

REVIEW

The role of *Propionibacterium acnes* in and Modic type 1 changes : A literature review

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Abstract : *Propionibacterium acnes* (*P. acnes*) is part of the normal flora of human skin, oral cavity, intestinal tract and external ear canal. However, breach in the mucosa as well as ruptured annulus fibrosus provide favorable pathway for *P. acnes* to nucleus pulposus where it can proliferate under anaerobic condition. In past two decades many authors have identified *P. acnes* in routine culture of discs. These studies showed that almost 50% of discs cultured were positive for various organism, and in vast majority of culture positive disc, *P. acnes* was the primary organism isolated. However, there are few studies that refute the hypothesis that *P. acnes* has a role in pathogenesis of Modic type 1 changes. Identification of *P. acnes* in culture indicates the infective patho-mechanism in the pathogenesis of Modic type 1 changes, which may be amenable to antibiotic treatment. However, it is still difficult to identify which subset of these patients (patients with low back pain with type 1 Modic change) are infective in nature. Further investigation and more clinical trails will be required for clear identification of the infective subgroup among low back patient in general. *J. Med. Invest.* 67:21-26, February, 2020

Keywords : *Propionibacterium acnes*, Modic change, Low back pain

INTRODUCTION

The low-virulent infectious organism *Propionibacterium acnes* (*P. acnes*) have been identified as a causative factor in the evolution of Modic type 1 changes. However, this theory has been controversial due to problems in the identification of *P. acnes* in routine culture or contamination of samples in positive culture. This article reviews the epidemiology of Modic changes and the relationship of *P. acnes* with Modic changes and discusses recent publications.

We performed a comprehensive search for published relevant studies on role of *P. acne* in Type 1 Modic change and low back pain in MEDLINE, PubMed, Google scholar and Cochrane database. Since the first paper on association between sciatica and *P. acnes* was published on June, 2001, the articles from 2001 to 2019 were searched in english language. The following key terms were included in our search : *Propionibacterium acnes*, Low back pain, type 1 Modic change, antibiotic, infections, bacteria/microorganism. These key words were searched with combination of the operators like “AND” and “WITH”. We also chose references cited in the articles and relevant review articles to identify additional studies.

EPIDEMIOLOGY

Multi-factorial nature of Low back pain including physical, functional, psychological, professional and social factors is now acknowledged. Few well described specific causes of low back pain are fractures, spondylodiscitis, metastasis, pathological fractures, osteoporosis, conus cauda syndrome, nerve root com-

pression (1). Similarly few risk factors for low back pain includes low work satisfaction, low social status, stress, age, female sex, possibility of morbid gain, passive lifestyle, nicotine, alcohol, drug abuse, obesity, insufficient self regulation, little physical and psychological resources (2).

Several countries developed guidelines in order to provide a systemic approach for treatment of low back pain with similar procedures both for diagnosis and treatment (3, 4). However both patients and physician are seldom aware of how to deal properly with LBP according to recommendation of common available guideline (4). Monomodal therapy often lead to insufficient therapeutic response. Hence it is important to identify the distinct factors of causing pain and treat them properly in terms of multidisciplinary therapeutic approach including physical therapy, analgesic, antibiotic, spinal injections and surgeries (5).

Modic changes are subchondral bone marrow edema associated with degenerated vertebral endplates first identified by deRoss *et al.* (6). Further classifications and clinical associations were subsequently provided by Modic *et al.* in 1988 (7, 8). Since then, Modic changes have been identified and described as the causative factor for low back pain in various studies (9, 10, 11, 12, 13). Modic *et al.* (7, 8) classified this magnetic resonance imaging (MRI) finding of Modic changes into 3 different types. Modic type 1 was classified as a hypointense signal on T1-weighted imaging and a hyperintense signal on T2-weighted imaging and represented bone marrow edema or inflammation. Modic type 2 was classified as high signal intensity changes on both T1- and T2-weighted images representing fatty degeneration. Similarly, Modic type 3 was classified as a hypointense signal on both T1- and T2-weighted images representing subchondral bone sclerosis.

