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龈沟液中骨硬化蛋白对慢性牙周炎患者疗效评价的临床价值 *

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摘要 目的:探讨龈沟液中骨硬化蛋白对慢性牙周炎疗效评价的临床价值。**方法**:选择 2013 年 1 月 -2017 年 12 月我院收治的 81 例慢性牙周炎患者作为观察组及同期 79 例牙周健康者为对照组,观察组患者给予基础治疗。观察和比较对照组和观察组治疗前及治疗后 1 个月、2 个月的牙周临床指标、龈沟液中的骨硬化蛋白水平,并分析牙周临床指标与龈沟液骨硬化蛋白水平的相关性。**结果**:治疗前,观察组的菌斑指数、出血指数、牙周探诊深度、附着丧失水平及龈沟液中骨硬化蛋白水平明显高于对照组;治疗后 1 个月、2 个月,观察组以上指标均明显低于治疗前,且治疗后 2 个月,观察组以上指标明显低于治疗后 1 个月,但附着丧失水平仍高于对照组 (P 均 <0.05),而两组的菌斑指数、出血指数、牙周探诊深度对比差异无统计学意义($P>0.05$)。龈沟液中骨硬化蛋白水平与菌斑指数、出血指数、牙周探诊深度、附着丧失水平呈高度正相关(r1=0.876,P1<0.001;r2=0.842,P1<0.00;r3=0.913,P1<0.001;r4=0.903,P1<0.001)。**结论**:慢性牙周炎患者龈沟液中骨硬化蛋白水平明显上调,并与与菌斑指数、出血指数、牙周探诊深度、附着丧失水平呈高度正相关,可作为慢性牙周炎疗效评价的参考指标。

关键词:龈沟液;骨硬化蛋白;慢性牙周炎;诊断;疗效评价

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Clinical Value of Osteoclast Protein in Gingival Crevicular Fluid for the Clinical Efficacy Evaluation of Patients with Chronic Periodontitis*

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ABSTRACT Objective: To investigate the clinical value of sclerosing protein in gingival crevicular fluid for the curative effect evaluation of chronic periodontitis. **Methods:** 81 patients with chronic periodontitis treated in our hospital from January 2013 to December 2017 were selected as the observation group, and 79 cases of periodontal health in the same period were selected as the control group. Patients in the observation group were treated by basic treatment. The clinical index of periodontal disease and the level of osteosclerin in gingival crevicular fluid before and after treatment were compared between two groups, and the correlation of periodontal clinical index with the level of sclerosing protein in gingival crevicular fluid was also analyzed. **Results:** Before treatment, the plaque index, bleeding index, depth of periodontal detection, loss of attachment and level of bone sclerosis protein in the gingival crevicular fluid of observation group were significantly higher than those in the control group. After 1 month and 2 months of treatment, the above index were significantly lower than those before treatment; and after 2 months of treatment, the index above in the observation group were significantly lower than those after 1 month of treatment. But the loss of attachment was still higher than that of the control group ($P < 0.05$), there was no significant difference in the plaque index, bleeding index, and depth of periodontal detection between the two groups ($P>0.05$). The level of sclerosing protein in gingival crevicular fluid was highly correlated with plaque index, bleeding index, periodontal detection depth and loss of attachment (r1=0.876, P1<0.001; r2=0.842, P1<0.00; r3=0.913, P1<0.001; r4=0.903, P1<0.001). **Conclusion:** The level of osteosclerin in gingival crevicular fluid is significantly up-regulated in patients with chronic periodontitis, it is highly correlated with plaque index, bleeding index, periodontal probing depth, and loss of attachment and can be used as reference indicators for the clinical efficacy evaluation.

