血清高迁移率族蛋白质 B1、组蛋白脱乙酰酶 3、抵抗素水平与踝关节周围损伤患者骨髓水肿和疼痛程度的关系

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摘　要　目的:分析血清高迁移率族蛋白质 B1(high mobility group protein B1,HMGB1)、组蛋白脱乙酰酶 3(histone deacetylase 3,HDAC3)、抵抗素水平与踝关节周围损伤患者骨髓水肿和疼痛程度的关系。**方法:**180 例踝关节周围损伤患者,根据 MRI 检查有无骨髓水肿,分为骨髓水肿组和无骨髓水肿组。采用 ELISA 法检测 2 组患者血清 HMGB1、HDAC3、抵抗素水平,评价 2 组患者的疼痛程度,根据 MRI 矢状面上 T2WI 脂肪抑制序列高信号区确定骨髓水肿组患者的骨髓水肿范围。分析血清 HMGB1、HDAC3、抵抗素水平与骨髓水肿的关系及其与骨髓水肿范围和疼痛程度的相关性。**结果:**骨髓水肿组血清 HMGB1、HDAC3、抵抗素水平均高于无骨髓水肿组($t = 10.518$,$P = 0.000$;$t = 8.213$,$P = 0.000$;$t = 10.497$,$P = 0.000$)。骨髓水肿组骨髓水肿范围(75.67 ± 18.88)mm^2,重度疼痛 33 例、中度疼痛 45 例、轻度疼痛 12 例;无骨髓水肿组,重度疼痛 9 例、中度疼痛 42 例、轻度疼痛 39 例;骨髓水肿组的疼痛程度重于无骨髓水肿组($Z = -5.287$,$P = 0.000$)。多因素 Logistic 回归分析结果显示,血清 HMGB1、HDAC3、抵抗素水平均为踝关节周围骨挫伤骨髓水肿的危险因素[$\beta = 1.153$,$P = 0.000$,$OR = 3.169$(2.027,4.954);$\beta = 1.266$,$P = 0.000$,$OR = 3.548$(2.070,6.082);$\beta = 1.006$,$P = 0.000$,$OR = 2.735$(1.649,4.535)]。相关性分析结果显示,骨髓水肿患者血清 HMGB1、HDAC3、抵抗素水平与骨髓水肿范围及疼痛程度均呈强正相关($r = 0.726$,$P = 0.000$;$r = 0.779$,$P = 0.000$;$r = 0.758$,$P = 0.000$;$r_s = 0.803$,$P = 0.000$;$r_s = 0.762$,$P = 0.000$;$r_s = 0.784$,$P = 0.000$)。无骨髓水肿患者血清 HMGB1、HDAC3、抵抗素水平与疼痛程度呈弱正相关($r_s = 0.215$,$P = 0.042$;$r_s = 0.208$,$P = 0.048$;$r_s = 0.221$,$P = 0.037$)。**结论:**血清 HMGB1、HDAC3、抵抗素水平是踝关节周围损伤骨髓水肿的危险因素,且其水平越高患者骨髓水肿范围越大、疼痛越严重。

关键词　踝损伤;HMGB1 蛋白;组蛋白脱乙酰基酶类;抵抗素;疼痛;骨髓;水肿

Relationship of serum high mobility group protein B1, histone deacetylase 3, and resistin levels with bone marrow edema and pain severity in patients with periankle injuries