The prevalence of Modic changes varies from 19% to 59% with type 1 and 2 being the most common (14). Modic changes are more prevalent in patients with degenerative disc disease but are uncommon in asymptomatic individuals without degenerative disc disease (15, 16). Kjaer *et al.* observed Modic changes in 9.6% of individuals without degenerative disc disease and 34.1% of those with degenerative disc disease (16).

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Similarly, *P. acnes* is a microaerophilic, anaerobic aerotolerant, gram-positive, pleiomorphic, rod-shaped bacteria that resides in the pilosebaceous follicles of the human skin, oral cavity, conjunctiva, intestinal tract, and external ear canal (17). The distinct phenotypes of *P. acnes* type I and type II were originally identified based on serological agglutination test and cell wall carbohydrate analysis; recently, a third lineage has been identified and designated as Type III (17).

P. acnes has been identified as the causative organism in various other infections besides skin infections, including cerebrospinal shunt, dental infections, musculoskeletal infections, endocarditis (native, prosthetic valves), neurosurgical infections (endophthalmitis, microbial keratitis), postoperative discitis, spondylodiscitis, spinal infections, and prosthetic joint/orthopedic device-related infections. Similarly, a few conditions have been identified in which *P. acnes* plays an associated role as in acne vulgaris and fatal bacterial granuloma after trauma. The range of conditions that *P. acnes* may be associated with and/or play a role in is continuously growing, with organisms being isolated from atherosclerotic lesions, primary biliary cirrhosis, prostate cancer, sarcoidosis, sciatica/low back pain; SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome. It is underdiagnosed and underreported as a cause of infection, either due to being viewed as a harmless contaminant or through failure to provide adequate culture conditions (17).

PATHOLOGY

As postulated by Modic *et al.*, changes in the signal intensity of intervertebral discs and adjacent endplates are due to biomechanical stress or instability (7, 8). Modic type 1 changes are associated with disruption and fissuring of the endplates along with formation of fibrovascular granulation tissue secondary to ongoing active inflammation (7, 18). Brown *et al.* (19) identified defects in endplates with increased vascular density and sensory nerve fibers postulating that these were a source of low back pain. In contrast, Burke *et al.* (20) emphasized that an increase in post-inflammatory mediators such as interleukin-6, interleukin-8, and prostaglandin E-2 in discs of patients was a major factor in the pathogenesis of discogenic low back pain. According to Crock *et al.* (21) repeated trauma to the disc induces production of inflammatory substances in the nucleus pulposus. These toxic chemicals diffuse through the vertebral endplates causing local inflammatory reaction resulting in back pain. Modic thus proposed this concept of Modic changes with degenerated disc as "internal disc disruption."

Modic type 1 changes / bone edema in the vertebrae are present in 6% of the general population and 35-40% of the low back pain population (22). Kjaer *et al.* (16) suggested that degenerative disc disease with Modic type 1 were more frequently associated with low back pain. Moreover, Mitra *et al.* (23) also observed that increase in Modic type 1 changes in number were clinically associated with worsening of symptoms.

P. acnes role in the pathophysiology of acne is well established (24); however, an increasing number of reports have implicated this organism as an opportunistic pathogen responsible for a wide range of inflammatory conditions and postoperative and device-related infections (25). Traditional description of *P. acnes* as a non-pathogenic organism should be disregarded, and its significance should be carefully considered following culture of the organisms from a clinical sample.

More recent studies are postulating *P. acnes* as a causative organism for the pathogenesis of Modic type 1 changes. Most of the authors have identified this anaerobic gram-positive bacterium from the disc sample and believe that the anaerobic environment

of the intervertebral disc enhances the growth and proliferation of *P. acnes* in that environment. *P. acnes* is part of the normal flora on human skin, oral cavity, intestinal tract and external ear canal. However, a breach in the mucosa and ruptured annulus fibrosus provide a favorable pathway for *P. acnes* to reach the nucleus pulposus, where it can proliferate under anaerobic conditions (26). Macrophages engulf *P. acnes* and transport them to the intervertebral disc via the circulation and release the viable bacteria after cell death where they have a favorable anaerobic environment for growth and proliferation (27).

