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Research article

Osteoarthritis Inflammatory Responses and Pulsed Electromagnetic Fields: A Possible Remediable Pathogenic Pathway Stimulator

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Abstract

Bone and cartilage, essential to mobility and functionality are sensitive structures whose qualitative and quantitative components depend not only on hormones, enzymes, vitamins, minerals and protein, but also on the stresses put upon them by function as well as their intrinsic and extrinsic environments. This paper reviews some recent pathological insights regarding the synovial membrane and its cells that indicate when injured may evoke a possible inflammatory pathway of inevitable joint destruction unless abated. One form of energy that may limit the spread of osteoarthritis severity known as pulsed electromagnetic field therapy appears promising here, despite claims to the contrary in the past. Here we argue in favor of its possible untapped utility as one that may serve to reverse or mitigate the onset of post traumatic arthritis, especially in the younger adult post trauma.

Keywords: Inflammation; Joint; Osteoarthritis; Pain; PEMF; Synovial; Treatment

Background

If one reviews the joint from an engineering viewpoint, it has the remarkable property of being a bearing relatively free from wear and in absence of disease appears to maintain its properties indefinitely [1]. Unsworth [2] attested to this fact when he stated that under normal conditions the fatigue life of cartilage was sufficient for a lifetime and one with potential viability even after 90 years of age. However, joints are frequently subjected to abnormal stresses and its lining tissue termed cartilage designed to absorb joint stresses may fail prematurely and continue to fail if trauma or stress ensue and despite decades of research that began to be reported electronically in 1885, its pathogenesis remains unclear, and is increasingly complex in its manifestations and cannot be effectively prevented from progressing or regressing readily [3]. Indeed, today in terms of prevalence rates, osteoarthritis alone is found to impact vast numbers of older adults as well as younger adults and although age is a factor, it is now recognized osteoarthritis contributors are largely embedded in remediable lifestyles and behaviors, but with a limited ability to reverse the condition unless addressed strategically and insightfully.

Historically intervention in this regard has focused on orthopedic management that has ranged from immobilization to mobilization. Since maintenance of tissue viability appears dependent on motion, the more recent trend has been towards the latter [4]. Physical therapists evaluate and treat patients with

limited or absent joint range of movement secondary to diverse painful musculoskeletal disease manifestations. The basic aim of physical therapy in this regard is to restore or improve optimal functional status. Problems arise however, in assessing objectively the relative benefits as well as the risks of some treatment approaches, and the dosage and methods of choice remain largely less than definitive and based on limited numbers of robust studies that may not represent clinical situations at all readily. As noted by Buckwalteret al. [5], in post-traumatic osteoarthritis, the joint degeneration, pain and dysfunction that develop following joint injury, and most common disease form is most directly related to elevated articular surface contact stresses, especially mechanical stress that exceeds the tolerance of the articular surface in one or more synovial joints. In some cases, decreasing mechanical forces on degenerated joint surfaces are however found to stimulate the formation of a new biologic articular surface.

By contrast, the potential abuse of excessive or repetitive fatiguing joint movement, as well as excess immobilization appears to be deleterious in differing ways on both intra- and periarticular structures. The effects of continuous as well as intermittent joint motion when studied in various clinical realms shows on average, the positive effects of intermittent non fatiguing non stressful movements on joint structures and thus their ability to function optimally.

Aim

The purpose of this mini review was to summarize and elucidate the known processes that appear to occur readily in post-acute traumatic osteoarthritis states as far as the key joint tissues of the synovium and cartilage are concerned. A second was to establish the potential for electromagnetic field applications [PEMF] to impact deleterious post traumatic synovial joint structure responses and pain associated with osteoarthritis development and progression as opposed to exercise adoption alone. This is based on acknowledging the intricate makeup of the synovial cells and tissues and their responses to trauma and repeated impacts. It specifically sought to uncover if improving synovial and joint microcirculation via PEMF is likely to help obviate or mitigate cartilage attrition due to factors such as hypoxia and abnormalities in the synovium located biochemical and molecular structures and pathways of influence.

