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## MODERN ASPECTS OF KNEE JOINTS DEGENERATIVE-DYSTROPHIC LESIONS PATHOGENESIS AS A BASIS FOR CONSERVATIVE TREATMENT

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The purpose of the study was to provide a comprehensive overview of the pathophysiological mechanisms underlying degenerative-dystrophic joint damage and to identify therapeutic approaches to improve joint function and intra-articular cartilage nutrition. This review examines the current etiological factors and pathophysiological mechanisms of degenerative-dystrophic and inflammatory lesions of the large joints of the lower limbs, with a view to explaining the rationale for the use of prolotherapy with hypertonic glucose and/or dextrose solutions. A systematic analysis of studies from 2020 to 2025, drawn from the medical databases PubMed, Google Scholar, Web of Science, and SCOPUS, demonstrates the complexity and cascade of osteoarthritis pathophysiological mechanisms, which significantly complicate the clinical manifestations of the disease and render drug therapy ineffective. The authors focus on prolotherapy, a regenerative medicine technique that uses hypertonic glucose and/or dextrose solutions, injected into damaged areas of the knee joint, to relieve chronic pain and stimulate the natural regeneration of intra-articular tissues. Clinical data confirms prolotherapy's efficacy in reducing pain and improving joint mobility, often achieving better results than traditional treatments. In their conclusion, the authors emphasize the alternative importance of prolotherapy for patients with gonarthrosis who are looking for non-invasive treatment options.

**Key words:** osteoarthritis, gonarthrosis, pathophysiological mechanisms, inflammation, cytokines, prolotherapy, hypertonic glucose solution.

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## СУЧАСНІ ПОГЛЯДИ НА ПАТОГЕНЕЗ ДЕГЕНЕРАТИВНО-ЗАПАЛЬНОГО УРАЖЕННЯ КОЛІННИХ СУГЛОБІВ В ЯКОСТІ БАЗИСУ ДЛЯ КОНСЕРВАТИВНОГО ЛІКУВАННЯ

Метою дослідження було з'ясування основних патофізіологічних механізмів дегенеративно-дистрофічного ураження суглобів з метою визначення лікувальних заходів, спрямованих на покращення функціонування суглобів та відновлення повноцінного живлення внутрішньосуглобної хрящової тканини. У цьому огляді досліджено сучасні етіологічні чинники та патофізіологічні механізми дегенеративно-дистрофічних та запальних уражень великих суглобів нижніх кінцівок з точки зору обґрунтування доцільності застосування лікувальної тактики пролотерапії гіпертонічними розчинами глюкози та/або декстози. Систематичний аналіз досліджень з 2020 по 2025 роки, взятих з медичних баз даних PubMed, Google Scholar, Web of Science and SCOPUS засвідчує складність та каскадність патофізіологічних механізмів остеоартрозу, що суттєво ускладнює клінічний перебіг захворювання і робить малоефективною медикаментозну терапію. Автори акцентують увагу на пролотерапії – методиці регенеративної медицини, застосування якої шляхом введення в пошкоджені ділянки колінного суглобу області гіпертонічні розчини глюкози та/або декстози забезпечує усунення хронічного болю та стимулює природне відновлення внутрішньосуглобних тканин. Клінічні дані підтверджують ефективність пролотерапії у зниженні болю та покращенні рухливості, забезпечуючи кращі результати порівняно з традиційними методами лікування. Автори висловлюють альтернативну важливість пролотерапії для хворих на гонартроз, які шукають неінвазивні варіанти лікування захворювання.

**Ключові слова:** остеоартроз, гонартроз, патофізіологічні механізми, запалення, цитокіни, пролотерапія, гіпертонічний розчин глюкози.

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Osteoarthritis (OA) is the most common chronic disease of large joints worldwide<sup>1</sup>, causing significant pain, increasing disability, and progressive cartilage degeneration, and contributing to increased global disability and healthcare consumption [11].

