Sp40: Are Modic Changes Representative of Primary Endplate Infections?

S Rajasekaran, Gnanaprakash Gurusamy, Mohammad El-Sharkawi, Mohamad Zaki Haji Mohd Amin, Kota Watanabe, Emre Acaroğlu, Ahmet Alanay

Response/Recommendation: There is growing evidence supporting the presence of *Cutibacterium acnes* (C. acnes) and various other bacteria in discs with Modic changes, as demonstrated through culture, polymerase chain reaction (PCR), and next-generation sequencing. Additionally, studies indicate that patients with Modic changes experience higher pain levels, increased incidence of night pain, and more frequent and prolonged pain episodes. Radiological findings further suggest a possible infective etiology. In patients with Modic changes, endplate alterations resembled those seen in infections rather than trauma. Moreover, discs exhibiting Modic changes have been associated with a higher incidence of postoperative infections. While a definitive causal relationship has yet to be fully established, current literature increasingly supports the hypothesis that subclinical infection may contribute to the development of Modic changes.

Level of Evidence: Low to Moderate

Delegate Vote:

Rationale:

A systematic review was conducted to analyze whether modic changes indicate primary endplate infection. PubMed, Web of Science, and Scopus were searched. We excluded publications in non-English languages, case reports, and review articles. Initial database screening resulted in 2,870 articles, which, after duplicate removal, led to 2,269 articles subjected to title and abstract screening. We shortlisted articles for full-text screening from the 2,269 articles and included the 32 articles that met the inclusion criteria in the review.

Modic changes (MCs) are distinct MRI signal alterations in the vertebral endplates and adjacent bone marrow associated with degenerative disc disease (1) and chronic back pain (2). Modic changes (MCs) can arise from two mechanisms: **Mechanical**: Disc degeneration causes endplate microfractures, which can lead to edema, inflammation, or toxicity from nucleus pulposus leakage, and **Infective**: Anaerobic bacteria like Propionibacterium acnes from a herniated disc may cause localized infection and inflammation in adjacent bone (MC Type 1), increasing after disc herniation (3). MCs are classified into three types: MC1 (edema and inflammation), MC2 (fatty infiltration), and MC3 (sclerosis) (4). They are linked to chronic lower back pain (LBP) but can also occur in people without LBP. MCs are considered an independent risk factor for LBP (5). MCs have a genetic component, with heritability estimated at 30% (6). Over time, MCs are recognized as important markers for spinal pathology, reflecting underlying degenerative changes and potential infectious factors.

1. Prevalence of Infection in MCs

Stirling's study found bacterial DNA in 53% of discectomy samples, predominantly Cutibacterium acnes (83%), suggesting a link between infection and Modic changes (MCs) (7). Fritzell et al. found bacterial DNA in painful, degenerated spinal discs of patients without signs of clinical infection, indicating a potential underlying bacterial component in disc degeneration (8). In a study by Agarwal et al., bacterial cultures from excised intervertebral

discs of immunocompetent patients undergoing lumbar microdiscectomy showed bacterial growth, potentially indicating an infectious role in disc degeneration (9). Chen et al.'s prospective study identified low-virulence bacterial infections in cervical intervertebral discs, supporting the idea that low-virulence bacterial infections could contribute to disc degeneration (10). Salehpour et al. demonstrated the presence of Propionibacterium acnes in disc material and examined its antibiotic susceptibility in patients with lumbar disc herniation, emphasizing the possible infectious role of P. acnes in disc pathology (11). Georgy et al. reported that 54% of MC1 cervical biopsy samples were positive for C. acnes, compared to 20% in non-MC1 samples (12). Aghazadeh and colleagues noted that 80% of MC samples were positive for C. acnes, while only 14% of MC-free samples were positive (13). Yuan and co-workers found 12 out of 15 (80%) of C. acnes positive cultures were from MC participants (14). Tang and colleagues reported that 26 out of 80 (33%) herniation samples were positive for bacteria using PCR, with one positive sample excluded from subsequent analysis. This analysis revealed that 15 out of 25 (60%) patients with disc bacteria had MC (15). One longitudinal study showed that bacterial proliferation precedes the development of MC1. Among 28 out of 61 (46%) herniation surgery patients who were positive for microorganisms, 80% developed new MC1 within 12 to 24 months (16). Among 37 patients in a study by Najafi et al., 62.2% tested positive for P. acnes using PCR, suggesting that lumbar disc infection with this anaerobic bacterium may contribute to the development and progression of Modic changes in LBP patients (17). Albert et al found that 46% of patients had positive microbial cultures, with anaerobic bacteria found in 43%. Infected discs with anaerobic bacteria were significantly more likely to develop MCs in adjacent vertebrae (80%) than those with aerobic bacteria (44%) or negative cultures (3). Certain other prospective studies in the recent literature have questioned the alleged association between infection and degenerative changes, providing only moderate support to the disc infection hypothesis in the pathology of MC. The study found a similar prevalence of Cutibacterium acnes in degenerated and non-degenerated discs, likely due to contamination, with no association between bacterial findings and Modic changes (18-20). Antibiotic treatment for lumbar disc herniation without clear signs of infection should be reconsidered. While some studies support a bacterial association, others found no consistent link, indicating variability in the infectious etiology of MCs.