Hypothesis

It was anticipated that a carefully stepped approach that includes PEMF can help to overcome the degree of inflammation and pain experienced by many in the face of a joint injury, especially in the post traumatic period.

Significance

Osteoarthritis, a highly disabling disease of the older adult population and one with few intervention options may yet be attenuated or prevented from an inevitable downward spiral of disability and derangement by careful upstream evaluations and early treatment, rather by any age-related wear and tear mechanism. If so, an enormous costly public health burden may be offset, as well as fostering lives of decreased suffering. Currently viewed as a multifactorial disease that emanates from the convergence of both genetic and environmental factors, it is reported that joint degeneration may be influenced by a single unanticipated injury, cumulative repetitive impact and loading effects, joint overuse, fatigue, instability, recurrent injuries and a too rapid a return to functions that provokes inflammation post injury. Several other risk factors for osteoarthritis include obesity, mitochondrial dysfunction, damage-associated molecular patterns, cytokines, metabolites and crystals in the synovium that can activate synovial cells and mediate synovial inflammation [6]. As a result, a concerted effort to improve the prevention and management of osteoarthritis has emerged wherein its biological processes and system alterations underpinning inflammation may be implicated [7], but where the ability to slow down or mitigate the disease progression and the role of inflammation is not always apparent.

Methods

To establish clarity as to current osteoarthritis inflammatory implications a review extending over the most recent studies published in the last five years [2020-25] was undertaken as regards the themes of osteoarthritis, joint synovium, and inflammation, plus PEMF as applied to joint lesions. Older articles of note were deemed informative and accepted if they were reports of structural biology and biochemistry. The review is an abbreviated one and is not a meta-analysis or systematic review, but one that strove to carefully examine key trends worthy of future study and clinical consideration, given new diagnostic modes of inquiry and novel questions not yet answered. Lab and clinical studies were deemed acceptable. Articles discussing rheumatoid arthritis and invasive approaches such as blood platelet rich plasma injections and surgery, as well as drug and exercise studies were not examined. For more detailed information, readers can examine prior comprehensive reports [8,9].

Current Observations

Osteoarthritis

Osteoarthritis, formally studied since at least 1885, remains the most prevalent joint disease and one that affects one or more freely moving joints such as the knee and commonly fosters progressively intense bouts of pain and disability among many older adults no matter where they reside. Largely deemed incurable, repetitive impact and loading, joint trauma and overuse and recurrent injuries especially in the face of acute injury or chronic disease manifestations may exacerbate the disease, especially with regard to the cartilage lining and its matrix. Although long accepted as an aging syndrome that is inherent and irreversible, the condition is currently conceived of as a multi-factorial one that implicates both genetic and environmental factors, rather than age alone. Indeed, not only do many older adults not suffer this condition, but some only incur problems at one joint and not others. Moreover, it is reported that joint degeneration has a higher prevalence in former athletes than the non athlete even though it can be accepted that

the athlete actively exercised to a high degree before and after being injured.

Repetitive impact and loading, joint overuse and recurrent injuries followed by a rapid return to the sport might explain athletes' or others predisposition to joint degeneration even in the modestly active case of osteoarthritis where medications to offset pain and various degrees of inflammation are common [10,11]. While drugs and surgery remain the key treatments for osteoarthritis, biophysics, the study of biological processes and systems using physics-based methods or those based on physical principles and are not always apparent in the broad recommendations currently listed for mitigating osteoarthritis, may well be highly relevant. For example, since the synovial environment can steer both cartilage degradation as well as regeneration [12] electromagnetic stimuli found to have like properties might be highly advantageous even at an advanced disease stage. Griffen [10] argues more discussion is needed here because osteoarthritis tends to involve persistent low-grade inflammation and activation of innate inflammatory pathways plus the recruitment of monocytes, lymphocytes, and other leukocytes.