In English literature, most researchers consider osteoarthritis (deforming osteoarthritis, DO) as degenerative-dystrophic changes in the joints, in which there may be, or is, an inflammatory component [24]. The definition “deforming osteoarthritis” (osteoarthritis deformatis) was introduced into medical practice by T. Muller in 1911 [23]. According to the latest international classification, the name “osteoarthritis” was adopted for this disease [4].

Degenerative-dystrophic joint diseases are characterized by progressive metabolic disorders of articular cartilage and the epiphyseal bone structure, with involvement of other joint elements [5, 32]. These chronic processes are accompanied by joint deformity, severe pain, reduced functional activity, secondary inflammatory changes, and a decrease in patients' quality of life [5, 22, 46].

The joint diseases division into degenerative-dystrophic (arthrosis) and inflammatory (arthritis) is quite relevant because degenerative changes are often detected in arthritis, along with inflammatory ones, and in arthrosis, some aspects of the inflammatory process [19, 37].

Osteoarthritis ranks first among joint diseases, accounting for 27.3 % of cases [6]. Osteoarthritis is diagnosed in 5.3–17.3 % of cases in the general morbidity of the population. Among all rheumatic diseases, it accounts for more than 40–50 % of cases [2].

This topic's importance stems from the following reasons. It is known that DO, which mainly affects the most loaded lower limbs' large joints, among which the knee and hip joints occupy the first places, is one of the most common diseases of the articular apparatus and a modern problem of civilization [23]. There has been a rapid development of regenerative medical technologies in recent years, significantly facilitating and optimizing the diagnostic process [19, 23]. As a result, the number of patients diagnosed with knee joint inflammatory-degenerative lesions has increased considerably, and the pharmacotherapeutic arsenal of doctors trying to treat this contingent of patients has increased dramatically.

This disease is of interest to researchers and clinicians because OA is one of the leading causes of disability in the elderly and is also the leading cause of disability in younger age groups [4, 22]. In 2019, OA ranked 15th position among the causes of years of life lost due to disability (YLD) worldwide and accounted for 2 % of the total number of YLDs worldwide [17].

Osteoarthritis causes an annual economic loss of at least \$89.1 billion in the USA, representing 1 % to 2.5 % of the gross domestic product in high-income countries, with the majority of these costs attributed to knee and hip replacements [39]. Moreover, OA is the second most common musculoskeletal disease after low back pain in terms of disability-adjusted life years among the elderly population [22, 26].

The pathophysiology of OA is complex and involves difficult, mutually reinforcing processes affecting multiple organs, organ systems, and regulatory systems, including inflammation, epigenetic control, cell death pathways, and the synovial lymphatic system. Danger-associated molecular patterns and immune activation trigger joint inflammation, leading to tissue damage. Epigenetic changes, such as DNA methylation and microRNA regulation, collectively contribute to cartilage degradation [27]. Understanding these complex molecular mechanisms is crucial to developing effective targeted therapies.

**The purpose** of the study was to provide a comprehensive overview of the pathophysiological mechanisms underlying degenerative-dystrophic joint damage and to determine therapeutic approaches to improve joint function and restore complete nutrition of intra-articular cartilage.

To achieve the goal of the review, three main literature searches were conducted across the databases PubMed, Google Scholar, Web of Science, and SCOPUS, covering English-language scientific articles from 01.01.2020 to 01.01.2025. The last search query was performed on January 11, 2025.

A meticulous, strategic search process was employed within each database, using a broad range of keywords relevant to joints, both inflammatory and degenerative-dystrophic lesions, with appropriate Boolean operators (e.g., AND, OR).

For explanation. Searching within the PubMed database the following verbatim search query was used: “osteoarthrosis”, “osteoarthritis”, “knee osteoarthritis”, “inflammation”, “degeneration”, “dystrophy”, “etiology”, “pathogenesis”, “treatment”, “surgical treatment”, “noninvasive treatment”, “physical therapy”, “prolotherapy”, “genetic therapy”, “cartilage”, “cytokines”, “epigenomics”, “platelet-rich plasma”, “dextrose prolotherapy”, “glucose prolotherapyand”, “systematic review”, and “evidence-based medicine”.