2. Mechanical and Degenerative Factors

MCs are thought to arise from mechanical stress resulting from disc herniation and degeneration, leading to endplate micro-fractures and inflammation. Toxic nucleus tissue or irritating substances may penetrate the vertebrae, triggering autoimmune responses. The mechanical theory is bolstered by histological findings and the resolution of MC type 1 with stabilization, although inconsistencies such as paradisial patterns and posterior endplate involvement challenge the trauma theory (21-24). The trauma theory regarding MCs is questioned as it does not adequately explain paradisial patterns, posterior endplate involvement, and changes in subchondral bone. Studies utilizing multimodal imaging have identified endplate CT changes characteristic of infective changes. The Endplate Infection Probability Score (EIPS) by Rajaseakarn et al effectively differentiates infectious and traumatic endplate changes, demonstrating that 67.64% of MC cases exhibit infection-like characteristics. This study supports the reconsideration of MC as a possible manifestation of ‘Primary Endplatitis’, warranting a shift in diagnostic and therapeutic approaches.(25).

3. Inflammation

Studies on MCs reveal molecular mechanisms indicating significant inflammation. Proteomic analysis demonstrated the downregulation of extracellular matrix components and the

upregulation of inflammatory molecules such as PLG, ANG, FGFBP2, and FTL. A total of 50 proteins, including 14 unique to MCs, were associated with host defence responses, with glutamic acid also linked to MCs. These findings suggest that MCs may involve immune activation and infectious causes (26-28).

4. Role of C. acnes and Other Bacteria

C. acnes is often linked to MCs but is not universally present. Its role might depend on disc degeneration, creating a favorable colonization environment. In their study, Rajasekaran et al. detected 424 bacterial species with distinct biodiversity in normal, degenerated, and herniated discs. Propionibacterium acnes was present but not predominant, as other pathogens were more abundant in all groups. Evidence suggests a gut/skin/spine microbiome axis and emphasizes "dysbiosis" as a potential cause of disc degeneration (29).

5. Clinical Implications

MCs, particularly MC1, are associated with chronic pain and inflammation.

Studies like Albert et al. (30) and Jensen et al. (31) have demonstrated strong associations between MC and the severity, frequency, and chronicity of back pain.

Subjects with MCs experienced more frequent and severe low back pain (LBP), with a higher severity of episodes and prolonged LBP linked to MC location and number. Regression models showed MCs were independently associated with prolonged severe LBP (31).

Albert et al. conducted a study examining the role of antibiotics in treating Modic Type 1 changes (MC1) linked to chronic low back pain. In their randomized controlled trial, they provided a 100-day course of amoxicillin-clavulanate to patients with MC1. The results indicated significant reductions in pain and disability in the antibiotic group compared to the placebo, suggesting that low-grade bacterial infections may contribute to MC1-related symptoms (32). However, concerns arose regarding study bias, conflicting findings, and the risks associated with long-term antibiotic use. A recent Norwegian study refuted this method, strongly advising against using antibiotics for MC. (34) Modic changes (MC), particularly type I and grade C, are related to higher rates of postoperative surgical site infections (SSI) following posterior lumbar fusion surgery. The findings propose that MC may be a potential risk factor for SSI (35). The ratio of Modic changes (MC) to the Total Endplate Score (TEPS) is an independent risk factor for surgical site infections (SSI) after lumbar spine surgery. An MC area ratio exceeding 24.62% significantly raises the risk of SSI. (36) Modic Type 1 changes pose a significant risk for postoperative pyogenic discitis following lumbar laminectomy without discectomy. Patients with Modic Type 1 should be monitored closely to prevent discitis. (37) Rajasekaran et al. discovered that the presence of preoperative Modic changes (MC) and a TEPS exceeding 6 are independent risk factors for postoperative surgical site infections (SSI). The study implies that MC may indicate chronic subclinical infection rather than mere degeneration (38).