In particular, macrophages can mediate synovial inflammatory activity and pathologic cartilage and bone responses. In the context of osteoarthritis, and many decades of research where it was believed that the articular cartilage defects were permanent, it is noteworthy that numerous studies especially those examining osteoarthritis progression and its repair potential show that articular cartilage exposed to an electrical field can increase or retain its proteoglycan content. As well, the cartilage proteoglycan molecules synthesised appear to be of normal size and composition. Importantly, this effect is also found to be maintained in the presence of interleukin-1beta, which commonly produces a net loss of tissue proteoglycan in osteoarthritic cartilage [13]. Moreover, Li et al. [11] who affirm osteoarthritis is a chronic and degenerative disease marked by inflammation and extracellular matrix degeneration show that contributing to synovial inflammation and cartilage destruction is a Liver receptor homolog-1 (LRH-1), an orphan nuclear receptor found to mediates inflammatory responses in the cartilage tissue in the face of joint damage, but is amenable to mitigation via specific signaling pathways.

Bolander et al. [12] highlight the fact that osteoarthritis was recently defined as being of epidemic proportions, and attributes this to the lack of effective treatment found to be highly correlated with the limited knowledge that prevails regarding the underlying pathophysiology of osteoarthritis. Failure to regenerate cartilage post trauma is also thought to be one of the underlying causes for degenerative diseases, including osteoarthritis. In this regard, it is conceivable non-ionizing physical energy and its usage as a form of physical stimulation might be oriented towards triggering a favorable biological response and down grading noxious sources of joint destruction. Data reveal it is possible to regulate specific intracellular pathways shown to have positive effects on articular cartilage, and synovial tissues that line the joint help in securing the integrity of the joint from day-to-day usages while fostering mobility.

Synovial Tissues

Osteoarthritis, a disease affecting one or more synovial or freely moving joints such as those at the knee, foot or hand commonly degrades well-being and may not adapt readily to provide for smooth almost frictionless movements at one or more articulation sites and for which these joints were designed [14]. These joints encompassing the ends of bones covered by cartilage, house a joint cavity, and are surrounded by an elastic and resistant skin covering, muscles, tendons, and veins [15]. Numerous blood vessels and nerves that lie adjacent to its capsule, and within a bi-layered lining known as the synovial membrane, are all sites of osteoarthritis pathology, especially as regards the synovial lining. This lining is a vital joint tissue component linked to cartilage viability and wherein its macrophage cell population may foster joint protection by forming an internal immunological barrier that can physically seclude the joint from undue insults [14].

However, if the joint capsule housing and surrounding the joint junctures and composed of an outer stratus fibrosis and an inner stratum of synovium are unduly stressed [16-18], cells in the synovium may become pro inflammatory, and as a result fail to produce that small quantity of highly viscous fluid that normally serves as a lubricant and termed synovial fluid. This fluid filtration system is vital because it constitutes the primary source of nutrition for the cartilage cells. While normally the fluid itself arises by diffusion from the synovial vasculature and represents a dialysate of plasma to which hyaluronate and some additional proteins are added, its disruption has immense consequences, including possible adverse impacts on the nutritive supply of the surrounding joint tendons, bursae, tendon sheaths, ligaments, nerves, and blood vessels. In addition, the synovium and its vascular tissue designed to serve as a shock-absorber, may undergo attrition, cellular, molecular, or dysregulation changes that can damage both cartilage as well as extra articular and support tissues and thereby multiple mobility challenges [19,20].

In turn, these alterations may forge an increase in pain and a gradual associated fibrosis of the subsynovial tissue that may not only foster ongoing inflammation, but may sensitize surrounding sensory neurons to further pain [21] and joint degeneration, joint swelling, inflammation, and stiffness. In this way it appears persistent inflammation of the synovial tissue may become an incremental and formidable driving force behind the destruction of articular cartilage, the hallmark of osteoarthritis disease [22]. In particular, repeated mechanical insults may tend to perpetuate any prevailing inflammatory series, even if initially designed to favor joint protection and recovery, and may lead to the onset of post traumatic osteoarthritis [23] wherein inherent synovial fibroblasts found to assume distinct functional identities, may alter Prg4hi levels that secrete Rspo2 and thereby may drive pathological joint crosstalk communications post injury.

