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原发性骨关节炎患者关节滑膜组织中 NLRP3 含量与炎症及氧化应激的相关性分析 *

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摘要 目的：探讨原发性骨关节炎患者关节中核苷酸结合寡聚化结构域样受体 3（NLRP3）含量与炎症及氧化应激的相关性。**方法：**选择 2018 年 6 月 -2019 年 6 月我院接诊的 100 例原发性骨关节炎患者进行研究，设为观察组，并选择我院同期体检健康者 80 例作为对照组。分析 NLRP3、凋亡相关斑点样蛋白（ASC）、半胱氨酸天冬氨酸蛋白酶 1（Caspase-1）与白介素 1β（IL-1β）、白介素 17（IL-17）、肿瘤坏死因子 α（TNF-α）、丙二醛（MDA）、8- 羟基脱氧鸟苷（8-OHdG）、3- 硝基酪氨酸（3-NT）、超氧化物歧化酶（SOD）、谷胱甘肽过氧化物酶（GSH-Px）的相关性。**结果：**观察组 NLRP3、ASC、Caspase-1 水平显著高于对照组，差异显著（P<0.05）；观察组 IL-1β、IL-17、TNF-α 水平显著高于对照组，差异显著（P<0.05）；观察组 MDA、8-OHdG、3-NT 水平显著高于对照组，SOD、GSH-Px 水平显著低于对照组，差异显著（P<0.05）；将炎症及氧化应激作为因变量，将 NLRP3 、ASC、Caspase-1 分别作为自变量，在相关性分析结果中显示，NLRP3、ASC、Caspase-1 和 IL-1β、IL-17、TNF-α、MDA、8-OHdG、3-NT 之间均呈正相关（P＜0.05），NLRP3、ASC、Caspase-1 和 SOD、GSH-Px 之间均呈负相关（P＜0.05）。**结论：**在原发性骨关节炎患者中 NLRP3 的含量和炎症及氧化应激之间存在着密切关系，可促使疾病进展。

关键词：原发性骨关节炎；核苷酸结合寡聚化结构域样受体 3；凋亡相关斑点样蛋白；半胱氨酸天冬氨酸蛋白酶 1；炎症；氧化应激

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Analysis of the Correlation between NLRP3 Content in the Joints and Inflammation and Oxidative Stress in Patients with Primary Osteoarthritis*

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ABSTRACT Objective: To studyAnalysis of thecorrelation between Domain like receptor 3 (NLRP3) content in the joints and inflammation and oxidative stress in patients with primary osteoarthritis. **Methods:** 100 patients with primary osteoarthritis admitted to our hospital from June 2018 to June 2019 were selected as the observation group, and 80 healthy patients who underwent physical examination in our hospital during the same period were selected as the control group. Analysis NLRP3, mottled protein (ASC) related to apoptosis, cysteine aspartic acid protease (Caspase 1) and interleukin 1 beta (IL-1 beta), interleukin 17 (IL-17), tumor necrosis factor alpha (TNF alpha), malondialdehyde (MDA), 8 - hydroxy deoxyguanosine (8-OHdG), 3-3-nitrotyrosine (3-NT) and superoxide dismutase (SOD), glutathione peroxidase (gsh-px) relevance. **Results:** The levels of NLRP3, ASC and caspase-1 in the observation group were significantly higher than those in the control group (P<0.05). Il-1 levels in the observation group were significantly higher than those in the control group (P<0.05). MDA, 8-ohdg and 3-nt levels in the observation group were significantly higher than those in the control group, while SOD and gsh-px levels were significantly lower than those in the control group (P<0.05). Inflammation and oxidative stress were taken as dependent variables, and NLRP3, ASC, and caspase-1 were taken as independent variables, respectively. Correlation analysis results showed that there was a positive correlation between NLRP3, ASC, caspase-1, il-1, il-17, TNF-, MDA, 8-ohdg, and 3-nt (P<0.05), and a negative correlation between NLRP3, ASC, caspase-1, SOD, and gsh-px (P<0.05). **Conclusion:** There is a close relationship between NLRP3 content and inflammation and oxidative stress in patients with primary osteoarthritis, which can promote disease progression.