Key words: Gingival crevicular fluid; Osteopetrosis protein; Chronic periodontitis; Diagnosis; Efficacy evaluation

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前言

慢性牙周炎的病因较为复杂,涉及宿主免疫反应、微生物菌群、炎症反应等。正常时,口腔内菌群与宿主间、菌群之间维持动态平衡[1]。若宿主免疫反应过度或不足或微生物与宿主间平衡打乱时,会造成不同程度的破坏牙周组织,引起慢性牙周炎。若此时慢性牙周炎未及时治疗,会有部分牙周炎向深部牙周组织发展,进一步破坏牙周膜、牙龈、牙骨质及牙槽骨[2]。

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骨硬化蛋白由骨细胞分泌,是 SOST 基因产物,与 DNA 蛋白家族相似,含一个胱氨酸结样结构[3]。骨硬化蛋白既往被认为是一种 BMP 拮抗蛋白,研究表明其是通过抑制 Wnt 信号活性发挥作用,作用机制与 BMP 拮抗蛋白不同[4-6]。Wnt 信号通路在骨质疏松症、骨形成、骨改建、骨折愈合中有关键作用,骨硬化蛋白可结合 Wnt 受体蛋白,阻挡 Wnt 相关蛋白与 Frizzle、LRP-5/6 复合体结合为三聚体复合物,导致 Wnt 不能被激活,表明骨细胞分泌的 DKK1 及骨硬化蛋白可作用于 Wnt 信号通路,抑制骨形成[7-10]。骨硬化蛋白在骨质疏松症、硬化性骨病、强直性脊柱炎、类风湿关节病、多发性骨髓炎中已成为关注热点,而其在慢性牙周炎中研究较少[11]。因此,本研究主要分析了龈沟液中骨硬化蛋白对慢性牙周炎患者的诊断及预后预测价值,以期为临床慢性牙周炎的诊断及预后判断提参考供依据。

1 资料与方法

1.1 一般资料

选择 2013 年 1 月至 2017 年 12 月收治的 81 例慢性牙周炎患者作为观察组,纳入标准:

符合美国牙周病分类研讨会的慢性牙周炎诊断标准(1999 年)[12];患者上、下颌磨牙数不低于 1 颗,余留自然牙超过 20 颗;牙周袋附着丧失不低于 3 mm,探诊深度超过 4 mm;6 个月内无非甾体抗炎药 / 抗生素 / 免疫抑制剂的药物治疗史,超过 6 个月未行牙周治疗。选择同期来我院体检的牙周健康者 79 例作为对照组,纳入标准:患者上、下颌磨牙数不低于 1 颗,余留自然牙超过 20 颗;牙周健康,且全口探诊深度低于 3 mm,6 个月内无非甾体抗炎药 / 抗生素 / 免疫抑制剂的药物治疗史,超过 6 个月未行牙周治疗。两组的排除标准:妊娠、哺乳期女性;吸烟或戒烟不满 5 年者;排除糖尿病、心血管疾病、肾病、肿瘤、骨质疏松、强直性脊柱炎、骨质愈合期、甲状腺相关疾病、类风湿关节炎等骨代谢异常疾病者;侵袭性牙周炎患者;有牙髓源性根尖周炎患者。本研究所有患者知情同意,并经医院伦理委员会批准同意。两组患者的一般资料对比差异无统计学意义(*P>0.05*),具有可比性。

表 1 两组患者的一般资料对比

Table 1 Comparison of the general data between two groups

Groups	n	Sex		Average age(year)	Average BMI(kg/m^2)
		Male	Femal		
Observation group	81	59	22	44.8± 5.1	22.8± 1.5
Control group	79	51	28	45.1± 5.7	23.2± 1.8
P	-	0.258	0.726	0.128	

1.2 方法

选择合适的受试牙,观察组在上、下颌第一、二磨牙中选择牙周炎炎症最重的牙齿(牙周袋探诊较高,出血指数较高,附着丧失水平较高且牙槽骨吸收较重)作为受试牙;对照组选择上、下颌第一、而磨牙中任一颗牙齿(探诊无明显出血且附着丧失不明显,牙槽骨无明显吸收)作为受试牙。

观察组患者由同一医师给予牙周基础治疗:治疗前给予观察组患者口腔卫生宣教;手动龈下刮治、根面平整及超声波龈上洁治。患者在超声波龈上洁治 1 周后,在 1 周内完成两次手动龈下根面平整、刮治术,使用 0.5%碘伏及 3%双氧水行牙周袋冲洗,第一次为上半口,第二次为下半口;治疗后采用氯己定漱口,连续 3 天,且治疗期间不使用抗生素。