References:

1. Kjaer P, Korsholm L, Bendix T, Sorensen JS, Leboeuf-Yde C. Modic changes and their associations with clinical findings. Eur Spine J. 2006 Sep;15(9):1312-9. doi: 10.1007/s00586-006-0185-x. Epub 2006 Aug 9. PMID: 16896838; PMCID: PMC2438570.
2. Määttä JH, Wadge S, MacGregor A, Karppinen J, Williams FM. ISSLS prize winner: vertebral endplate (Modic) change is an independent risk factor for episodes of severe and disabling low back pain. Spine. 2015 Aug 1;40(15):1187-93.

3. Albert HB, Lambert P, Rollason J, Sorensen JS, Worthington T, Pedersen MB, Nørgaard HS, Vernallis A, Busch F, Manniche C, Elliott T. Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? Eur Spine J. 2013 Apr;22(4):690-6. doi: 10.1007/s00586-013-2674-z. Epub 2013 Feb 10. PMID: 23397187; PMCID: PMC3631023.
4. Albert HB, Manniche C. Modic changes following lumbar disc herniation. Eur Spine J. 2007 Jul;16(7):977-82. doi: 10.1007/s00586-007-0336-8. Epub 2007 Mar 3. PMID: 17334791; PMCID: PMC2219661.
5. Hopayian K, Raslan E, Soliman S. The association of modic changes and chronic low back pain: A systematic review. J Orthop. 2022 Nov 17;35:99-106. doi: 10.1016/j.jor.2022.11.003. PMID: 36438174; PMCID: PMC9682331.
6. Määttä JH, Kraatari M, Wolber L, Niinimäki J, Wadge S, Karppinen J, Williams FM. Vertebral endplate change as a feature of intervertebral disc degeneration: a heritability study. Eur Spine J. 2014 Sep;23(9):1856-62. doi: 10.1007/s00586-014-3333-8. Epub 2014 May 15. PMID: 24828957.
7. Stirling A, Worthington T, Rafiq M, Lambert PA, Elliott TS. Association between sciatica and Propionibacterium acnes. Lancet. 2001 Jun 23;357(9273):2024-5. doi: 10.1016/S0140-6736(00)05109-6. PMID: 11438138.
8. Fritzell P, Bergström T, Welinder-Olsson C. Detection of bacterial DNA in painful degenerated spinal discs in patients without signs of clinical infection. Eur Spine J. 2004 Dec;13(8):702-6. doi: 10.1007/s00586-004-0719-z. Epub 2004 May 8. PMID: 15138861; PMCID: PMC3454053.
9. Agarwal V, Golish SR, Alamin TF. Bacteriologic culture of excised intervertebral disc from immunocompetent patients undergoing single level primary lumbar microdiscectomy. J Spinal Disord Tech. 2011 Aug;24(6):397-400. doi: 10.1097/BSD.0b013e3182019f3a. PMID: 21150662.
10. Chen Y, Wang X, Zhang X, Ren H, Huang B, Chen J, Liu J, Shan Z, Zhu Z, Zhao F. Low virulence bacterial infections in cervical intervertebral discs: a prospective case series. Eur Spine J. 2018 Oct;27(10):2496-2505. doi: 10.1007/s00586-018-5582-4. Epub 2018 Apr 19. PMID: 29675672.
11. Salehpour F, Aghazadeh J, Mirzaei F, Ziaeii E, Alavi SAN. Propionibacterium acnes Infection in Disc Material and Different Antibiotic Susceptibility in Patients With Lumbar Disc Herniation. Int J Spine Surg. 2019 Apr 30;13(2):146-152. doi: 10.14444/6019. PMID: 31131213; PMCID: PMC6510207.
12. Georgy MM, Vaida F, Stern M, Murphy K. Association between Type 1 Modic Changes and Propionibacterium Acnes Infection in the Cervical Spine: An Observational Study. AJNR Am J Neuroradiol. 2018 Sep;39(9):1764-1767. doi: 10.3174/ajnr.A5741. Epub 2018 Aug 23. PMID: 30139754; PMCID: PMC7655275.
13. Aghazadeh J, Salehpour F, Ziaeii E, Javanshir N, Samadi A, Sadeghi J, Mirzaei F, Naseri Alavi SA. Modic changes in the adjacent vertebrae due to disc material infection with Propionibacterium acnes in patients with lumbar disc herniation. Eur Spine J. 2017 Dec;26(12):3129-3134. doi: 10.1007/s00586-016-4887-4. Epub 2016 Nov 24. PMID: 27885471.
14. Yuan Y, Chen Y, Zhou Z, Jiao Y, Li C, Zheng Y, Lin Y, Xiao J, Chen Z, Cao P. Association between chronic inflammation and latent infection of Propionibacterium acnes in non-pyogenic degenerated intervertebral discs: a pilot study. Eur Spine J. 2018 Oct;27(10):2506-2517. doi: 10.1007/s00586-017-5363-5. Epub 2017 Oct 31. PMID: 29086028.
15. Tang G, Wang Z, Chen J, Zhang Z, Qian H, Chen Y. Latent infection of low-virulence anaerobic bacteria in degenerated lumbar intervertebral discs. BMC Musculoskelet Disord.