Key words: Primary osteoarthritis; Nucleotide binding oligomerization domain like receptor 3; Apoptosis-associated spot-like proteins; Cysteine aspartic proteinase 1; Inflammation; Oxidative stress

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前言

骨关节炎是关节的一种常见疾病，多发于50岁以上中老年人，根据其病理过程可分为原发性骨关节炎和继发性骨关节炎[1,2]。原发性骨关节炎是关节成熟后，关节肿的软骨等慢性退变，发病慢，早期无明显症状，常伴有多个关节的慢性退变，晚期有僵硬感，关节内摩擦，同时伴有疼痛，严重影响患者的生活质量[3,4]。目前，原发性骨关节炎的治疗主要是对症支持治疗，未能从根本上逆转其病理过程。因此，早期预测疾病对临床具有重要意义。

NLRP3炎性体是一种多蛋白复合物，广泛存在于人体的细胞胞浆中，可通过诱导IL-13、IL-18等多种细胞因子分泌，促进炎症反应过程[5-7]。氧化应激是指在应激条件下，人体产生的一种自我调控机制。虽然目前NLRP3炎性体、氧化应激已被证实在多种自身免疫性疾病中与关节软骨的破坏有关，但目前NLRP3炎性体、氧化应激等在原发性骨关节炎患者中的作用及机制有待深入研究[8-10]。因此，本研究主要分析了原发性骨关节炎患者关节中NLRP3含量及其与炎症及氧化应激的相关性，现报道如下。

1 资料与方法

1.1 一般资料

选择2018年6月-2019年6月我院接诊的100例原发性骨关节炎患者设为观察组，其中男61例，女39例，年龄46~73岁，平均(62.58± 4.82)岁，病程2~8月，平均(4.56± 0.28)月。选择我院同期体检健康者80例作为对照组，年龄45~75岁，平均(62.63± 4.83)岁，其中男49例，女31例。两组基线资料比较无明显差异，具有可比性。

纳入标准：(1)X片显示单膝骨关节炎，伴有疼痛症状；(2)年龄18~75岁；(3)行膝盖关节镜检查；(4)知情同意本次研究。排除标准：(1)外伤、手术继发性关节炎；(2)恶性肿瘤；(3)肝肾等重要脏器功能不全者；(4)急性、慢性感染。

1.2 方法

所有患者禁食8小时后采集静脉血液标本，置于冷冻箱内储存以备检测，使用酶联免疫吸附法对血清白介素1β(IL-1β)、白介素17(IL-17)、肿瘤坏死因子α(TNF-α)、丙二醛(MDA)、8-羟基脱氧鸟苷(8-OHdG)、3-硝基酪氨酸(3-NT)、超氧化物歧化酶(SOD)、谷胱甘肽过氧化物酶(GSH-Px)进行检测，试剂盒购于英国Abcam公司(批号：20180426)，取血清标本，按照酶联免疫吸附试剂盒说明书中的操作步骤配制蛋白浓度梯度的标准品、适当稀释血清标本，而后进行点样、抗体孵育、洗板等操作，最后在酶标仪上读取吸光值；关节镜检查，取少量滑膜组织，4000 r/min离心10 min后，取上清液检测NLRP3、ASC、Caspase-1水平，按照酶联免疫吸附试剂盒说明书中的操作步骤配制蛋白浓度梯度的标准品、适当稀释标本，而后进行点样、抗体孵育、洗板等操作，最后在酶标仪上读取吸光值。

1.3 统计学分析

以spss19.0软件包处理，计量资料用均数± 标准差($\bar{x}\pm s$)表示，组间比较采用t检验，相关性分析使用Spearman相关系数，以P<0.05表示差异具有统计学意义。

2 结果

2.1 两组NLRP3炎性体水平比较

观察组NLRP3、ASC、Caspase-1水平显著高于对照组，差异显著(P<0.05)，见表1。

表1 两组NLRP3炎性体水平比较($\bar{x}\pm s$)

Table 1 Comparison of NLRP3 inflammasome levels between the two groups($\bar{x}\pm s$)