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ABSTRACT　Objective: To analyze the relationship of serum high mobility group protein B1 (HMGB1), histone deacetylase 3 (HDAC3), and resistin levels with bone marrow edema (BME) and pain severity in patients with periankle injuries. **Methods:** One hundred and eighty patients with periankle injuries were enrolled and divided into a BME group and a non-BME group based on the presence or absence of BME on MRI. The serum levels of HMGB1, HDAC3, and resistin in both groups were detected using ELISA, and the pain levels were assessed. The extent of BME in the BME group was determined by the area of high-signal intensity on fat-suppressed T2-weighted images in the sagittal plane. The relationship between serum HMGB1, HDAC3, and resistin levels and BME, as well as their correlation with the extent of BME and pain severity, were analyzed. **Results:** The serum levels of HMGB1, HDAC3, and resistin were significantly higher in BME group compared to non-BME group ($t = 10.518$, $P = 0.000$; $t = 8.213$, $P = 0.000$; $t = 10.497$, $P = 0.000$). The extent of BME in the BME group was (75.67 ± 18.88) mm2, with 33 cases of severe pain, 45 cases of moderate pain, and 12 cases of mild pain. In the non-BME group, there were 9 cases of severe pain, 42 cases of moderate pain, and 39 cases of mild pain. The pain severity was significantly greater in BME group compared to non-BME group ($Z = -5.287$, $P = 0.000$). Multivariate logistic regression analysis identified serum HMGB1, HDAC3, and resistin levels as risk factors for BME following periankle bone contusions ($\beta = 1.153$, $P = 0.000$, $OR = 3.169$ (2.027, 4.954); $\beta = 1.266$, $P = 0.000$, $OR = 3.548$ (2.070, 6.082); $\beta = 1.006$, $P = 0.000$, $OR = 2.735$ (1.649, 4.535)). Correlation analysis revealed that, in patients with BME, serum HMGB1, HDAC3, and resistin levels were all strongly positively correlated with both the extent of BME and the degree of pain ($r = 0.726$, $P = 0.000$; $r = 0.779$, $P = 0.000$; $r = 0.758$, $P = 0.000$; $r_s = 0.803$, $P = 0.000$; $r_s = 0.762$, $P =$

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0.000;r_s = 0.784,P = 0.000). While in patients without BME,these serum markers were all weakly positively correlated with the degree of pain(r_s = 0.215,P = 0.042;r_s = 0.208,P = 0.048;r_s = 0.221,P = 0.037). **Conclusion**:Elevated serum levels of HMGB1,HDAC3,and resistin are risk factors for BME in patients with periankle injuries,and higher levels of these biomarkers are associated with a larger extent of BME and greater pain severity.

Keywords　ankle injuries;HMGB1 protein;histone deacetylases;resistin;pain;bone marrow;edema

踝关节周围骨挫伤是踝关节的骨组织遭受外力后发生的损伤,是踝关节周围损伤中常见的骨损伤类型,主要表现为软组织损伤和骨髓水肿导致的局部疼痛、肿胀及功能障碍[1-2]。骨髓水肿与骨挫伤的严重程度和临床症状关系密切[3]。骨髓水肿造成的持续、剧烈的疼痛会严重影响患者的日常生活质量[4-5]。MRI 检查能准确识别骨髓水肿,但费用较高、扫描时间较长,且有较多禁忌证,临床应用有一定的局限性。因此,如何通过生物标志物评估患者的骨髓水肿和疼痛程度,对于踝关节周围骨挫伤的诊断和治疗具有重要意义。

在急性损伤或感染情况下,高迁移率族蛋白质 B1(high mobility group protein B1,HMGB1)可通过激活下游的信号传导通路,引发强烈的炎症反应[6]。组蛋白脱乙酰酶 3(histone deacetylase 3,HDAC3)通过调节炎症相关基因的表达和成骨细胞分化参与骨组织修复及疼痛调控,其水平能反映骨挫伤后的修复和炎症状态[7]。抵抗素能通过影响成骨细胞和破骨细胞的功能,参与骨代谢的调控,抵抗素的升高常伴随骨密度的下降和骨折风险的增加[8]。为寻找与踝关节周围损伤患者骨髓水肿及疼痛程度相关的血清标志物,为损伤评估和预后判断提供依据,我们分析了踝关节周围损伤患者血清 HMGB1、HDAC3、抵抗素水平与骨髓水肿的关系及其与骨髓水肿范围、疼痛程度的相关性,现报告如下。

1　临床资料

1.1　一般资料

以 2022 年 10 月至 2024 年 10 月,在邯郸市中心医院就诊的 180 例踝关节周围损伤患者为研究对象。研究方案经邯郸市中心医院伦理委员会审查通过,伦理批件号:2022-0098。

1.2　纳入标准

①有踝关节周围疼痛、肿胀、瘀血,及关节活动受限表现;②受伤至就诊时间 <7 d;③影像检查无明显骨折;④对本研究方案知情同意,并签署知情同意书。

1.3　排除标准

①合并严重的韧带损伤者;②有踝关节手术史,或合并其他踝关节疾病者;③开放性损伤者;④合并心脑血管疾病及呼吸系统疾病者。

2　方　法

2.1　样本量估算方法

采用 PASS15 软件。设定条件:α = 0.05(双侧检验),检验效能 1 − β = 0.80,Cohen's d = 0.50。计算得到样本量为 68 例,按 30% 的脱落率进行样本量校正,最终确定每组样本量为 90 例。