Similar search strategies were subsequently used in other databases - Google Scholar, Web of Science, and SCOPUS. This extensive collection of keywords ensured a broad, exhaustive search that captured recent clinical discoveries and advances, as well as the latest fundamental data on the etiology and pathogenesis of knee osteoarthritis and its non-invasive treatment options.

The inclusion criteria for the review were strictly defined to ensure the inclusion of high-quality, relevant studies. Only original research articles, systematic reviews, and meta-analyses published in peer-reviewed journals were considered for inclusion. Emphasis was placed on studies published in English, which were prioritized for their broader accessibility and relevance to the international scientific community. Studies published in Ukrainian were also included to reflect regional contributions to the field.

Exclusion criteria were also considered essential. Conference abstracts, editorials, preprints, and non-peer-reviewed articles were excluded because they did not align with the review objectives. Only studies that provided substantive information on the use of non-invasive treatment methods for gonarthrosis, such as the specifics of prolotherapy with hypertonic dextrose and glucose solutions, and the comparative efficacy, were selected for inclusion.

As this is a review article based on publicly available literature, ethical approval was not required. The study protocol was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Hence, a total of 512 articles were selected. After

removing duplicates and those not meeting the inclusion criteria, a portion was designated for full-text review. Therefore, 50 manuscripts were included (Table 1).

Table 1

## Simplified PRISMA Flow

Stage	Description	Number of Records/Studies
1. Identified	Total number of records identified through database searching and other sources	512
2. Duplicates Removed	Number of records removed before screening (e.g., duplicates)	73
3. Screened (Title/Abstract)	Number of records screened after duplicates were removed	439
4. Assessed for Eligibility (Full-text)	Number of full-text articles assessed for eligibility against the inclusion/exclusion criteria	117
5. Included in Review	Total number of primary studies finally included in the systematic review	50

Knee osteoarthritis (gonarthrosis) is the most common manifestation of the disease, with a significant impact on both patients and healthcare systems [21, 43]. It refers to structural changes in the knee joint that affect articular cartilage, subchondral bone, and other joint structures.

Gonarthrosis is characterized by a complex metabolic disorder of articular cartilage, which leads to its gradual thinning. Proinflammatory cytokines, i.e., IL-1 $\beta$  and TNF- $\alpha$ , play a key role in activating catabolic cascades and in cartilage matrix destruction. Subchondral bone damage, including bone marrow lesions, contributes to the progression of degeneration and the onset of pain.

Synovitis in OA is a major source of pain and inflammation, and muscle-joint imbalance around the knee increases mechanical load on the cartilage and compromises joint stability. This disease progression is manifested by osteophyte formation, joint space narrowing, and subsequent functional impairment [36].

A specific pathogenetic contribution of the vascular factor to OA is assumed. The popliteal artery ligation was shown in an experimental trial to induce knee joint changes that closely resemble those in OA [34]. The leading role of arteriolar spasm and changes in the venous part of capillaries, with the development of postcapillary stasis in OA, has also been demonstrated, outlining the regional blood flow disturbance. Knee joint rheovasographic indices were impaired in the majority of OA patients, indicating hemodynamic deterioration in periarticular tissues [45].

Additionally, it is worth mentioning that gonarthrosis is relatively common in patients with impaired fat metabolism [39, 50]. There is evidence that OA development is facilitated by the joint mechanical loading and its microtrauma.

Thus, a simple list of pathophysiological mechanisms proved that many etiological factors are involved in OA development. Moreover, some of them probably play a leading role, for instance, microtrauma, ischemia, hypoxia, and joint physical exertion. In contrast, others are considered concomitant factors, for example, hormonal-metabolic, infectious-allergic, and age-related factors [14, 27].

It's evident that OA's main links of pathogenesis are multifaceted; moreover, they function according to a mutually aggravating principle, according to the "vicious circle" mechanisms with cascade complementary chains, among which, in our opinion, the following deserve attention.

