLR9		HbA1c		25-(OH)D ₃	
	r	P	r	P	r	P
PNI value	-0.568	0.000	-0.619	0.000	0.576	0.000
BMI	-0.614	0.000	-0.706	0.000	0.561	0.000
TP	-0.736	0.000	-0.631	0.000	0.685	0.000
ALB	-0.505	0.000	-0.577	0.000	0.701	0.000
PA	-0.621	0.000	-0.597	0.000	0.569	0.000
FBG	0.726	0.000	0.648	0.000	-0.657	0.000
PBG	0.641	0.000	0.655	0.000	-0.704	0.000
TC	0.085	0.563	0.038	0.695	-0.097	0.476
TG	0.032	0.710	0.047	0.627	-0.122	0.398

3 讨论

近些年来, 受人们生活方式以及饮食结构的变化的影响, 糖尿病发病率逐年上升^[13]。足溃疡是糖尿病足常见的并发症之一, 其治疗难度大、患者致残率以及致死率较高^[14-16]。相关的学者研究显示^[17], 充足的营养是创面愈合的重要条件之一, 细胞

的移行、增殖、蛋白质的合成等均有赖于机体营养充足, 当机体营养不良时, 可导致皮肤变薄, 极容易形成溃疡, 引起促生长因子的缺乏, 使创面长时间不能愈合, 并增加了细菌感染的风险。因此糖尿病足溃疡患者合并营养不良发生率较高, 且研究认为机体营养不良与糖尿病足溃疡疾病严重程度密切相关。

TLR9 属于是天然免疫系统识别病原微生物以及内源性危

险信号的重要受体之一,不仅可诱导机体防御所必须的炎症反应,同时也可启动机体适应性免疫^[18,19]。近年来学者研究认为^[20],TLR9 其促炎症性质在糖尿病足溃疡的形成机制中发挥着重要作用。HbA1c 可有效反映取血前 4~12 周血糖水平,较 FBG 可更为全面地反映患者血糖控制情况^[21]。学者研究显示^[22],HbA1c 与糖尿病足溃疡疾病的发生发展有关,认为糖尿病足溃疡发生的风险、疾病的进展与长期的血糖状态有关,长期高血糖造成神经微血管病变,导致大量糖基化终末产物在血管壁的沉积,同时引起自由基的增多,血管内皮细胞功能障碍,从而引发糖尿病大血管及微血管病变。研究显示^[23,24],25-(OH)D₃ 可在胰岛 β 细胞内表达,从而有助于维持细胞内外钙离子浓度,维生素 D 缺乏将减弱糖负荷而引起胰岛素分泌不足,及时补充维生素 D 可有效恢复正常的胰岛素分泌,因此 25-(OH)D₃ 在糖尿病患者血糖维持过程中具有着重要作用。

PNI 通过反映机体营养以及免疫状态,从而预测手术风险、术后并发症以及远期不良事件发生风险^[25]。临床上常用 PNI 值对慢性疾病患者营养状况进行危险分层并指导患者的临床治疗^[26]。PNI 值由血清白蛋白以及淋巴细胞总数所组成,对营养状况的评估价值大于单一指标,从而可更准确的评估 2 型糖尿病患者的营养状况^[27]。本研究根据 PNI 值将患者分为营养不良组以及营养正常组,研究显示,营养不良组患者 PNI 值、BMI、TP、ALB、PA 显著低于营养正常组,营养不良组患者 FBG、PBG 显著高于营养正常组 ($P<0.05$)。营养不良组患者血清 TLR9、HbA1c 水平显著高于营养正常组 ($P<0.05$),而 25-(OH)D₃ 水平显著低于营养正常组 ($P<0.05$)。提示血清 TLR9、HbA1c、25-(OH)D₃ 水平与糖尿病足溃疡患者营养状况密切相关。分析其原因为 2 型糖尿病足溃疡患者血清 TLR9 可诱导炎症因子的释放,还可激活核转录因子- κ 、激活蛋白 1,加剧炎症级联反应,不利于营养物质吸收,营养不佳;长期 HbA1c 水平较高可引起神经髓鞘蛋白的糖基化,导致髓鞘及神经轴突变性,进一步导致神经营养障碍,机体营养不良^[28]。研究表明,25-(OH)D₃ 水平较低,导致巨噬细胞趋化及吞噬功能出现障碍,抗炎反应失衡,进一步损伤机体免疫反应^[29,30]。此外,TLR9、HbA1c 与患者营养状况指标、PNI 值、BMI 呈显著负相关关系,而与血糖呈显著正相关关系;25-(OH)D₃ 水平与患者营养状况指标、PNI 值、BMI 呈显著正相关关系,而与血糖水平呈显著负相关关系。提示 TLR9、HbA1c 高水平与机体高血糖状态有关,同时反映了患者营养不良风险的增加,而 25-(OH)D₃ 水平缺乏作为高血糖的危险因素之一,25-(OH)D₃ 水平低下将导致患者营养不良风险增加。表明 TLR9、HbA1c、25-(OH)D₃ 水平不仅与糖尿病足溃疡患者血糖控制状况有关,同时与患者营养不良状况有关,可有效预测患者疾病控制情况及营养不良发生风险,提示血糖的有效控制以及维生素 D 的及时补充,可能是有效改善糖尿病足溃疡患者营养不良的重要影响因素。

综上所述,2 型糖尿病足溃疡合并营养不良患者血清 TLR9、HbA1c 及 25-(OH)D₃ 水平与机体营养状况及血糖控制密切相关,有望成为患者疾病监测及营养风险评估的潜在指标。

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