2018 Dec 20;19(1):445. doi: 10.1186/s12891-018-2373-3. PMID: 30572849; PMCID: PMC6302300.
16.Singh S, Siddhlingeswara GI, Rai A, Iyer RD, Sharma D, Surana R. Correlation Between Modic Changes and Bacterial Infection: A Causative Study. Int J Spine Surg. 2020 Oct;14(5):832-837. doi: 10.14444/7118. PMID: 33184123; PMCID: PMC7671451.
17.Najafi S, Mahmoudi P, Bassampour SA, Shekarchi B, Soleimani M, Mohammadimehr M. Molecular detection of Propionibacterium acnes in biopsy samples of intervertebral disc with modic changes in patients undergoing herniated disc surgery. Iran J Microbiol. 2020 Dec;12(6):516-521. doi: 10.18502/ijm.v12i6.5025. PMID: 33613905; PMCID: PMC7884273.
18.Ahmed-Yahia S, Decousser JW, Flouzat-Lachaniette CH, Dervin G, Roubineau F, Audureau E, Hourdille A, Royer G, Eymard F, Chevalier X. Is the discopathy associated with Modic changes an infectious process? Results from a prospective monocenter study. PLoS One. 2019 Aug 15;14(8):e0221030. doi: 10.1371/journal.pone.0221030. PMID: 31415619; PMCID: PMC6695213.
19.Rigal J, Thelen T, Byrne F, Cogniet A, Boissière L, Aunoble S, Le Huec JC. Prospective study using anterior approach did not show association between Modic 1 changes and low grade infection in lumbar spine. Eur Spine J. 2016 Apr;25(4):1000-5. doi: 10.1007/s00586-016-4396-5. Epub 2016 Jan 27. PMID: 26818032.
20.Fritzell P, Welinder-Olsson C, Jönsson B, Melhus Å, Andersson SGE, Bergström T, Tropp H, Gerdhem P, Hägg O, Laestander H, Knutsson B, Lundin A, Ekman P, Rydman E, Skorpil M. Bacteria: back pain, leg pain and Modic sign-a surgical multicentre comparative study. Eur Spine J. 2019 Dec;28(12):2981-2989. doi: 10.1007/s00586-019-06164-1. Epub 2019 Oct 1. Erratum in: Eur Spine J. 2020 Jan;29(1):196-197. doi: 10.1007/s00586-019-06199-4. PMID: 31576463.
21.Elfering A, Semmer N, Birkhofer D, Zanetti M, Hodler J, Boos N. Risk factors for lumbar disc degeneration: a 5-year prospective MRI study in asymptomatic individuals. Spine (Phila Pa 1976). 2002 Jan 15;27(2):125-34. doi: 10.1097/00007632-200201150-00002. PMID: 11805656.
22.Crock HV. Internal disc disruption. A challenge to disc prolapse fifty years on. Spine (Phila Pa 1976). 1986 Jul-Aug;11(6):650-3. PMID: 3787337.
23.Vital JM, Gille O, Pointillart V, Pedram M, Bacon P, Razanabola F, Schaelderle C, Azzouz S. Course of Modic 1 six months after lumbar posterior osteosynthesis. Spine (Phila Pa 1976). 2003 Apr 1;28(7):715-20; discussion 721. doi: 10.1097/01.BRS.0000051924.39568.31. PMID: 12671361.
24.Esposito P, Pinheiro-Franco JL, Froelich S, Maitrot D. Predictive value of MRI vertebral end-plate signal changes (Modic) on outcome of surgically treated degenerative disc disease. Results of a cohort study including 60 patients. Neurochirurgie. 2006 Sep;52(4):315-22. doi: 10.1016/s0028-3770(06)71225-5. PMID: 17088711.
25.Rajasekaran S, Pushpa BT, Soundararajan DCR, Sri Vijay Anand KS, Murugan C, Nedunchelian M, Kanna RM, Shetty AP, Tangavel C, Muthurajan R. Are Modic changes 'Primary infective endplatitis'?-insights from multimodal imaging of non-specific low back pain patients and development of a radiological 'Endplate infection probability score'. Eur Spine J. 2022 Nov;31(11):2884-2896. doi: 10.1007/s00586-022-07335-3. Epub 2022 Aug 5. PMID: 35931790.
26.Rajasekaran S, Tangavel C, Aiyer SN, Nayagam SM, Raveendran M, Demonte NL, Subbaiah P, Kanna R, Shetty AP, Dharmalingam K. ISSLS PRIZE IN CLINICAL SCIENCE 2017: Is infection the possible initiator of disc disease? An insight from proteomic analysis. Eur Spine J. 2017 May;26(5):1384-1400. doi: 10.1007/s00586-017-4972-3. Epub 2017 Feb 6. PMID: 28168343.

