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葛根素注射液对糖尿病大鼠牙周炎的治疗效果及血清 AGEs、炎症因子表达的影响 *

彭 博¹ 王 菲² 鲍庆红² 管丽敏² 吉玲玲^{2Δ}

(1 空军军医大学口腔医院牙周科 陕西 西安 710004; 2 西安交通大学口腔医院正颌科 陕西 西安 710004)

摘要 目的:分析葛根素注射液对糖尿病大鼠牙周炎的治疗效果及血清晚期糖基化终末产物(advanced glycosylation end products, AGEs)、炎症因子表达的影响。**方法:**随机选取 10 只大鼠作为正常对照组,另选 40 只建立糖尿病牙周炎大鼠,将建模成功的大鼠随机分成模型组、实验组和阳性组,每组 10 只。给药处理 6 周后,取血清检测 AGEs、白细胞介素-6(interleukin-6, IL-6)、IL-8 及肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)表达情况;取牙周组织观察压槽骨丧失程度。**结果:**与健康对照组相比,模型组大鼠胰岛素水平显著降低,血糖、AGEs、IL-6、IL-8 和 TNF- α 水平显著升高,压槽骨降低高度显著增大($P<0.05$)。与模型组相比,实验组和阳性组大鼠水平显著升高,血糖、AGEs、IL-6、IL-8 和 TNF- α 水平显著降低,压槽骨降低高度升高减小($P<0.05$)。**结论:**葛根素注射液可通过促进胰岛素表达,减少 AGEs 积聚,降低血糖及炎症因子 IL-6、IL-8、TNF- α 的表达抑制糖尿病大鼠牙周炎的发展。

关键词:葛根素注射液;糖尿病;牙周炎;炎症因子;晚期糖基化终末产物

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Effect of Puerarin Injection on Periodontitis and Expression of Serum Ages and Inflammatory Factors in Diabetic Rats*

PENG Bo¹, WANG Fei², BAO Qing-hong², GUAN Li-ming², JI Ling-ling^{2Δ}

(1 Department of Periodontology, Stomatological Hospital of Air Force Military Medical University, Xi'an, Shaanxi, 710004, China;

2 Department of Orthodontics, Hospital of Stomatology, Xi'an Jiaotong University, Xi'an, Shaanxi, 710004, China)

ABSTRACT Objective: To analyze the effect of Puerarin Injection on periodontitis and expression of serum ages and inflammatory factors in diabetic rats. **Methods:** Ten rats were randomly selected as the normal control group, and another 40 rats were established as diabetic periodontitis rats. The rats were randomly divided into model group, experimental group and positive group, with 10 rats in each group. After 6 weeks of treatment, serum was taken to detect the expression of ages, IL-6, IL-8 and TNF- α ; periodontal tissue was taken to observe the degree of alveolar bone loss. **Results:** Compared with the healthy control group, the insulin level of the model group was significantly decreased, the levels of blood glucose, ages, IL-6, IL-8 and TNF- α were significantly increased, and the height of alveolar bone reduction was significantly increased ($P<0.05$). Compared with the model group, the levels of blood glucose, ages, IL-6, IL-8 and TNF- α in the experimental group and positive group were significantly increased, and the height of alveolar bone was decreased ($P<0.05$). **Conclusion:** Puerarin injection can inhibit the development of periodontitis in diabetic rats by promoting the expression of insulin, reducing the accumulation of ages, reducing the expression of blood glucose and inflammatory factors IL-6, IL-8 and TNF- α .