STUDIES SUPPORTING THE ROLE OF *P. ACNES* IN THE PATHOGENESIS OF DISC DEGENERATION AND MODIC TYPE 1 CHANGES

Table 1 presents studies that support the hypothesis that *P. acnes* has a role in the pathogenesis of Modic type 1 changes and thereby cause low back pain. In the past two decades many authors have identified *P. acnes* in routine culture of discs. These studies showed that almost 50% of discs cultured were positive for various organisms, and in the vast majority of culture-positive discs, *P. acnes* was the primary organism isolated. Stirling *et al.* (28) found 16 of 19 culture-positive discs to have isolated *P. acnes*. Similarly, Agrawal *et al.* (31) demonstrated 7 *P. acnes* positive discs out of 10 positive culture results in total. Arndt *et al.* (32) isolated various organisms out of 40 culture-positive discs but the majority demonstrated *P. acnes* (18 cases). Albert *et al.* (33) demonstrated direct correlation between *P. acnes* and Modic changes where the disc with nucleus with anaerobic bacteria, 80% developed New Modic change in the adjacent to the previous disc herniation. In contrast, none of those with aerobic bacteria and only 44% of patients with negative cultures developed new Modic change. The association between an anaerobic culture and new Modic change was highly statistically significant. In above study isolated anaerobic organism was identified in 22 patients out of which 20 were *P. acnes*. Similarly, Yuan *et al.* (36) harvested intervertebral discs from 76 patients with low back pain and/or sciatica without any symptoms of discitis or spondylodiscitis, 16 intervertebral discs were found to be positive for *P. acnes* via 16s rDNA PCR and prevalence was 21.05%; among them, 7 samples had visible microbes. They concluded that *P. acnes* is capable of colonizing some degenerated intervertebral discs without causing discitis.

Capoor *et al.* (35) conducted a study involving 290 adult patients (mean age 47 ± 13 years) who underwent lumbar microdiscectomy for symptomatic lumbar disc herniation. The posterior midline approach was used in all cases. The obtained intervertebral disc samples were then homogenized and used for quantitative anaerobic culture and a sample was frozen and used for quantification of the *P. acnes* genome by real-time PCR. Bacteria were identified in 130 of 290 disc samples. Threshold was defined as $\geq 1 \times 10^3$ CFU/mL for discs with abundant *P. acnes*. The prevalence of disc samples with abundant *P. acnes* was 11% (39 cases) and *P. acnes* was not abundant in the remaining 29% (76 cases) of positive disc samples. The number of *P. acnes* genomes by PCR in 259 *P. acnes*-positive discs ranged from 2 to 5831 with median of 260 genomes per 500 ng of total DNA. The authors believed that *P. acnes* is involved in the pathological process in at least a subset of patients with degenerative disc disease.

In a pilot study conducted by Yuan *et al.* (37), 76 degenerated intervertebral discs were harvested from patients with low back pain and/or sciatica. After anaerobic culture and PCR analysis, 15 intervertebral discs were categorized into the *P. acnes*-positive group and another 15 discs were selected from the remaining bacteria-free samples and formed a matched *P. acnes*-negative group.

Table 1 : Studies supporting the role of *P. acnes* in the pathogenesis of disc degeneration and Modic type 1