The above-mentioned inflammatory component of OA pathogenesis is strongly linked with cytokine signalling.

Osteoarthritis was shown not to be simply a condition that develops due to inadequate loading of weight-bearing joints and repetitive stress, but a disease in which an abnormal immune response drives cartilage degradation, bone remodelling, and typical symptoms such as swelling, pain, and stiffness [14]. The exact mechanism of this inflammatory response is still unclear, but it is known that joint tissue cells can produce inflammatory stimuli and respond to them [25].

Experimental trials and clinical observations on OA demonstrated an imbalance between pro- and anti-inflammatory processes, leading to a persistent low-grade inflammatory condition [35]. A pro-inflammatory state favours catabolism over anabolism in the joint, leading to cartilage degeneration and destruction by disrupting the balance that maintains stable cartilage and extracellular matrix metabolism [14, 36]. Cytokines are the primary OA of the immune response signalling molecules.

IL-1 $\beta$  plays an essential role in knee cartilage. Collagen type IX is cleaved along its chains after IL-1 $\beta$  stimulation [32]. The primary OA pathogenetic IL-1 $\beta$  and TNF- $\alpha$  effect is to uphold the inflammatory response by inducing cascades that regulate the essential genes of signalling pathways expression, such as NF- $\kappa$ B, ERK, JNK, and p38 kinase genes. They also increase the prostaglandin E2 synthesis and induce the ADAMTS synthesis in chondrocytes [32]. NF- $\kappa$ B activation is considered the main catabolic regulatory pathway in chondrocytes [14, 32].

In turn, NF- $\kappa$ B activation promotes the production of hypoxia-inducible factor 2 $\alpha$ , together with nitric oxide synthase, COX2, and IL-1, which stimulate the inflammatory process. NF- $\kappa$ B induces MMPs and ADAMTS and self-perpetuates this mechanism through IL-1 synthesis [33]. IL-1 synthesis also potentiated IL-6, IL-8, IL-17, and IL-18 synthesis [9].

Hence, cytokines, owing to their pathogenetic significance, are of interest as prognostic biomarkers in OA. Studies showed that some of the aforementioned cytokine levels vary with OA severity, underscoring their importance in clinical practice. For instance, TNF- $\alpha$ , IL-1Ra, IL-4, and IL-8 correlate more strongly with OA severity than X-ray images [15].

Obesity, which is currently reaching pandemic proportions, is a well-known risk factor for OA development, with knee OA incidence in obese patients being four times higher than in controls [12, 50]. It is supposed that the OA increased risk is associated with increased joint load [39]. Other studies showed that both biomechanical and metabolic factors, in combination, are responsible for the interaction between obesity and gonarthrosis [50].

Gelber (2024) showed that obesity is also associated with OA in non-weight-bearing joints [17]. This suggests that OA is likely caused by factors other than overload. Some authors suggest that adipokines play an important, but not yet fully understood, role in OA pathogenesis [18].

It should be noted that, from a time-dependent perspective, the onset of the disease was associated with pathological changes in cartilage tissue. Indeed, the products of articular cartilage degradation under the specified conditions initiate inflammatory changes in the synovial membrane, which gradually alter the physicochemical properties of synovial fluid. These disturbances contribute to worsening cartilage tissue nutrition and to the progression of degenerative changes [32]. As a result of these changes, the primary cartilage substance is depleted by proteoglycans through depolymerization. Cartilage thus loses elasticity, and stretches and defects appear.

At the same time, early changes in the surface of the intra-articular cartilage, initiating inflammatory processes and catabolic reactions, spread distally, forming deep cracks that lead to cartilage delamination, exposing calcified cartilage and subchondral bone [26].

The thinning of hyaline articular cartilage is accompanied by underlying calcified cartilage expansion, which further increases mechanical load and promotes the formation of catabolic factors [47].