Groups	n	NLRP3	ASC	Caspase-1
Observation group	100	241.35± 30.57	268.57± 19.48	302.13± 35.67
Control group	80	100.25± 14.58	99.56± 15.04	101.12± 12.92
t value		37.959	63.765	47.929
P value		0.000	0.000	0.000

2.2 两组炎症因子水平比较

观察组IL-1β、IL-17、TNF-α水平显著高于对照组，差异显著(P<0.05)，见表2。

表2 两组炎症因子水平比较($\bar{x}\pm s$)

Table 2 Comparison of levels of inflammatory cytokines between the two groups($\bar{x}\pm s$)

Groups	n	IL-1β(ng/L)	IL-17(pg/mL)	TNF-α(pg/mL)
Observation group	100	78.71± 9.05	156.28± 18.71	85.54± 21.38
Control group	80	13.85± 2.02	31.64± 18.52	35.56± 9.35
t value		62.829	44.612	19.465
P value		0.000	0.000	0.000

2.3 两组氧化应激水平比较

观察组MDA、8-OHdG、3-NT水平显著高于对照组，SOD、GSH-Px水平显著低于对照组，差异显著(P<0.05)，见表3。

表 3 两组氧化应激水平比较($\bar{x}\pm s$)

Table 3 Comparison of oxidative stress levels between the two groups($\bar{x}\pm s$)

Groups	n	MDA(μmol/L)	8-OHdG(ng/mL)	3-NT(nmol/L)	SOD(U/mL)	GSH-Px (U/mL)
Observation group	100	12.51± 1.43	2.36± 0.29	35.93± 5.65	76.85± 9.32	59.64± 7.71
Control group	80	4.56± 0.61	0.74± 0.12	16.37± 2.02	164.42± 20.34	128.51± 14.36
t value		46.439	46.839	29.480	38.334	41.135
P value		0.000	0.000	0.000	0.000	0.000

2.4 原发性骨关节炎患者关节中 NLRP3 含量与炎症及氧化应激的相关性分析

将炎症及氧化应激作为因变量，将 NLRP3 、ASC、Caspase-1 分别作为自变量，在相关性分析结果中显示，NLRP3 、ASC、Caspase-1 和 IL-1β、IL-17、TNF-α、MDA、8-OHdG、3-NT 之间均呈正相关（$P<0.05$），NLRP3 、ASC、Caspase-1 和 SOD、GSH-Px 之间均呈负相关($P<0.05$)见表 4。

表 4 原发性骨关节炎患者关节中 NLRP3 含量与炎症及氧化应激的相关性分析

Table 4 Correlation analysis of NLRP3 content in joints in patients with primary osteoarthritis with inflammation and oxidative stress

Factors	NLRP3		ASC		Caspase-1	
	r	*P*	r	*P*	r	*P*
IL-1β	0.523	<0.01	0.526	<0.01	0.501	<0.01
IL-17	0.514	<0.01	0.551	<0.01	0.247	<0.01
TNF-α	0.476	<0.01	0.479	<0.01	0.743	<0.01
MDA	0.625	<0.01	0.713	<0.01	0.526	<0.01
8-OHdG	0.284	<0.01	0.632	<0.01	0.258	<0.01
3-NT	0.426	<0.01	0.524	<0.01	0.196	<0.01
SOD	-0.156	<0.01	-0.211	<0.01	-0.174	<0.01
GSH-Px	-0.179	<0.01	-0.183	<0.01	-0.196	<0.01