1.3 实验仪器

采用美国 Schick 公司生产的数字化牙科成像系统;德国 Sartorius 公司生产的电子天平;上海雅吉生物科技有限公司生产的人硬化蛋白 SOST 酶联免疫试剂盒;英国 Whatman 公司生产的吸潮纸;瑞士 EMS Master-400 超声波洁牙器。

1.4 观察指标

(1)观察两组治疗前及观察组治疗后 1 个月、2 个月的牙周临床指标,包括菌斑指数、出血指数、牙周探诊深度及附着丧失水平;(2)对比观察组患者治疗前、治疗后 1 个月、治疗后 2 个月及对照组龈沟液中的骨硬化蛋白,龈沟液中骨硬化蛋白分析方法:收集前将吸潮纸置于 EP 管中称重、编号,在所选受试牙的近、远颊、近、远舌 4 个位点处收集龈沟液,收集前去除牙面上菌斑,之后将牙面吹干,将受试牙隔湿,之后将吸潮纸分别插入 4 个位点龈袋内,10 min 后取出。之后每颗受试牙再重复取一次龈沟液,每颗受试牙取 2 次龈沟液,共有 8 个吸潮纸,将其置于 EP 管中,两次称量之差为龈沟液重量。采用全自动生化分析仪,用 ELISA 法检测骨硬化蛋白浓度,试剂盒为人硬化蛋白 SOST 酶联免疫试剂盒;(3)分析牙周临床指标与龈沟液骨硬化蛋白水平的相关性。

1.5 统计学方法

采用 SPSS21.0 软件,计量资料用 $\bar{x}\pm s$ 表示,组间比较采用 t 检验,计数资料用百分率表示,组间比较采用卡方检验,相关性采用 Sperman 等级相关分析,以 *P<0.05* 为差异具有统计学意义。

2 结果

2.1 对照组及观察组治疗前后牙周临床指标的对比

治疗前,观察组的菌斑指数、出血指数、牙周探诊深度、附着丧失水平明显高于对照组;治疗后 1 个月、2 个月,观察组以上指标均明显低于治疗前,且治疗后 2 个月,观察组以上指标明显低于治疗后 1 个月,但附着丧失水平仍高于对照组 (*P* 均 <0.05),而两组的菌斑指数、出血指数、牙周探诊深度对比差异无统计学意义(*P>0.05*)。

表 2 对照组及观察组治疗后 1 个月、2 个月的牙周临床指标对比

Table 2 Comparison of the periodontal clinical indexes between the two groups before treatment and at 1 month and 2 months after treatment

Groups	n	Time	Plaque Index	Bleeding Index	Probing depth(mm)	Loss of attachment(mm)
Observation group	81	Before treatment	4.0± 0.7	3.0± 0.3	5.3± 0.6	5.0± 0.8
		At month after treatment	2.3± 0.5*	1.0± 0.2*	3.7± 0.5*	3.6± 1.0*
		At 2 months after treatment	1.2± 0.3*#	0.7± 0.2*#	2.1± 0.4*#	2.2± 0.5*#
Control group	79	-	1.0± 0.2*#	0.6± 0.1*#	2.0± 0.3*#	0.2± 0.02*#^

Note: Compared with before treatment, *$P<0.05$; Compared with after treatment for 1 month, #$P<0.05$; Compared with after treatment for 2 months, ^$P<0.05$.

2.2 两组龈沟液中骨硬化蛋白水平对比

观察组治疗前龈沟液中骨硬化蛋白水平明显高于对照组。治疗后 1 个月、2 个月，观察组龈沟液中骨硬化蛋白水平均明显低于治疗前，且治疗后 2 个月，观察组龈沟液中骨硬化蛋白水平明显低于治疗后 1 个月和治疗前(P 均 <0.05)，而与对照组比较差异无统计学意义 (P>0.05)。

表 3 对照组及观察组治疗后 1 个月、2 个月龈沟液中骨硬化蛋白水平对比

Table 3 Comparison of the osteoclast protein level in gingival crevicular fluid between the two groups before treatment and at 1 month and 2 months after treatment

Groups	Observation group			Control	P
Time	Before treatment	After treatment for 1 month	After treatment for 2 months	group	
osteoclast protein level(pg/mL)	178.5± 31.6	116.8± 25.8*	79.2± 15.7*#	78.4± 17.2*#	<0.001*#

Note: Compared with before treatment, *$P<0.05$; Compared with after treatment for 1 month, #$P<0.05$.