Key words: Puerarin injection; Diabetes; Periodontitis; Inflammatory factors; Advanced glycation end products

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前言

糖尿病是一组以高血糖为特征的代谢性疾病,随着生活水平的不断提高,糖尿病的发病率呈逐年增加的趋势,目前全球有超过 1.7 亿人被诊断为糖尿病,据估计到 2030 年这一数字将达到 3.7 亿,我国有超过 2 亿糖尿病患者,严重影响患者的身心健康^[1-3]。牙周炎是由牙菌斑引起的牙周组织慢性感染性疾

病,被认为糖尿病的第 6 大并发症,与糖尿病之间存在双向的生物学联系^[4-6]。研究表明,糖尿病患者牙周病的发生率明显高于正常患者,且牙周病变进展速度和严重程度明显增大^[7-9]。血糖控制不理想的糖尿病患者往往会出现严重的牙周病变,可以说,牙周损害程度与患者糖尿病病情呈正相关关系。目前,临床上对糖尿病牙周炎的治疗尚没有有效的方法,抗生素治疗单纯的牙周炎不仅毒副作用比较大,而且易影响降糖药物的吸收与

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作者简介:彭博(1982-),男,硕士研究生,主治医师,研究方向:牙周病学,电话:15332337765, E-mail: pengbo0082@163.com

Δ 通讯作者:吉玲玲(1980-),女,硕士研究生,主治医师,研究方向:正颌牙周,电话:13571865568, E-mail: jilingling9803@126.com

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血糖控制,导致病情进一步恶化。实践证明,采用中药治疗,疗效确切,毒副作用较小,患者接受度比较高。

葛根素是葛根中提取出来的一种异黄酮类化合物^[10],研究显示,其可具有促进血液循环、改善胰岛素抵抗、降血糖、降血脂、清除氧自由基等作用^[11,12],广泛应用于肿瘤、肾病、心肌损伤、周围神经病变、糖尿病及并发症等治疗^[13-15]。葛根素对糖尿病牙周炎的治疗研究相对较少,本文就葛根素注射液对糖尿病大鼠牙周炎的治疗效果及血清 AGEs、炎症因子表达的影响进行分析,结果如下。

1 材料与方法

1.1 主要试剂和仪器

葛根素注射液天津药业集团新郑股份有限公司;链脲佐菌素购自上海沪峥生物科技有限公司;大鼠 IL-8、IL-6 ELISA 试剂盒购自上海纪宁实业有限公司;大鼠 TNF- α ELISA 试剂盒购自南京卡米洛生物工程有限公司;大鼠血清 AGEs ELISA 试剂盒购自上海江莱生物科技有限公司;血糖仪购自南京贝登医疗股份有限公司;酶标仪购自济南欧莱博科学仪器有限公司;光学显微镜购自日本 Olympus。

1.2 实验动物

SPF 级健康 SD 大鼠 50 只,体重 180~210 g,购自陕西省医学实验动物中心。将所有大鼠均饲养在温度 20℃~24℃,相对湿度为 40%~60%,每天光照 12 h,自由摄食和饮水,适应性喂养一周后开展相关实验。

1.3 动物模型的建立与分组

将 SD 大鼠随机分成对照组(10 只)和造模组(40 只)。造模组大鼠提前禁食禁水 12 h 后,经腹腔注射 2%链脲佐菌素 60 mg/kg 建立糖尿病大鼠模型^[16,17]。72 h 后,大鼠禁食禁水 12 h 后,按照 2 g/kg 灌胃 200 g/L 标准葡萄糖溶液,2 h 后取尾静脉血,将空腹血糖 ≥ 16.7 mmol/L 的大鼠为建模成功。1 周后,将大鼠麻醉后,使用 0.2 mm 的正畸结扎丝与丝线,对糖尿病大鼠上颌第一磨牙牙颈部结扎,术后给予大鼠高糖饮食。4 周后,随机选取 3 只大鼠,观察牙周,确认牙周炎模型建立成功。然后,随机选取 30 只建模成功大鼠,随机分成模型组、实验组和阳性组(n=10)。实验组于大鼠腹腔注射葛根素注射液 100 mg/(kg·d),

阳性组于大鼠腹腔注射二甲双胍 100 mg/(kg·d),健康对照组和模型组给予等量生理盐水注射,连续给药 6 周。

1.4 正常观察指标与评价方法

1.4.1 一般情况观察 治疗结束后,观察各组大鼠的饮食、饮水、牙龈红肿、牙龈充血等变化。

1.4.2 胰岛素、血糖测定 治疗结束后,取提前禁食 12 h 的大鼠尾静脉血,离心后取上清,采用 ELISA 试剂盒检测血清中胰岛素分泌水平,操作方法严格按照试剂盒说明书进行;采用血糖仪检测空腹血糖水平。