In addition, the lubricating properties of synovial fluid may be undermined, with a concomitant decline in cartilage and

bone status and with this, the joint's load bearing capacity [20, 24]. Indeed, even though once refuted to be a non-inflammatory arthritis, recent research shows the histological changes observed in the osteoarthritis synovial membrane generally includes features of an inflammatory "synovitis"; plus a range of abnormalities, such as synovial lining hyperplasia, macrophage and lymphocyte infiltration, neo angiogenesis and fibrosis. This pattern of synovial reaction varies with disease duration and associated metabolic and structural changes in other joint tissues and thus a one size fits all approach applied to a vulnerable osteoarthritis joint and expecting some permanently favorable result appears more elusive than not [20].

This is because as proposed by Bolander et al. [12] a role for synovial fluid treatment applications to restore the articular cartilage and joint homeostasis of osteoarthritis that may be effective cannot be forthcoming on the basis of oftentimes limited joint evaluation procedures, limited related insights, and non specific generic practice recommendations that follow. Information on how synovial fluid composition may foster pro-regenerative immune cell influences on possible progenitor cells, and thereby pain and radiographic disease progression is especially indicated [25]. In addition, even if attempts to mitigate synovial inflammation should be studied as well in efforts towards obviating excess cartilage destruction [25-28], clinical practices that attempt to minimize inflammation are strongly indicated [29,30]. In particular, it appears attempts to offset hypoxia, and that limit the apparent mechano-sensitive synovial pathway of inflammatory metabolic responses if evoked can cause a cascade of joint destruction processes, including alterations in joint blood flow, synovial diffusing capacity and oxygen consumption of the synovial membrane [31,32].

Moreover, associated with joint effusion and elevated intraarticular pressure is the possible compression of the intracapsular vein, followed by possible future joint damage in the face of increased outflow resistance and fall in the regional blood flow of the joint and a state of tissue hypoxia [33]. Indeed, it is observed via new technologies that the synovium may show significant changes, even before visible cartilage degeneration has occurred, including the infiltration of mononuclear cells, the thickening of the synovial lining and the production of inflammatory cytokines or degrading catabolic inducing compounds [15]. In another study of a sizeable number of primary total knee joint arthroplasty surgery cases, synovial tissue samples were found to be colocalized and positively correlated with markers of synovial macrophages and fibroblasts tissue inflammation. As well, a parallel study showed the primary human fibroblasts stimulated with peptidoglycan [an arthritogenic bacterial cell wall component whose role in human osteoarthritis is poorly understood] tended to yield high levels of a pro inflammatory cytokine termed IL-6.

Consistent with the ex vivo findings was an observed and significant inverse correlation between the peptidoglycan presence and age at time of knee surgery, indicating younger age was associated with higher deposition and inflammatory levels [34].

Further Pathogenic Observations

As per emerging data osteoarthritis is no longer conceptualized solely as a condition that evolves due to age and joint wear and tear, rather, it appears to represent one or more understandable responses and diverse subgroup manifestations as well as uniform attributes in many cases subject to either a lack of movement or excess non physiological movements or joint stresses. Kofoed et al. [35] for example showed osteoarthritis is a complex joint disease of multiple features and one strongly subject to mechanical influences that overload or induce joint instability rather than any age inevitable condition. In the former case, it was implied that additional problems unfold in the event the tendons associated with the joint capsule lose their tensile strength and became overstretched if subjected to undue tensions and tensional forces and possible joint subluxation, tendon adhesions, suboptimal tendon repair and cell dysfunction [30]. Excess joint pressure in turn, potentially further increases stresses on the joint capsule and may foster its possible rupture in some cases, as well as foster joint effusion and muscle inhibition, plus the suboptimal transfer of oxygen to the cartilage across the synovial membrane.

As per Georgino et al. [36] it appears safe to say, a well-defined, albeit subliminal inflammatory process may not only underpin the development and progression of osteoarthritis, but a failure to establish its upstream origins is the reason for its increasing prevalence. This process commonly implicates the synovial membrane of one or more joints and thereafter, the activation of its local immune system linkages such as "damage-associated molecular patterns" (DAMPs) that are observed to foster joint degradation [37]. As well, pattern recognition receptors (PPRs), and complement play a role in synovial inflammation and cartilage degradation. In addition, crosstalk between joint tissues such as the synovium and cartilage at the cellular level is said to occur within the innate immune inflammatory network, especially in the absence of soundly construed therapeutic approaches [38]. Liu et al. [39] argued furthermore that synovial situated macrophages potentially play an important role in both the formation and progression of osteoarthritis. Of these, they indicate six key cells may be latent targets for future immunoregulatory therapy applications.