2.2　分组方法

纳入患者均行 MRI 检查,检查结果有骨髓水肿者纳入骨髓水肿组,无骨髓水肿者纳入无骨髓水肿组,直至各组纳入病例数满足样本量设定要求。骨髓水肿诊断标准:T1WI 序列上表现为低信号、T2WI 序列上表现为高信号,T2WI 脂肪抑制序列上周围正常脂肪及骨髓被抑制后软骨下出现不规则、边界欠清的异常高信号区域[9]。

2.3　血清 HMGB1、HDAC3、抵抗素水平检测方法

就诊 24 h 内,采集 2 组患者外周静脉血,采用 ELISA 法检测血清 HMGB1、HDAC3、抵抗素水平。

2.4　骨髓水肿范围测量和疼痛程度评价方法

由 2 名经验丰富的影像科医生,根据 MRI 矢状面上 T2WI 脂肪抑制序列高信号区确定骨髓水肿组患者的骨髓水肿范围。采用视觉模拟量表法[10]评价 2 组患者的患肢疼痛程度,<3 分为轻度疼痛,3 ~ 6 分为中度疼痛,>6 分为重度疼痛。

2.5　数据统计方法

采用 SPSS27.0 统计软件处理数据。2 组患者年龄、受伤至就诊时间,以及血清 HMGB1、HDAC3、抵抗素水平的组间比较均采用 t 检验,2 组患者性别、受伤侧别、受伤原因的组间比较均采用 χ^2 检验,疼痛程度的比较采用秩和检验;血清 HMGB1、HDAC3、抵抗素水平与骨髓水肿的关系分析采用多因素 Logistic 回归分析;血清 HMGB1、HDAC3、抵抗素水平与骨髓水肿范围的相关性分析采用 Pearson 相关分析;血清

HMGB1、HDAC3、抵抗素水平与疼痛程度的相关性分析采用 Spearman 相关分析。

3　结　果

3.1　一般结果

2 组患者年龄、性别、受伤侧别、受伤至就诊时间、受伤原因等基线资料比较,差异均无统计学意义,具有可比性(表 1)。

3.2　血清 HMGB1、HDAC3、抵抗素水平检测结果

骨髓水肿组血清 HMGB1、HDAC3、抵抗素水平均高于无骨髓水肿组(表 2)。

3.3　骨髓水肿范围测量和疼痛程度评价结果

骨髓水肿组骨髓水肿范围(75.67 ± 18.88)mm^2,重度疼痛 33 例、中度疼痛 45 例、轻度疼痛 12 例;无骨髓水肿组,重度疼痛 9 例、中度疼痛 42 例、轻度疼痛 39 例;骨髓水肿组的疼痛程度重于无骨髓水肿组($Z = -5.287$,$P = 0.000$)。

3.4　血清 HMGB1、HDAC3、抵抗素水平与骨髓水肿的关系分析结果

以患者是否有骨髓水肿为因变量,血清 HMGB1、HDAC3、抵抗素水平为自变量,进行多因素 Logistic 回归分析。结果显示,血清 HMGB1、HDAC3、抵抗素水平均为踝关节周围损伤骨髓水肿的危险因素(表 3)。

3.5　血清 HMGB1、HDAC3、抵抗素水平与骨髓水肿范围及疼痛程度的相关性分析结果

相关性分析结果显示,骨髓水肿患者血清 HMGB1、HDAC3、抵抗素水平与骨髓水肿范围及疼痛程度均呈强正相关(表 4)。无骨髓水肿患者血清 HMGB1、HDAC3、抵抗素水平与疼痛程度呈弱正相关($r_s = 0.215$,$P = 0.042$;$r_s = 0.208$,$P = 0.048$;$r_s = 0.221$,$P = 0.037$)。

4　讨　论

HMGB1 是一种具有位置依赖性的多功能蛋白。胞内 HMGB1 可参与维持细胞自噬过程,而胞外的 HMGB1 则作为重要介质,参与炎症反应、免疫应答及代谢过程[11-12]。研究表明,HMGB1 与感染、缺血再灌注损伤、炎症反应等多种病理过程关系密切[13-15]。而骨髓水肿的典型病理特征包括软骨下区血流灌注异常、局部组织缺血缺氧,以及少量炎症细胞浸润等