| Study | Number of patients (n) | Culture/Polymerase Chain Reaction (PCR) | | | % of <i>P. acnes</i> among total positive cases |
|------------------------------------|-------------------------------|---|--|-----------------|---|
| | | Positive, n (%) | Organism isolate | Negative, n (%) | |
| Stirling <i>et al.</i> (2001) [28] | 36 | 19 (53) | <i>P. Acnes</i> : 16 Coagulase-negative staphylococci (CNS) : 2 Corynebacterium propinquum: 1 | 17 (47) | 84 |
| Coscia <i>et al.</i> (2003) [29] | 30 (Lumbar disc herniation) | 21 (71) | Staphylococcus : 11 (36) <i>P. Acnes</i> : 5(18) | 9 (29) | 24 |
| | 30 (cervical disc herniation) | 18 (59) | <i>P. Acnes</i> : 11 (37) | 12 (41) | 61 |
| Fritzell <i>et al.</i> (2004) [30] | 10 | 2 (20) | <i>Bacillus cereus</i> : 1 <i>Citrobacter braaki / freundii</i> : 1 | 8 (80) | 0 |
| Agrawal <i>et al.</i> (2011) [31] | 52 | 10 (20) | <i>P. Acnes</i> : 7 Peptostreptococcuspp : 1 Staphylococcus aureus : 1 Coagulase-negative Staphylococcus spp : 1 | 42 (80) | 70 |
| Arndt <i>et al.</i> (2012) [32] | 83 | 40 (48) | <i>P. acnes</i> : 18 Coagulase-negative staphylococcus : 16 Gram negative bacilli : 3 Micrococcus : 3 Corynebacterium : 3 Others : 5 10 biopsies presented 2 different species. | 43 (52) | 45 |
| Albert <i>et al.</i> (2013) [33] | 61 | 28 (46) | <i>P. acnes</i> : 20 Coagulase-negative staphylococci : 2 <i>P. acnes</i> + Gram positive cocci : 3 <i>P. acnes</i> + Neisseria spp : 1 Gram positive cocci : 1 Gram negative rod : 1 | 33 (54) | 72 |
| Zhou <i>et al.</i> (2015) [34] | 46 | 11 (24) | <i>P. acnes</i> : 11 | 35 (76) | 100 |
| Capoor <i>et al.</i> (2016) [35] | 290 (discs) | 130 (45) | <i>P. acnes</i> : 115 Coagulase-negative staphylococci : 31 Alpha hemolytic streptococci : 8 Two micro-organism : 24 | 160 (55) | 88 |
| Yuan <i>et al.</i> (2017) [36] | 76 | 16 (21) | <i>P. acnes</i> : 16 | 60 (79) | 100 |

IL-8, MIP-1 α , MCP-1, IP-10, TNF- α , and neutrophils were much higher in the *P. acnes*-positive group than that in the matched *P. acnes*-negative group. Furthermore, 7 of 15 *P. acnes*-positive samples were histologically positive and a subgroup analysis suggested that both histological and PCR-positive samples had the highest concentration of cytokines of IL-8, MIP-1 α , TNF- α , and MCP-1 and the greatest number of neutrophils. They concluded that latent *P. acnes* infection was associated with chronic inflammation in degenerated intervertebral discs, especially in samples with visible bacteria on histology, which manifested as increased number of cytokines and neutrophils. Discs with *P. acnes* infection had extensive severe degeneration and this may be attributed to *P. acnes*-associated chronic inflammation (37).

STUDIES REFUTING THE ROLE OF *P. ACNES* IN THE PATHOGENESIS OF DISC DEGENERATION AND MODIC TYPE 1 CHANGES

Table 2 presents the studies that refute the hypothesis that *P. acnes* has a role in the pathogenesis of Modic type 1 changes. Ben Galim *et al.* (38) and Wedderkopp *et al.* (40) identified only 2 culture-positive cases in their series, and neither of the cases were positive for *P. acnes*.

Rigal *et al.* (41) conducted a prospective study in which all the

patients underwent minimally invasive video-assisted anterior lumbar fusion or disc prosthesis placement at L4/L5 and/or L5/S1 via an anterior retroperitoneal approach to eliminate the risk of contamination on posterior approach. In 385 samples of 313 patients (mean age 47.6 \pm 13 months) preoperative MRI demonstrated Modic type 1 changes in 303 cases (78.7%), Modic type 2 in 58 cases (15.1%), and absence of Modic changes in 24 cases (6.2%). By Pfirrmann classification there were 50 cases with grade 2, 211 with grade 3, and 124 with grade 4 changes. Out of 6 patients with a positive culture, 5 patients had Modic 1 changes and 1 patient had type 2 Modic changes. A total of 262 (68%) biopsies were done from the L5/S1 level and 123 (32%) from the L4/L5 level. The biopsies were then cultured for 4 weeks with specialized enrichment culture and subjected to histopathological analysis. All 6 positive samples originated from L5/S1 disc biopsies. Histological examination of the disc showed non-specific fibrous remodeling of the intervertebral disc with no features of acute inflammatory response, which were similar to that of fibrocartilage tissue. They concluded that the 6 positive samples were related to contamination and emphasized that biological modulators as well as biochemical and genetic mechanisms were factors responsible for the degeneration. The absence of infection at the 1-year follow-up was an additional argument in favor of no relation between disc degeneration and infection.