Other researchers [40] have found that there is indeed a low-grade inflammation presence in osteoarthritis joints, along with hyperplasia and an increased cell proliferation and fibrosis process. There is also a substance termed CEMIP, a regulator of the inflammatory response pathway and inflammatory cytokine production in vitro. Others show alterations of cartilage surface or degradation of biomacromolecules within synovial fluid that increases the wear and tear of the cartilage and hence determes the onset of the most common joint disease, osteoarthritis [24]. Di Carlo et al. [41] propose a further role for mesenchymal stem/stromal cells recruited in the synovium in the osteoarthritis disease cycle known as Synovial-Derived Stromal Cells that could also be involved in fostering its pathophysiology. Attention to a specific stromal cell type with a peculiar ultrastructure called a telocyte appears especially noteworthy here because these cells

can stimulate the formation of osteoclasts or bone resorptive cells. Macfarlane et al. [78]. propose inflammation is a potential pain generator and treatment target in osteoarthritis and here they propose that it is white blood cells that may be implicated.

Another observation is that innate immunity processes that stem from the immune receptor Dectin-1 located on macrophages influences the progression of osteoarthritis [42,43].

The differences reported above refer to diverse inflammatory mechanisms rather than other degrading causes of joint attrition even though they require more systematic appraisal [42]. However, their differences, impacts and spatial and transcriptional linkage mechanisms with immune cell and cartilage dynamics should be studied systematically in light of some novel ideas proposed by Niu et al. [44]. Niu et al. [44] propose that in addition to the impact of mechanical stress on cartilage degradation and loss recent studies have consistently revealed the involvement of a critical inflammatory component in nearly all joint tissues.

These responses have implicated complex mechanisms, such as alterations in immune responses, apoptosis, pyroptosis, and metabolic programming that may all play a pivotal role in the disease progression. As such, this group discusses and lucidly elaborates upon the term 'efferocytosis' referring in this regard to the process by which macrophages, other immune cells, and non-professional phagocytes, such as epithelial and endothelial cells, efficiently engulf and clear apoptotic cells to mediate, or alleviate inflammation and enabling the restoration of tissue homeostasis and its possible repair. However, if impaired in cases with osteoarthritis, the cells may fail to provide adequate clearance of apoptotic cells that leads to the activation of a prolonged immune response, chronic synovitis, and progressive joint degeneration and possible pain.

Pulsed Electromagnetic Field Therapy [PEMF]

In light of the need to intervene more successfully in the osteoarthritis pathogenic cycle in the future, one devise that produces low risk anti-inflammatory and pro anabolic cartilage effects is a form of low dose pulsed electromagnetic current and that can reduce pain and joint stiffness - plus muscle pain [45,46] in addition to joint inflammation has been discussed for some time [37]. In a recent clinical controlled study conducted in this realm PEMF applications appeared to provide global disease correlated benefits as well as pain relief [40]. This supports Ma et al. [41] who have reported that PEMF treatments appear to have great potential in the treatment of osteoarthritis in extremity joints. They specifically propose that appropriate PEMF stimulation can reverse the loss of cartilage extracellular matrix, as well as possible chondrocytes death.

Its application can also be expected to impact the expression of pro-inflammatory and degradative cartilage factors, restore any decreased cartilage thickness, and synovium inflammation, commonly induced at the early stage of osteoarthritis, a conclusion supported by Liu et al. [39]. The stimulation of PEMF also has a beneficial effect on trabecular bone microarchitecture; the downregulates of degrading IL-6 and TNF-α expression in cartilage, and functional progression of osteoarthritis through its inhibitory impacts of TNF-α and IL-6 signaling as confirmed by numbers of cell culture and animal studies [50]. Similarly, Fini et al. [51] found the application of pulsed electromagnetic fields preserved the articular cartilage morphology in the knee of aged guinea pigs, while preventing the development of osteoarthritic lesions. Ouyang et al. [52] who investigated the anti-inflammatory effects of PEMF on synovitis and its underlying mechanisms showed that PEMF does exhibit an anti-inflammatory effect on synovitis via upregulation of macrophages, which may be involved in the phosphorylation of P38.