1.4.3 血清 AGEs 测定 采用 ELISA 试剂盒检测方法对各组大鼠血清中 AGEs 含量进行测定,操作严格按照试剂盒说明书进行。

1.4.4 血清炎症因子测定 采用 ELISA 试剂盒检测方法对血清中 IL-8、IL-6 和 TNF- α 含量进行测定,操作严格按照试剂盒说明书进行。

1.4.5 大鼠压槽吸收情况 末次给药后,断颈处死大鼠,并迅速取其上颌骨、上槽牙、牙组织及牙周组织,去除丝线,置于 4%多聚甲醛溶液中固定 24 h,将组织修整后留磨牙区段颌骨、牙周组织,颊舌向拍摄三维 CT 片,并对图片中大鼠牙槽骨高度降低程度进行测量,对牙槽骨吸收情况进行观察。

1.5 统计学分析

采用 SPSS 20.0,计量资料以($\bar{x} \pm s$)表示,以 t 检验作差异显著性分析。 $P < 0.05$ 为方差有统计学意义。

2 结果

2.1 一般情况观察

给药 6 周后,模型组大鼠出现多饮、多食、多尿、体重减轻等症状,大鼠牙龈组织红肿、充血,牙齿松动;与模型组相比,阳性组和实验组大鼠以上症状均有所减轻。

2.2 胰岛素、血糖测定

与健康对照组相比,模型组大鼠体内胰岛素水平显著降低,血糖水平显著升高(P 均 <0.05)。与模型组相比,实验组和阳性组大鼠胰岛素水平显著升高,血糖水平显著降低(P 均 <0.05)。实验组和阳性组大鼠胰岛素水平和血糖水平对比无差异($P > 0.05$),见表 1。

表 1 各组大鼠胰岛素及血糖比较(n=10, $\bar{x} \pm s$)

Table 1 Comparison of insulin and blood glucose of rats in each group (n=10, $\bar{x} \pm s$)

Groups	Insulin(mIU/mL)	Blood glucose(mmol/L)
Healthy control group	13.65 $\pm$ 0.49	5.29 $\pm$ 0.20
Model group	6.65 $\pm$ 0.39*	25.90 $\pm$ 0.63*
Experimental group	10.20 $\pm$ 0.70**	10.04 $\pm$ 0.58**
Positive group	9.87 $\pm$ 1.03**	9.69 $\pm$ 0.20**

Note: Compared with healthy control group, * $P < 0.05$; compared with model group, ** $P < 0.05$.

2.3 血清 AGEs 测定

与健康对照组相比,模型组大鼠血清 AGEs 表达水平显著升高,差异均有统计学意义($P < 0.05$)。与模型组相比,实验组和阳性组大鼠血清 AGEs 表达水平显著升高降低,差异均有统计学意义($P < 0.05$);实验组血清 AGEs 表达水平显著高于阳

性组($P < 0.05$),见表 2。

2.4 血清炎症因子测定

与健康对照组相比,模型组大鼠血清中 IL-6、IL-8 和 TNF- α 表达水平显著升高,差异均有统计学意义(P 均 <0.05)。与模型组相比,实验组和阳性组大鼠血清中 IL-6、IL-8 和 TNF- α 表

达水平显著降低,差异均有统计学意义(P 均 <0.05);与实验组相比,阳性组大鼠血清中 IL-6、IL-8 和 TNF- α 表达水平显著降低,差异均有统计学意义(P 均 <0.05),见表3。

表 2 各组大鼠血清 AGEs 比较($n=10$, $\bar{x} \pm s$)

Table 2 Comparison of rat serum AGEs in each group ($n=10$, $\bar{x} \pm s$)

Groups	Serum AGEs(ng/L)
Healthy control group	188.89 $\pm$ 3.00
Model group	539.33 $\pm$ 5.01*
Experimental group	261.80 $\pm$ 5.02**
Positive group	243.92 $\pm$ 6.62***

Note: Compared with healthy control group, * $P<0.05$; compared with model group, ** $P<0.05$, compared with experimental group, *** $P<0.05$.