Table 2 : Studies refuting the role of *P. acnes* in the pathogenesis of disc degeneration and Modic type 1 changes

| Study | Number of patients (n) | Culture/Polymerase chain reaction (PCR) results | | | % of <i>P. acnes</i> among total positive cases |
|--------------------------------------|----------------------------|---|---|-----------------|---|
| | | Positive, n (%) | Organism isolate | Negative, n (%) | |
| Ben-Galim <i>et al.</i> (2006) [38] | 30 | 2 (7) | Coagulase-negative staphylococci : 2 | 28 (93) | 0 |
| Carricajo <i>et al.</i> (2007) [39] | 54 | 2 (4) | <i>P. acnes</i> : 2 | 52 (96) | 100 |
| Wedderkopp <i>et al.</i> (2009) [40] | 24 | 2 (8) | <i>Staphylococcus epidermidis</i> : 1 Coagulase-negative staphylococci : 1 | 22 (92) | 0 |
| Rigal <i>et al.</i> (2016) [41] | 385 samples (313 patients) | 6 (1.5) | <i>P. acnes</i> : 2 <i>Staphylococcus epidermidis</i> : 2 <i>Citrobacter freundii</i> : 1 <i>Saccharopolyspora hirsute</i> : 1 | 379 (98.5) | 33 |

EXPERIMENTAL STUDIES DEMONSTRATING THE ROLE OF *P. ACNES* IN MODIC TYPE 1 CHANGES

Experimental studies by Dudli *et al.* (42) and Chen *et al.* (43) demonstrated that aseptic isolation of *P. acnes* from the intervertebral disc of symptomatic patients with Modic type 1 changes and subsequent injection into rat and rabbit intervertebral disc induces Modic type 1 changes in the adjacent bone marrow (Table 3). The intervertebral disc changes were more like discitis if the inoculation was with *Staphylococcus aureus*, however, changes caused by *P. acnes* would be considered Modic type 1 changes and disc degeneration rather than discitis (43).

STUDIES DEMONSTRATING THE ROLE OF ANTIBIOTICS IN LOW BACK PAIN

The role of antibiotics in low back pain indirectly provides evidence of microbial infestation at the intervertebral disc, following a course of antibiotic treatment. In 1984 Modic *et al.* (44) performed MRI of the intervertebral disc in 20 healthy individuals, 8 patients with degenerative lumbar disc disease, 27 with both degenerative disc disease and herniation, and 5 with disc space infection to demonstrate the diagnostic role of MRI in low back pain. Five patients with suspected disc space infection were found to have markedly increased signal intensity of the entire disc as well as the adjacent endplates. Follow-up scan after 4 weeks of antibiotic therapy again revealed increased signal intensity in both the bodies and disc, but there was a central area of decreased signal intensity within the disc suggestive of both

healing and degeneration.

Similarly, Albert *et al.* (45) conducted a pilot study in 2008, where they assessed the clinical effect of antibiotic treatment in a cohort of patients with low back pain and Modic type 1 changes. All the 32 patients with low back pain and Modic changes were treated with amoxicillin-clavulanate (500 mg / 125 mg) 3 × day for 90 days. The authors found clinically important and statistically significant improvement in all outcome measures in 29 patients who completed the treatment at the long-term follow-up (mean 10.8 months). They highlighted the need for a randomized controlled trial (RCT) to test the hypothesis that bacterial infection plays a role in low back pain with Modic changes.