表 1　2 组踝关节周围损伤患者的基线资料

组别	样本量/例	年龄/($\bar{x} \pm s$,岁)	性别/例		受伤至就诊时间/($\bar{x} \pm s$,h)	受伤侧别/例		受伤原因/例	
			男	女		左	右	扭伤	压砸伤
骨髓水肿组	90	38.46 ± 8.27	51	39	35.68 ± 7.63	48	42	52	38
无骨髓水肿组	90	37.89 ± 8.15	49	41	35.09 ± 7.75	50	40	47	43
检验统计量		$t = 0.466$	$\chi^2 = 0.090$		$t = 0.515$	$\chi^2 = 0.090$		$\chi^2 = 0.561$	
P 值		0.642	0.764		0.607	0.765		0.454	

表 2　2 组踝关节周围损伤患者的血清高迁移率族蛋白 B1、组蛋白脱乙酰酶 3 和抵抗素水平

组别	样本量/例	高迁移率族蛋白质 B1/($\bar{x} \pm s$,ng · mL^{-1})	组蛋白脱乙酰酶 3/($\bar{x} \pm s$,单位 · L^{-1})	抵抗素/($\bar{x} \pm s$,ng · mL^{-1})
骨髓水肿组	90	25.68 ± 5.42	110.65 ± 24.36	30.15 ± 5.48
无骨髓水肿组	90	17.69 ± 4.75	82.43 ± 21.66	22.29 ± 4.52
t 值		10.518	8.213	10.497
P 值		0.000	0.000	0.000

表 3　踝关节周围损伤骨髓水肿危险因素的多因素 Logistic 回归分析结果

自变量	β 值	P 值	OR 值(95% CI)
高迁移率族蛋白 B1	1.153	0.000	3.169(2.027,4.954)
组蛋白脱乙酰酶 3	1.266	0.000	3.548(2.070,6.082)
抵抗素	1.006	0.000	2.735(1.649,4.535)

表 4　骨髓水肿患者血清高迁移率族蛋白 B1、组蛋白脱乙酰酶 3、抵抗素水平与骨髓水肿范围及疼痛程度的相关性分析结果

变量	骨髓水肿范围		疼痛程度	
	r 值	P 值	r_s 值	P 值
高迁移率族蛋白 B1	0.726	0.000	0.803	0.000
组蛋白脱乙酰酶 3	0.779	0.000	0.762	0.000
抵抗素	0.758	0.000	0.784	0.000

改变。这提示 HMGB1 在骨髓水肿的发生、发展中发挥重要作用[16-17]。

HDAC3 是一类参与组蛋白脱乙酰化修饰、调控基因表达的关键酶，已被证实是关节炎等炎症性疾病中炎症反应的重要表观遗传调控因子。巨噬细胞特异性 HDAC3 异常表达可诱导痛风模型小鼠出现足垫水肿与踝关节肿胀[18]。抑制 HDAC3 基因表达能够减轻类风湿关节炎患者成纤维样滑膜细胞异常活化，并减少相关促炎性细胞因子的释放[19]。HDAC3 还可参与骨关节炎进程中软骨细胞的损伤调控[20]。HDAC3 表达上调可能通过增强炎症反应、促进免疫细胞浸润、提高血管通透性，导致局部液体积聚，进而推动骨髓水肿的发生与进展[21]。

抵抗素与炎症反应关系密切，其异常表达可能与骨关节炎发病及疼痛程度相关[22]。作为一种重要的促炎性细胞因子，抵抗素在类风湿关节炎患者滑膜组织中高表达，并与多种炎症标志物呈显著相关[23]。此外，抵抗素的基因多态性是中国患者术后疼痛的影响因素和中国汉族人群发生类固醇性股骨头坏死的遗传易感因素[24-25]。抵抗素可在损伤局部促进免疫细胞聚集与活化，诱发持续性炎症反应，同时通过增加血管通透性，促进液体与炎症因子外渗，进一步加重局部组织水肿[23-24]。

本研究结果表明，血清 HMGB1、HDAC3、抵抗素水平是踝关节周围损伤骨髓水肿的危险因素，且其水平越高患者骨髓水肿范围越大、疼痛越严重。但本研究样本量较小，在多因素回归分析中可能导致模型过拟合或结果不稳定，影响独立危险因素的识别。此外，本研究为单一时间点的观察，未分析患者血清 HMGB1、HDAC3、抵抗素水平在损伤早期和恢复阶段的动态变化。未来将通过多中心合作，提高样本的多样性和代表性；并增加采集血清样本和临床数据的时间点，以观察损伤修复过程中患者血清 HMGB1、HDAC3、抵抗素水平的动态变化。

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