27.Rajasekaran S, Soundararajan DCR, Nayagam SM, Tangavel C, Raveendran M, Thippeswamy PB, Djuric N, Anand SV, Shetty AP, Kanna RM. Modic changes are associated with activation of intense inflammatory and host defense response pathways - molecular insights from proteomic analysis of human intervertebral discs. Spine J. 2022 Jan;22(1):19-38. doi: 10.1016/j.spinee.2021.07.003. Epub 2021 Jul 22. PMID: 34303868.
28.Kumar H, Kawai T, Akira S. Toll-like receptors and innate immunity. Biochem Biophys Res Commun. 2009 Oct 30;388(4):621-5. doi: 10.1016/j.bbrc.2009.08.062. Epub 2009 Aug 15. PMID: 19686699.
29.Rajasekaran S, Soundararajan DCR, Tangavel C, Muthurajan R, Sri Vijay Anand KS, Matchado MS, Nayagam SM, Shetty AP, Kanna RM, Dharmalingam K. Human intervertebral discs harbour a unique microbiome and dysbiosis determines health and disease. Eur Spine J. 2020 Jul;29(7):1621-1640. doi: 10.1007/s00586-020-06446-z. Epub 2020 May 14. PMID: 32409889.
30.Albert HB, Kjaer P, Jensen TS, Sorensen JS, Bendix T, Manniche C. Modic changes, possible causes and relation to low back pain. Med Hypotheses. 2008;70(2):361-8. doi: 10.1016/j.mehy.2007.05.014. Epub 2007 Jul 10. PMID: 17624684.
31.Määttä JH, Karppinen J, Paananen M, Bow C, Luk KDK, Cheung KMC, Samartzis D. Refined Phenotyping of Modic Changes: Imaging Biomarkers of Prolonged Severe Low Back Pain and Disability. Medicine (Baltimore). 2016 May;95(22):e3495. doi: 10.1097/MD.0000000000003495. PMID: 27258491; PMCID: PMC4900699.
32.Albert HB, Sorensen JS, Christensen BS, Manniche C. Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. Eur Spine J. 2013 Apr;22(4):697-707. doi: 10.1007/s00586-013-2675-y. Epub 2013 Feb 13. PMID: 23404353; PMCID: PMC3631045.
33.Bråten LCH, Rolfsen MP, Espeland A, Wigemyr M, Aßmus J, Froholdt A, Haugen AJ, Marchand GH, Kristoffersen PM, Lutro O, Randen S, Wilhelmsen M, Winsvold BS, Kadar TI, Holmgard TE, Vigeland MD, Vetti N, Nygaard ØP, Lie BA, Hellum C, Anke A, Grotle M, Schistad EI, Skouen JS, Grøvle L, Brox JI, Zwart JA, Storheim K; AIM study group. Efficacy of antibiotic treatment in patients with chronic low back pain and Modic changes (the AIM study): double blind, randomised, placebo controlled, multicentre trial. BMJ. 2019 Oct 16;367:l5654. doi: 10.1136/bmj.l5654. Erratum in: BMJ. 2020 Feb 11;368:m546. doi: 10.1136/bmj.m546. PMID: 31619437; PMCID: PMC6812614.
34.Deng S, Xie J, Niu T, Wang J, Han G, Xu J, Liu H, Li Z. Association of modic changes and postoperative surgical site infection after posterior lumbar spinal fusion. Eur Spine J. 2024 Aug;33(8):3165-3174. doi: 10.1007/s00586-024-08329-z. Epub 2024 May 31. PMID: 38816538.
35.Liu Y, Chen Q, Wang Y, He J. The area ratio of Modic changes has predictive value for postoperative surgical site infection in lumbar spine surgery: a retrospective study. BMC Musculoskelet Disord. 2024 Feb 13;25(1):137. doi: 10.1186/s12891-024-07257-9. PMID: 38347482; PMCID: PMC10863181.
36.Ninomiya K, Fujita N, Hosogane N, Hikata T, Watanabe K, Tsuji O, Nagoshi N, Yagi M, Kaneko S, Fukui Y, Koyanagi T, Shiraishi T, Tsuji T, Nakamura M, Matsumoto M, Ishii K. Presence of Modic type 1 change increases risk of postoperative pyogenic discitis following decompression surgery for lumbar canal stenosis. J Orthop Sci. 2017 Nov;22(6):988-993. doi: 10.1016/j.jos.2017.07.003. Epub 2017 Aug 10. PMID: 28802716.
37.Pradip, I., Dilip Chand Raja, S., Rajasekaran, S. et al. Presence of preoperative Modic changes and severity of endplate damage score are independent risk factors for developing postoperative surgical site infection: a retrospective case-control study of 1124 patients. Eur Spine J 30, 1732–1743 (2021).