In 2013 Albert *et al.* (22) published the results of their RCT which aimed to test the efficacy of antibiotic treatment in patients with chronic low back pain (> 6 months) and Modic type 1 changes. In this double-blind RCT, 162 patients were randomized to either 100 days of antibiotic treatment (Bioclavid) or placebo and were blindly evaluated at baseline, end of treatment, and at 1-year follow-up. The 2 groups were similar at baseline and 144 of 162 patients were evaluated at 1-year follow-up. The antibiotic group improved significantly on all outcome measures. At baseline, 100-day follow-up, and 1-year follow-up disease-specific disability using the Roland Morris Disability Questionnaire score changed as follows : antibiotic 15, 11, 5.7 vs placebo 15, 14, 14. For leg pain : antibiotic 5.3, 3.0, 1.4 vs placebo 4.0, 4.3, 4.3. For lumbar pain : antibiotic 6.7, 5.0, 3.7 vs placebo 6.3, 6.3, 6.3. They concluded that the antibiotic protocol was significantly more effective than placebo in all the primary and secondary outcomes for treatment of patients with chronic low back pain and Modic type 1 changes.

Table 3 : Experimental studies demonstrating the role of *P. acnes* in Modic type 1 changes

| Experimental study | Methods | Results |
|---------------------------------|--|---|
| Dudli <i>et al.</i> (2016) [42] | <i>P. acnes</i> was aseptically isolated from a symptomatic lumbar L4-5 disc with Modic changes type I and injected into rat tail disc. | Day 3 : apparent upregulation of interleukin 1 and interleukin 6. Day 14 : T-cells and tumor necrosis factor α immunoreactivity were identified at the disc; or marrow junction and MRI showed Modic type I-like changes in the adjacent bone marrow. |
| Chen <i>et al.</i> (2016) [43] | Wild-type <i>P. acnes</i> isolated from a patient with Modic changes and disc degeneration was injected into the intervertebral disc of rabbit. Also, <i>staphylococcus aureus</i> was also injected into the disc for comparison. | Compared with <i>staphylococcus aureus</i> , the pathological changes caused by <i>P. acnes</i> would be considered Modic changes type I and disc degeneration rather than discitis. |

Table 4 : Studies demonstrating the role of antibiotics in low back pain

| Study | No. of patients | Type of antibiotics | Duration of treatment | Changes observed |
|---|-----------------|---|--------------------------------|--|
| Modic <i>et al.</i> (1984) [44] | 5 | | 4 weeks | Changes in signal intensity observed in repeat MRI suggesting healing and degeneration |
| Albert <i>et al.</i> (Non-randomized prospective trial) (2008) [45] | 32 | Amoxicillin-Clavulanate (500 mg / 125 mg) | Three times a day for 90 days | 29 patients reported clinically relevant and statistically significant improvement on all outcome measures. |
| Albert <i>et al.</i> (Double-blind randomized clinical control trial) (2013) [22] | 162 | Amoxicillin-Clavulanate (500 mg / 125 mg) | Three times a day for 100 days | 144 of 162 original patients were evaluated at the 1-year follow-up. The antibiotic group had significant improvement compared with the placebo group on all outcome measures; improvement continued from 100 days follow-up until the 1-year follow-up. |

SUMMARY

Given all the controversy surrounding the role of *P. acnes* in Modic type 1 changes, many clinical and experimental studies have been conducted to investigate this issue. These studies have clearly demonstrated the presence of *P. acnes* in a subset of patients with low back pain. Identification of *P. acnes* in culture indicates the infective patho-mechanism in the pathogenesis of Modic type 1 changes, which may be amenable to antibiotic treatment. However, it is still difficult to identify which subset of these patients (patients with low back pain with type 1 Modic change) are infective in nature. Although the use of antibiotics has improved the outcomes significantly, this does not mean that all patients that have low back pain with Modic changes are eligible for long-term antibiotic therapy. Moreover, no studies demonstrate improvement if Modic change in MRI study after antibiotic treatment. Also, further investigations for clear identification of the infective subgroup among low back pain patients in general may be helpful. Thus, more clinical trials are required to arrive at any conclusion.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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