This is important because the synovium may show significant histological and functional changes, even before visible cartilage degeneration has occurred, including mononuclear cell infiltration, thickening of the synovial lining and the production of inflammatory cytokines that could worsen if left untreated. Alternately, it is increasingly evident that pulsed electromagnetic field applications may be helpful in fostering, stimulating, or preserving extracellular articular cartilage matrix integrity, especially in the late stages of the disease, where excessive proteoglycan losses are common, or as an adjuvant to a larger treatment regimen as suggested by Sadoghi et al. [53] and Varani et al. [53]. It may also confer a chondroprotective effect in early osteoarthritis, where excessive proteoglycan is laid down [55, 56], but its size and composition may not be the same as that normally found under healthy conditions. In addition, their application may stimulate important DNA synthetic mechanisms in both prevailing and newly formed chondrocytes [57, 58].

In sum:

a) Extrinsically applied bouts of pulsed electromagnetic field applications may be helpful in preventing as well as relieving joint inflammation attributable to joint damage impacts.

b) Even if unproven, pulsed electromagnetic fields may provide a unique way of stimulating joint tissue and bone repair in cases of osteoarthritis that reduces inflammation indirectly.

c) Pulsed electromagnetic fields have unique biological effects that warrant further study.

d) Since mature articular cartilage cells do not mount a repair response that results in adequate matrix reconstitution at all readily [59], pulsed electromagnetic field therapy and an extension of this termed pulsed signal therapy may be helpful in stimulating this process [60].

e) Additional documented benefits of pulsed electromagnetic fields in the context of osteoarthritis include its potential to aid or diminish swelling, enhance collagen production, ligamentous tissue healing, nerve regeneration, and tendon and muscle improvements [9,61]. Its application can modulate chondrocytes apoptosis and inflammatory cytokines and is a valid option in the conservative management of several articular diseases, including early osteoarthritis [9,61].

Discussion

Osteoarthritis a widespread painful disabling disease and one of great suffering is generally deemed incurable with no safe disease modulating remedies is quite often associated with a low-grade inflammatory response that hastens its severity and progression [62,63]. Yet, interventions for osteoarthritis seen as very important commonly focus on efforts to mobilize the joints, in addition to weight management, and assistive devices such as canes or braces, along with patient education and lifestyle modifications, but not electrophysiological modes to any degree, even though these are known to have anti-inflammatory and regenerative properties [62]. Moreover, this broadly somewhat limited set of generic treatment options does not really embrace the extent and complexity of the disease, generally omits a role for averting low grade immune impacts. None target intricate pathways that sustain low-grade inflammatory processes- a key mediator of osteoarthritis pathology [63].

Even though low-energy pulsed electromagnetic fields delivered in single or pulse burst quasi-rectangular or triangular waveforms may impact the biochemical and physiological properties of articular cartilage and the cells within this tissue favourably in the lab [17] its application is not routinely mentioned as a specific clinical approach that can be directed and implemented for mitigating osteoarthritis in those cases requiring non-pharmacologic interventions or desire to employ its application in light of its anti-inflammatory disease mitigating and reparative properties. This is despite a rich growing volume of attention to the osteoarthritis inflammatory implications and many PEMF lab and at least some clinic based successes that could potentially prove restorative even though the research to date is limited and based on lab studies of induced arthritis and the use of AI as a diagnostic and prognostic tool rather than upstream causative factors.