表 3 各组大鼠血清炎症因子表达情况比较($n=10$, $\bar{x} \pm s$)

Table 3 Comparison of the expression of serum inflammatory factors in each group of rats ($n=10$, $\bar{x} \pm s$)

Groups	IL-6(ng/L)	IL-8(ng/L)	TNF- α (ng/L)
Healthy control group	148.75 $\pm$ 1.23	180.76 $\pm$ 4.20	59.86 $\pm$ 1.37
Model group	356.09 $\pm$ 1.81*	378.19 $\pm$ 2.77*	137.94 $\pm$ 1.70*
Experimental group	243.37 $\pm$ 1.80*	282.12 $\pm$ 2.98**	94.63 $\pm$ 2.12**
Positive group	236.82 $\pm$ 1.15***	268.62 $\pm$ 4.92***	92.83 $\pm$ 2.05***

Note: Compared with healthy control group, * $P<0.05$; compared with model group, ** $P<0.05$, compared with experimental group, *** $P<0.05$.

表 4 各组大鼠压槽骨降低高度比较($n=10$, $\bar{x} \pm s$)

Table 4 Comparison of the height reduction of indentation bone in each group of rats ($n=10$, $\bar{x} \pm s$)

Groups	Height reduction of indentation bone(mm)
Healthy control group	0.28 $\pm$ 0.02
Model group	1.59 $\pm$ 0.14*
Experimental group	1.17 $\pm$ 0.16**
Positive group	1.27 $\pm$ 0.05**

Note: Compared with healthy control group, * $P<0.05$; compared with model group, ** $P<0.05$.

炎相比,糖尿病牙周炎采用单一的方法难以控制,主要原因为糖尿病患者对抗生素耐受力较低,毒副作用比较大,而且采用抗生素治疗会影响降糖药物的吸收与血糖控制,导致病情进一步恶化^[24]。实践证明,采用中药治疗,疗效确切,毒副作用较小,患者接受度比较高。本研究观察了葛根素注射液对糖尿病大鼠牙周炎的治疗效果,结果显示葛根素注射液可明显改善牙龈红肿、出血情况,效果明显优于模型组。

晚期糖基化终末产物(AGEs)是体内蛋白质经非酶催化反应形成的结构稳定而不可逆的化合物^[25]。正常人体内 AGEs 表达水平随年龄增长而缓慢增加,糖尿病患者体内因长期高血糖导致糖基化反应及 AGEs 生成加速,而大量 AGEs 的过度积累是导致糖尿病慢性并发症的原因之一^[26-28]。孙文利^[29]表明,糖尿病患者血清 AGEs 水平均高于正常人,糖尿病肾病患者血清 AGEs 表达量明显高于糖尿病患者。郑琪等^[30]证明,糖尿病溃疡

2.5 大鼠压槽吸收情况

与健康对照组相比,模型组大鼠压槽骨降低高度显著增大,差异均有统计学意义($P<0.05$)。与模型组相比,实验组和阳性组大鼠压槽骨降低高度减小,差异均有统计学意义($P<0.05$),实验组和阳性组大鼠大鼠压槽骨降低高度无差异($P>0.05$),见表4。

3 讨论

糖尿病患者体内长期高糖状态可诱导氧化应激反应^[19,20],大量氧自由基的产生,不但可直接损伤牙周组织,还改变 NF- κ B、蛋白激酶 C(PKC)等信号传导途径引起 IL-6、ICAM-1 等炎症因子的表达,激活破骨细胞和胶原酶,破坏骨与牙周组织,因此抑制炎症反应可抑制牙槽骨吸收速度^[21-23]。与单纯牙周