2.3 牙周临床指标与龈沟液骨硬化蛋白水平的相关性

龈沟液中骨硬化蛋白水平与菌斑指数、出血指数、牙周探诊深度、附着丧失水平呈高度正相关(r1=0.876，P1<0.001；r2=0.842，P1<0.00；r3=0.913，P1<0.001；r4=0.903，P1<0.001)。

3 讨论

研究表明骨硬化蛋白除抑制 Wnt 信号通路减少骨吸收外，还能增加破骨细胞骨的生成、激活破骨细胞活性，促进其吸收[13]。有研究发现，动物不同病变程度牙周组织及健康牙周组织(牙槽骨、牙龈、牙骨质及牙周膜内)中均存在骨硬化蛋白，在出生 4、8 周的小鼠牙周膜中骨硬化蛋白呈阳性，而新生小鼠及 1、2 周小鼠牙周膜骨硬化蛋白呈阴性，而在人类机体中，骨硬化蛋白参与了牙周膜成骨及矿化过程，但其在人类龈沟液中是否也存在，相关研究较少[14,15]。人类龈沟液存在于牙周袋或龈沟中，其成分为宿主炎性细胞、血清、口腔内微生物及牙周组织结构细胞[16]。牙周炎症及健康状态下，龈沟液成分不同，其中某些成分可用来判断牙周炎症状不明显时炎细胞浸润、组织代谢及结缔组织重塑的情况[17]。临床对于牙周炎诊断、预后判断多基于牙周临床指标，但其多用于评估已发生的疾病活动水平，且而龈沟液中的生物标志物可实时了解牙周疾病的病变及转归情况，且龈沟液采集简单、无创，是一种理想的牙周炎客观检验指标[18-20]。因此，本研究分析了龈沟液中骨硬化蛋白水平对慢性牙周炎诊断及疗效评价的临床意义。

菌斑指数、出血指数、牙周探诊深度、附着丧失水平均是临床上常用的检测牙周病的指标。本研究结果显示：治疗前，观察组的菌斑指数、出血指数、牙周探诊深度、附着丧失水平明显高于对照组；治疗后 1 个月、2 个月，观察组以上指标仍明显高于治疗前，且治疗后 2 个月，观察组以上指标明显低于治疗后 1 个月，但附着丧失水平仍高于对照组，而两组的菌斑指数、出血指数、牙周探诊深度对比差异无统计学意义，表明观察组在经过基础治疗后，牙周临床指标明显改善，治疗 2 个月时牙周临床指标水平除附着丧失水平外已接近健康体检者，可能是由于基础治疗无法改善患牙的菌斑附着程度有关 [21-24]。此结果与 Sharma C G 等研究结果相似[25]。此外，观察组治疗前骨硬化蛋白水平明显高于对照组。治疗后 1 个月、2 个月，观察组骨硬化蛋白水平均明显低于治疗前，且治疗后 2 个月，观察组骨硬化蛋白水平明显低于治疗后 1 个月和治疗前，而与对照组比较差异无统计学意义，表明龈沟液中骨硬化蛋白水平与疾病病变程度有相关性，可能是由于骨硬化蛋白参与调节牙周炎疾病的发病、转归过程[26-28]。但其作用机制有待进一步研究，此结果与 Kaur A 等研究相似[29]。骨硬化蛋白可通过 LRP5/6 抑制 Wnt/β 蛋白信号，抑制成骨功能及骨细胞分化，从而抑制骨硬化蛋白的产生，可成为促进牙周组织再生的新治疗方案[30]。龈沟液中骨硬化蛋白与菌斑指数、出血指数、牙周探诊深度、附着丧失水平呈高度正相关，表明龈沟液中骨硬化蛋白作用等同于牙周临床指标，可用于判断慢性牙周炎的疾病程度及预后。

综上所述，慢性牙周炎患者龈沟液中骨硬化蛋白水平明显上调，并与与菌斑指数、出血指数、牙周探诊深度、附着丧失水平呈高度正相关，可能作为慢性牙周炎的诊断及疗效评价的参考指标。

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