Some new insights, and tailoring rather than the application of generic global recommendations could heighten as opposed to lowering inflammation in all likelihood. Non-functional potentially harmful exercise strategies such as exercising an effused osteoarthritis knee joint in full extension, and the lack of importance delegated to carrying out behaviorally graded carefully construed non fatiguing and non stressful rather than impactful activities is strongly indicated. Those who are overweight or obese, plus those who are frail, those suffering neuropathic pain, or involved in high intensity sports should be wary of narcotics that relieve pain but foster motion, but aware of PEMF benefits that are deemed safe. Education is indeed vital here because a failure to appreciate or value the importance of rest for short time periods only and addressing the upstream factors that appear noteworthy in osteoarthritis pathology, such as sensory innervation alterations, may prove especially beneficial when combined with PEMF applied to muscles and possibly integrated into joint support systems such as braces or other or wearables, such as compression gloves.

Modulated to avoid harmful inputs, and applied in loose packed or functional joint positions PEMF may allow synovial fluid to be optimized and enabled to flow more freely thus favoring cartilage nutrition and overall defect size and extent. At the same time lab data show electromagnetic field applications can stimulate chondrocyte cell receptors and related transcription and synthetic processes [64]. Moreover, by interacting with molecules on the chondrocyte cell surface membrane, pulsed fields can modify internal calcium concentrations and other ions that stimulate DNA transcription and trigger proteoglycan production [58]. By up-regulating members of the transforming growth factor B super gene family that have important regulatory functions in joints [64], electromagnetic fields may prove of high value because they are found to increase chondrocyte synthesis of proteoglycans that constitutes its matrix directly [59,65].

Other post PEMF observed mechanisms of action are altered rates of transcription of c-myc and other genes, a reduction in spontaneous chondrocyte cell death, increased messenger RNA levels, and changes in receptor activity that stimulate second messenger systems and positive plasma membrane changes [66]. According to Ganesan et al. [67] pulsed electromagnetic fields may increase ionic permeability of membrane channel proteins, resulting in a stimulation of secondary messengers that have diverse biological effects. They can also impact inflammation and enhance antioxidant status. It is also possible biochemical composition, histology, and gene expression are stimulated favorably as revealed by associated elevations in matrix constituents and collagen levels following PEMF treatment exposure. In addition to fostering a pro-anabolic effect on, cartilage and joint with complementary repair properties may be favorably impacted. Selective homing of target cells to defect sites, which theoretically may especially augment any natural repair process involved in improving cartilage repair and healing, such as its anti-inflammatory and restorative impacts [68-72].

In the interim, despite many limitations, this realm of inquiry appears of high value and in our view should be vastly extended to verify or elucidate upon findings that synovial fluid, but not plasma interleukin-8, is associated with clinical severity and inflammatory markers in knee osteoarthritis women with joint effusion [73]. Also requiring insights is the view that the synovium secretome may prove to be a valuable disease-modifying treatment target for osteoarthritis, but its idea has not been adequately examined [74]. The nature of the complexity of synovial fluid-derived monocyte-macrophage-lineage cells in knee osteoarthritis also warrants study in our view [75]. As well, how humans will respond to pulsed electromagnetic field attributes found to alleviate synovitis and inhibits the NLRP3/Caspase-1/GSDMD signaling pathway in rats and whether this will impact trauma care also appears worthy of future study [76,77].

Until the, there can be no doubt that a high degree of suffering among the older adult osteoarthritis population is related to past or present synovial joint tissue status and its presence should be averted and duly acknowledged [78-82].

Concluding Remarks

Despite the limitations of this brief overview, we believe there is supportive data as regards possible-

a) Increases in the osteoarthritis burden over time if osteoarthritis dogma remains grounded in the belief it is an inevitable degenerative age-related disease where inflammation is of a low grade or negligible mediator.

b) Inflammation that is provoked beyond the immediate post-acute trauma response stage can perpetuate joint damage in its own right and should be sought and studied in more depth as it appears a leading pathogenic factor.

c) Careful manipulation of the synovial microenvironment and its molecular pathways via PEMF as indicated coupled with the prevention of harmful mechanical stimuli may prove fruitful.

d) Further basic and clinical research to validate the use of pulsed electromagnetic fields in lessening osteoarthritic inflammation and pain and facilitating function and joint repair is strongly indicated.

Acknowledgement

None.

Conflict of Interest

No conflict of interest.

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