Articular cartilage morphological changes in OA are characterized primarily by destructive and minor reparative changes, as well as by a reactive process in the bone with OA development. Matrix glycosaminoglycans loss primarily in the superficial and intermediate zones is a characteristic feature of cartilage destruction in OA. Both chondroitin and keratosulfate levels decrease, correlating with degenerative and necrotic changes in chondrocytes, while proteoglycan synthesis is inhibited [3, 8].

Synovitis is frequently observed in OA (in more than 50 % of patients) [36]. Synovitis is recognized as an essential sign in patients with OA and is associated with both symptoms and structural progression. Arthroscopy reveals changes in the menisci, intra-articular ligaments, synovitis, erosion of the articular surfaces, and osteophytes [31].

Synovitis contributes to chondrocyte and intercellular substance degeneration in cartilage [36]. Reactive synovitis, which is common in OA, led to the widespread use of the “osteoarthritis” definition in the English literature [3]. Hence, reactive synovitis is considered an essential factor in OA progression [36].

Inflammation in OA causes synovial proliferation and induces T- and B-lymphocyte infiltration as well as mast cells [30]. Stimulated by inflammatory mediators, i.e., by IL-1 and TNF, MMPs and other proteases encourage chondrocytes, synovial cells, and lymphocytes to produce IL-6, IL-8, IL-15, IL-17, leukemia inhibitory factor, and prostaglandin E<sub>2</sub> [13]. Synovitis was shown to induce extensive proteolytic enzyme production, leading to cartilage damage [29].

Chronic synovitis gradually leads to sclerosis, lipomatosis, and thickening of the microcirculatory bed, resulting in secondary damage to articular cartilage. Reactive synovitis is one factor in OA progression. The development of massive, severe changes in the osteochondral tissue leads to the rejection of its fragments, which can remain loose within the joint cavity. Being inside the joint space, they cause severe pain and so-called joint blockage, with temporary, severe difficulty walking [36].

Seventy-one new genetic risk loci for knee OA have been identified since the UK Biobank genotyping data were published in 2017, bringing the total to 90, supporting its polygenic etiology [41]. Among the 90 genetic loci identified across multiple GWAS studies, 16 genes were found to be significant in knee OA. These genes are the following: GDF5, ZNF345, SOX9/ROCR, SMG6, NF1, NFAT/WWP2, USP8, ALDH1A2, SBNO1, COL27A1, COL6A4P1, DUS4L/COG5, BTNL2, AP3B1, SDPR, and LTBP1. The prognostic value of variants in genetic risk loci for OA may serve as a potential tool for predicting disease onset and progression.

We consider essential data on histone modifications in chondrocytes, which demonstrated the presence of 12 chromatin states [41]. In vitro studies showed that histone deacetylases suppress transcription factors essential for chondrocyte hypertrophy and MMP-13 synthesis [42].

Mitochondrial dysfunction was reported in human chondrocytes with OA, characterized by decreased mitochondrial electron transport chain activity and altered ATP synthesis. It is believed that there are two possible pathways for mitochondrial dysfunction: somatic mutations in mtDNA and direct exposure to cytokines, prostaglandins, reactive oxygen species, and nitric oxide [39, 49].

Therefore, the literature data suggest that many etiologic factors contribute to OA development, with multiple pathways in its pathogenesis affecting joint tissues, particularly articular cartilage. The role of vascular factors, hypoxia-induced changes in cartilage structure and bone metabolism, and synovitis development in OA was clearly confirmed. All of this is crucial for OA development, understanding fundamental mechanisms, and the search for effective methods to prevent and treat its etiopathogenetic mechanisms.

Although gonarthrosis is the most common progressive musculoskeletal disorder affecting over 250 million patients worldwide, basic treatment methods have remained almost unchanged since 1968, when the first total knee arthroplasty was performed [24]. Since then, joint replacement has remained the gold standard for surgical treatment of gonarthrosis. However, knee arthroplasty is considered a failure not only in orthopedics but in medicine as a whole, as modern medicine remains unable to halt OA progression in its early stages and avoid surgical intervention. Therefore, significant research efforts were devoted to studying and better understanding its pathogenesis, genetics, and biomarkers [1, 6, 11, 14, 35, 41, 42, 46].