Summary Table: Modic Changes and Infection Hypothesis

Study	Key Findings	Strengths	Limitations
Stirling et al. [7]	Identified Propionibacterium acnes in disc samples from patients with sciatica, suggesting a bacterial association.	Clear bacterial association.	Small sample size (n=36).
Fritzell et al. [8]	Found bacterial DNA in degenerated discs without clinical infection signs, indicating detection without establishing causation.	Detection without clinical signs.	No causation established.
Agarwal et al. [9]	Conducted bacterial cultures from intervertebral discs, indicating a potential infectious role.	Direct bacterial culture evidence.	Limited sample size (n=25).
Chen et al. [10]	Reported low-virulence bacterial infections in cervical discs linked to degeneration, based on a prospective design focusing on cervical discs.	Prospective design.	Focus on cervical discs only.
Salehpour et al. [11]	Identified C. acnes in herniated discs, emphasizing antibiotic susceptibility, but did not establish causation.	Antibiotic relevance highlighted.	Does not establish causation.
Georgy et al. [12]	Detected C. acnes in 54% of MC1 cervical samples compared to 20% non-MC1, focusing on cervical samples.	Focus on cervical samples.	Limited to cervical samples.
Aghazadeh et al. [13]	Found 80% of MC samples positive for C. acnes; only 14% non-MC positive, indicating a strong bacterial association but focusing on one bacterium.	Strong bacterial association.	Focus on one bacterium.
Yuan et al. [14]	Reported 80% of cultures from MC participants positive for C. acnes, with a high association rate but a small sample size.	High association rate with MC.	Small sample size (n=20).
Tang et al. [15]	Found 33% of herniated disc samples positive for bacteria, with 60% having MC, providing longitudinal evidence but with possible PCR contamination.	Longitudinal evidence of bacterial role.	Possible contamination in PCR.
Najafi et al. [17]	Reported 62.2% of lumbar disc biopsies positive for P. acnes via PCR, providing molecular evidence without establishing direct causation.	Molecular evidence with PCR.	No direct causation established.
Albert et al. [3]	Found 46% of microbial cultures positive, linking anaerobic bacteria to	Randomized controlled trial.	Methodological concerns.

Study	Key Findings	Strengths	Limitations
	MC development, based on a randomized controlled trial with methodological concerns.		
Ahmed-Yahia et al. [18]	Found no consistent association between C. acnes and MC, suggesting contamination, addressing contamination but failing to confirm causation.	Addresses contamination.	Fails to confirm causation.
Rigal et al. [19]	Found no association between Modic 1 changes and low-grade infection, challenging the infectious hypothesis but failing to confirm causation.	Challenges infectious hypothesis.	Fails to confirm causation.
Fritzell et al. [20]	Found no clear bacterial link between Modic changes and degenerative pathology, based on a multicenter comparison with confounding factors not fully addressed.	Multicenter comparison.	Confounding factors not fully addressed.