3 讨论

原发性骨关节炎是一种常见的中老年关节疾病，发病率较高，是损害中老年人身心健康的主要疾病之一。该病可能是源于长期活动、慢性劳损等导致的软骨损伤退变，而膝盖在日常生活中承受了人体大部分重量，是原发性骨关节炎的好发部位[11-13]。随着我国人口的老龄化，我国原发性膝骨关节炎患者可高达数百万之多。据调查统计，骨关节炎患者占用医疗资源占全球人口的 10%，在老年人中发病率仅次于心血管疾病，是致残的主要原因之一[14,15]。因此，明确原发性骨关节炎患者关节等组织退变的病理过程及分子机制，有助于临床医师防治原发性骨关节炎。原发性骨关节炎病理学早期表现为滑膜衬覆细胞增生，淋巴细胞增生浸润，淋巴滤泡形成，晚期可见纤维素性渗出物及坏死组织机化，导致关节面粘连形成纤维性及骨性强直。NLRP3 是一类胞质型模式识别受体，是由核苷酸结合寡聚化结构域样受体家族成员，NLRP3 与 ASC、Caspase-1 可形成炎性体，是内源性或外源性危险信号的胞质内感受器，是活化 caspase-1 的分子平台，调控 IL-1β 和白介素 18(IL-18)等促炎细胞因子的成熟和分泌。已有研究证实 NLRP3 炎性体在类风湿性关节炎等自身免疫性疾病中可加速加速患者关节软骨的退变过程[16,17]。国外研究显示，姜黄素可通过抑制 NLRP3 炎性体的激活，预防骨关节炎[18-20]。但其在原发性骨关节炎患者中研究极为缺乏。本研究结果显示，原发性骨关节炎患者 NLRP3、ASC、Caspase-1 水平显著高于健康人群。结果提示，NLRP3 炎性体介导的炎性反应参与了原发性骨关节炎的发生。NLRP3 炎性体还能将白细胞介素 IL-1βL 前体剪切为 IL-1 将白成熟体并分泌至细胞外，参与关节炎的炎性反应过程[21,22]。IL-1β 是体内炎性反应的始动因子，能激活炎性反应增加炎症介质的释放；IL-17 是一种前炎症细胞因子，能够减轻自身免疫 、胶原或佐剂诱发关节炎的关节损伤程度；TNF-α 是参与类风湿的重要促炎因子，能激活内皮细胞的破骨细胞等，导致炎症反应持续发生于软骨渐进性破坏[23-25]。本研究结果显示，原发性骨关节炎患者 IL-1β、IL-17、TNF-7 水平显著高于健康人群。结果提示，IL-17、TNF-7 等炎症因子与原发性骨关节炎发生的关系较为密切。

在原发性骨关节炎患者中，活性氧自由基、活性氧自由基产生过多，导致体内氧化应激系统失衡，进而导致关节等组织损伤[26,27]。氧化应激是指在应激条件下，人体产生的一种自我调控机制，同时氧化应激还可以促进炎症的发展过程[28-30]。本研究结果显示，原发性骨关节炎患者 MDA、8-OHdG、3-NT 水平显著高于健康人群，SOD、GSH-Px 水平显著低于健康人群，结果提示，原发性骨关节炎患者中氧化应激过度，参与了疾病的发展，可以加速器病理发展过程。分析其原因是因为原发性骨关

节炎患者关节腔内产生大量氧自由基,通过增加氧自由基的生成来造成氧化产物的生成,同时抗氧化酶的消耗显著增多引起关节发生氧化应激损伤。

此外,研究结果还显示,NLRP3 、ASC、Caspase-1 和 IL-1β、IL-17、TNF-α、MDA、8-OHdG、3-NT 之间均呈正相关,和 SOD、GSH-Px 之间均呈负相关,结果提示,NLRP3 炎性体随着 IL-1β、IL-17、TNF-α、MDA、8-OHdG、3-NT 的增高而增高,随着 SOD、GSH-Px 的降低而增高,与炎症及氧化应激关系密切。结果提示,NLRP3 炎性小体及其在原发性骨关节的滑膜增生及炎性过程中发挥重要作用,通过抑制 NLRP3 炎症小体的激活,能阻断 IL-1β 的成熟和释放,导致中性粒细胞产生大量的 IL-17,从而引起原发性骨关节炎发展恶化,且这一作用并不依赖 NLRP3 炎性小体的信号通路。分析其原因是因为氧化压力的增加会导致关节液中存在大量的过氧化物沉积,对软骨细胞的分泌、修复功能造成氧化损伤,从而加重患者的炎症反应,因此氧化应激促进炎症的发展过程,且与 NLRP3 含量关系密切。综上所述,在原发性骨关节炎患者中 NLRP3 的含量和炎症及氧化应激之间存在着密切关系,可促使疾病进展。

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