Today, leading rheumatological and traumatological/orthopedic organizations distinguish three main approaches to OA treatment: non-pharmacological, pharmacological, and surgical.

Drug therapy includes compounds with both local (ointments, gels containing non-steroidal anti-inflammatory compounds, glucocorticosteroids, and hyaluronic acid injections) and systemic action – remedies of fast and slow action [28, 32].

OA treatment should be early, aimed at etiologic and pathogenetic factors, and comprehensive. This approach may consist primarily of non-drug therapies that provide a high therapeutic effect and, when used correctly, have virtually no side effects typical of long-term medication use, such as allergies, damage to mucous membranes and other tissues, adverse impact on blood, and drug dependence.

Minimally invasive interventions should be considered selectively and in case of disease significant progression - surgery (arthroscopy, osteotomy, endoprosthesis). Current trends include accelerated recovery and navigation during operations, which can increase the safety and efficacy of surgical interventions.

Gonarthrosis treatment optimization requires a comprehensive approach that combines early identification of patients at high risk of disease progression, implementation of evidence-based recommendations, and ensuring access to effective therapies.

The main approach to gonarthrosis management is non-pharmacological treatment supported by all leading international guidelines [2, 24]. When non-pharmacological methods are insufficient to control pain or functional limitations, it is the turn of pharmacological therapy.

Rapid scientific and technological advances in medicine have enabled new treatment methods to improve patient outcomes and optimize medical care [20, 24].

Prolotherapy is one of the innovative regenerative therapy methods aimed at pain relief. Prolotherapy is an injection-based regenerative medicine method that involves injecting a special solution (usually concentrated glucose) into damaged ligaments, tendons, or joints to stimulate the natural healing process, strengthen connective tissue, and reduce pain by activating collagen and growth factor synthesis.

Prolotherapy, used for decades, involves the injection of dextrose or other proliferating agents into diseased tissue. Given its availability and potential to improve patient outcomes, dextrose-based prolotherapy has become a valuable addition to physicians' arsenals for treating musculoskeletal disorders [16]. Prolotherapy is believed to be a promising alternative to various pharmacological remedies used intra- or periarticularly for gonarthrosis.

An analysis of the available literature on prolotherapy highlights its potential benefits in OA treatment, particularly in knee OA. Prolotherapy with hypertonic dextrose solution was shown to effectively reduce pain and improve function, stiffness, and quality of life in patients with gonarthrosis [48].

This technique involves a hypertonic dextrose solution injection into the affected joint or surrounding tissue. This results in a local inflammatory response that stimulates the body's natural healing process and promotes tissue regeneration.

While its mechanisms of action remain unclear, prolotherapy is believed to activate growth factors and cytokines, promoting the formation of new connective tissue, strengthening ligaments and tendons, and stabilizing joints [24]. This regenerative process can improve joint function, reduce pain, and potentially slow the OA progression [48].

Despite extensive clinical research worldwide, the effects of prolotherapy on gonarthrosis remain controversial, and study results are inconsistent [24, 44].

Some authors report positive results [19, 24], while others show minimal or no benefit compared with placebo or other treatments, such as hyaluronic acid and corticosteroids [48]. This variability may be due to differences in study design, treatment protocols, and patient groups. Nevertheless, the potential of prolotherapy to stimulate tissue repair represents a promising avenue for further research, especially given the limitations of existing OA treatments.

We were interested in a similar therapeutic effect in patients with gonarthrosis. From a scientific point of view, we decided to test our own hypothesis, which is ultimately connected with an attempt to check the efficacy of a hypertonic (30 %) solution of another sugar-containing substance – glucose therapeutic effect being administered intra-articularly. We start from the fact that cartilage tissue lacks a blood supply, which makes its destruction irreversible and leads to chondrocyte death.