足患者血清中 AGEs、IL-6 和 IL-8 等均高表达,经治疗后,患者血清中 AGEs、IL-6 和 IL-8 等表达均降低,创面愈合明显变好,均与本研究的结果类似。AGEs 是单核巨噬细胞的趋化物质,能刺激吞噬细胞释放炎症细胞因子 TNF- α 、IL-1 β 、IL-6 等炎症因子的产生,破坏牙周组织。Asadipooya K 等^[31]表明,糖尿病损害骨细胞代谢和功能,导致脆性骨折的风险增加。AGEs 与 AGEs 受体(RAGE)相互作用,对骨细胞代谢和 / 或功能改变有重要作用。AGE-RAGE 信号通路参与糖尿病并发症,包括糖尿病性骨病。

炎症是许多疾病的主要因素,糖尿病体内高血糖易导致牙周病原体诱导过度的免疫反应。IL-6 是一种来源广泛的多功能细胞因子,具有刺激破骨细胞生成,参与骨吸收的作用^[32]。研究表明,IL-6 在牙周炎、牙龈炎、糖尿病患者体内均高表达,抑制 IL-6 的表达,可缓解患者相关症状^[33]。IL-8 属于中性粒细胞趋化因子和破骨细胞活化因子,在糖尿病患者体内高表达,可通过趋化和活化中性粒细胞释放各种酶,吞噬、杀伤、消化微生物,造成组织病理学损伤和骨质吸收^[34]。TNF- α 作为一种具有炎症介导活性的细胞因子,与牙周疾病密切相关,同时在胰岛素抵抗的发生机制中发挥着重要作用。研究表明,牙周炎患者、糖尿病患者体内 TNF- α 均高表达,通过药物控制 TNF- α 表达水平,可缓解患者病症^[35]。

葛根素是葛根中提取出来的一种异黄酮类化合物,具有舒张血管、抗氧化、保护神经细胞及免疫调节等药理作用。由于葛根素的溶解度和生物利用度低、半衰期短,临床上多采用葛根素注射、葛根素滴眼液等。目前,葛根素已广泛应用心脑血管、周围神经病变、肿瘤和糖尿病等的治疗,研究证实,葛根素通过

抗氧化、抑制非酶糖基化、降血糖、抗炎等对糖尿病肾病、糖尿病足、骨质疏松等多种并发症具有良好的治疗作用。葛根素对牙周炎的治疗效果及机制研究相对较少,张黎等^[9]表明葛根素可能通过 IL-23/Th17 炎症轴上调 OPG 表达,下调 RANKL、RANK 蛋白表达,控制牙槽骨吸收,促进牙周炎大鼠牙槽骨的修复和重建。Turer 等^[10]表明葛根素对糖尿病和非糖尿病牙周病牙槽骨丢失和结缔组织破坏有一定的预防作用。Jun Li 等^[11]表明葛根素可促进人牙周膜干细胞的增殖和碱性磷酸酶活性,从而促进牙周膜干细胞的分子分化和成骨分化。谭佳玮等表明葛根素注射液对牙周炎有一定的治疗效果。与本研究结果一致,结果显示葛根素注射液可通过促进胰岛素表达,减少 AGEs 积聚,降低血糖及炎症因子 IL-6、IL-8、TNF- α 的表达抑制糖尿病大鼠牙周炎的发展。研究表明,葛根素因在糖尿病治疗中具有降血糖、抗炎、抗氧化、抑制非酶糖基化等作用,被广泛应用于糖尿病、糖尿病并发症及糖尿病合并肾病、心肌损伤等方面的治疗,但其在糖尿病牙周炎方面应用较少。本研究参考谭佳玮等^[39]研究,除了观察葛根素注射液对糖尿病牙周炎组织、AGEs 积聚、炎症因子的影响基础上进一步观察了其对大鼠血糖、胰岛素表达水平的影响,确定葛根素注射液可通过促进胰岛素表达,减少 AGEs 积聚,降低血糖及炎症因子 IL-6、IL-8、TNF- α 的表达抑制糖尿病大鼠牙周炎的发展。

综上,本研究为糖尿病牙周炎的治疗提供了一定的理论依据,但具体作用机制及临床使用过程的注意事项等还需要进一步研究和论证。

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