Cartilage typically receives nutrition from the synovial membrane using a simple physiological transport mechanism – diffusion [30]. We assume that, in a hypertonic fluid environment around the knee joint created by periarticular administration of hypertonic glucose solution, a concentration gradient will be established, driving diffusion towards the joint and the joint space, thereby improving knee joint function and promoting therapeutic effects.

At the same time, additionally to obtaining a positive effect in patients with gonarthrosis in the form of pain syndrome relief, the joint movements amplitude increases and having the laboratory (X-ray and CT) confirmation of cartilage tissue thickening in 11 patients after 14 months of treatment (our own unpublished data), it is significant to clarify the mechanism of the achieved effect realization. Our preliminary data are consistent with the positive effects of dextrose-based prolotherapy in the treatment of symptomatic gonarthrosis [7].

It's essential to consider the simple physical process and physiological mechanism by which, when a hypertonic solution is injected into a joint, a diffusion gradient is created, forcing the solution (in our case, hypertonic glucose) into the joint space and directly contacting the damaged cartilage.

We believe this process mediates the following mechanisms.

The first mechanism we believe is local inflammation reduction, whereby a proliferative solution injection may reduce inflammation and accelerate healing, potentially alleviating symptoms such as pain and stiffness in patients with gonarthrosis [25].

The inflammatory cascade triggered by prolotherapy is believed to promote tissue proliferation and remodelling, thus strengthening the healing process [7, 16]. This may lead to reduced swelling, decreased pain, and increased comfort in patients with gonarthrosis.

The real mechanism for the proliferant anti-inflammatory effect is increased expression of cytokines that mediate chemomodulation, resulting in new connective tissue proliferation and strengthening, joint stability, and both joint dysfunction and pain reduction [10].

Another proposed prolotherapy mechanism is proliferation stimulation in joints or soft tissues, since dextrose and glucose solutions stimulate tissue growth and repair, leading to improved joint function [17, 24]. Significant is the so-called prechondrogenic effect of hypertonic sugar-containing solutions administered intra-articularly, which is also a controversial issue among specialists [10].

Thirdly, prolotherapy is associated with pain reduction through pain signal modulation and the achievement of analgesic effect. The prolotherapy analgesic effects are most likely mediated by its anti-inflammatory and anti-edematous impact, as well as by accelerated tissue repair in the affected joint [38].

Nevertheless, even in this case, we call for careful and long-term research into the prolotherapy, which shows promising positive effects, since, for example, according to Raeissadat et al. (2021), intra-articular hyaluronic acid administration is more effective than the hypertonic dextrose solution [40].

Therefore, prolotherapy represents a promising regenerative approach to the treatment of gonarthrosis, stimulating natural tissue repair and improving clinical manifestations of the disease by restoring damaged joint tissue structures.

This non-invasive treatment option for knee osteoarthritis is of promising interest, given the growing number of patients in this population. The need for effective utilization of medical services and sustainable treatment strategies to improve outcomes will be critical to minimizing the burden of OA at the individual and social levels.

## Conclusions

1. Degenerative-dystrophic and inflammatory lesions of large joints of the lower limbs, such as gonarthrosis, are characterized by complex cascading pathogenetic mechanisms that significantly aggravate the disease's symptoms and make drug therapy extremely ineffective.
2. Prolotherapy is an injection-based regenerative medicine method used to treat chronic knee joint pain by stimulating natural tissue repair through the administration of hypertonic glucose and/or dextrose solutions into damaged areas.
3. Clinical data confirms prolotherapy efficacy in pain reduction and joint mobility improvement, often achieving better results than traditional treatments such as hyaluronic acid injections.
4. Given the existing treatment's limitations, prolotherapy offers a valuable alternative, especially for patients searching for non-invasive treatment options for knee osteoarthritis.
5. Standardized treatment protocols, more robust research methodologies, and OA clinical manifestation prolonged studies are critical to fully understand the potential of prolotherapy with hypertonic glucose and/or dextrose solutions and establish it as a primary option for gonarthrosis treatment.

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