Transdermal Bio-identical Progesterone Cream as Hormonal Treatment for Osteoarthritis

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ABSTRAK

Osteoartritis (OA) adalah kondisi yang dijumpai di seluruh dunia, sangat berkaitan dengan proses penuaan dan merupakan tipe artritis yang paling sering ditemukan. Karena berpengaruh terhadap kemampuan berjalan dan mobilitas, maka artritis mempunyai dampak fungsional yang bermakna dan berkaitan dengan biaya kesehatan yang cukup tinggi. Proses penuaan dalam masyarakat dan epidemi obesitas menjadikan beban OA dapat diperkirakan semakin meningkat dalam 20 tahun mendatang. Meskipun pada awalnya OA telah dianggap kelainan sendi tanpa peradangan, namun gejala peradangan lokal dan sinovitis didapatkan pada sebagian besar pasien dan gejala tersebut ditemukan bahkan tanpa adanya peradangan klasik yang ditandai oleh infiltrasi netrofil dan makrofag ke dalam jaringan sendi, meningkatnya sitokin peradangan yang diukur dalam cairan sinovial OA. Meskipun lesi tulang rawan ditemukan pada lokasi yang cukup jauh dari sinovium, tetapi fibroblas dan sel-sel sinovial yang menyerupai makrofag serta sel tulang rawan itu sendiri (kondrosit) merupakan sumber sitokin yang potensial dan dapat menginduksi kondrosit untuk melakukan sintesis dan sekresi enzim cartilage-degrading protease, sitokin dan mediator peradangan lainnya. Progesteron bio-identik menunjukkan efek anti-peradangannya pada OA dengan menekan ekspresi gen yang berperan dalam produksi sitokin peradangan melalui interaksi negatif antara faktor transkripsi nukleus dan reseptor progesteron dan/atau peningkatan inhibisi faktor transkripsi nukleus yang diinduksi oleh progesteron di dalam nukleus. Progesteron bio-identik dapat mengatur remodeling tulang secara tidak langsung dan juga memainkan peran penting dalam perkembangan dan pemeliharaan tulang rawan. Kajian ini akan membahas tentang krim progesterone bioidentik transdermal sebagai pengobatan hormonal yang disarankan untuk OA, berdasarkan proses patogeniknya.

Kata kunci: *osteoartritis, proses patogenik, krim progesteron.*

ABSTRACT

Osteoarthritis (OA) is a condition found worldwide, is strongly associated with aging and is the most common type of arthritis. Because of its effect on ambulation and mobility, it has significant functional impact and is associated with considerable medical costs. Because of the aging of the society and the obesity epidemic, the burden of OA can be expected to increase over the next 20 years. Although OA has been regarded primarily as a non-inflammatory arthropathy, symptoms of local inflammation and synovitis are present in many patients and have been observed and even in the absence of classical inflammation, which is characterized by infiltration of neutrophils and macrophages into joint tissue, elevated levels of inflammatory cytokines have been measured in OA synovial fluid. Although the cartilage lesion is present at sites remote from synovium, the fibroblast- and

macrophage - like synovial cells, as well as the chondrocytes itself, are potential sources of cytokines that could induce chondrocytes to synthesize and secrete cartilage-degrading proteases, cytokines, and other inflammatory mediators. The bio-identical progesterone shows its anti-inflammatory effects in OA by suppressing gene expressions in the production of inflammatory cytokines through the negative interaction between nuclear transcription factor and the progesterone receptor and/or the progesterone–induced increase of nuclear transcription factor inhibition in the nucleus. The bio-identical progesterone may indirectly regulate bone remodeling and may also play a role in the development and maintenance of cartilage. This review will discuss about transdermal bio-identical progesterone cream as suggested hormonal treatment of OA, based on its pathogenic process.

Key words: *osteoarthritis, pathogenic process, progesterone cream.*

INTRODUCTION

Osteoarthritis is a slowly and continuously progressive degenerative disease characterized by gradual loss of articular cartilage.[1] It is a well known disease that is part of the aging process and also one of the most common joint disorder. There is evidence that a majority of individuals over the age of 65 have radiographic and/or clinical evidence of OA.[2] Since OA lesion is often localized to weight-bearing cartilage or to sites of trauma, repetitive mechanical injury has been proposed as the critical signal for the initiation and progression of OA.[1]

Osteoarthritis is affecting 21 million people in the United States in 1990 and 1-2 millions aging people in Indonesia have disability caused by OA.[3,4] Because of its effect on ambulation and mobility, OA of the knee and hip has significant functional impact and is associated with considerable medical costs, accounting for most of the 478,000 total knee replacements and 234,000 total hip replacements for the arthritis in 2004. Approximately, 56.7% of outpatient clinic of Rheumatology Department, in Cipto Mangunkusumo Hospital has been diagnosed with one of OA variants.[4] The burden of OA can only be expected to increase over the next 20 years.[3]

Although OA has been regarded primarily as a non-inflammatory arthropathy, symptoms of local inflammation and synovitis are present in many patients and have been observed and even in the absence of classical inflammation, which is characterized by infiltration of neutrophils and macrophages into joint tissue, elevated levels of inflammatory cytokines have been measured in OA synovial fluid.[1] Osteoarthritis typically affects the knees, hips, hands, spine, and feet. A number of risk factors have lately been identified. There is now strong evidence that the structural changes globally observed in OA are due to a combination of factors, raging from mechanical to the biochemical. The joint degeneration in OA affects all structures in the joint and should considered a failure of the total joint.[5] It is characterized by thinning and fibrillation of the cartilage with loss of joint space, osteophyte formation, subchondral bony sclerosis, cyct and deformity. Clinically, this can be accompanied by pain on use of the join, stiffness particulary after inactivity, bony enlargement and tenderness, synovial hypertrophy and effusion, limited range of motion and decreased joint fuction.[3]

The treatment of OA should be based on the mechanism of this disease to control symptoms and pathologic process. In OA, drugs are used to control the symptoms, restore the daily activities (symptom modifying effect), prevent and restore the degradation of the cartilage (structure modifying effect).[6] The role of catabolic factors in cartilage degradation and the implication of synovial inflammation and cytokines in disease progression have made possible more precise identification of pathways that have the potential to become treatment targets.[5] The clinicians usually give the non-steroidal anti-inflammatory drugs (NSAIDs) to reduce pain, but it all has gastrointestinal and cardiovascular side effect, even inducing and causing the degradation of cartilage itself.[6] In this review, we will discuss about the transdermal progesterone cream as suggested hormonal treatment of OA, based on its pathogenic process.

THE PATHOGENIC PROCESS OF OA

In OA, although the cartilage lesion is present at sites remote from synovium, the fibroblast- and macrophage - like synovial cells, as well as the chondrocytes itself, are potential sources of cytokines that could induce chondrocytes to synthesize and secrete cartilage-degrading proteases, cytokines, and other inflammatory mediators.[1] The chondrocyte exhibits a transient proliferative response (clonal growth), increased synthesis of cartilage matrix as an early attempt at repair, and increased synthesis of catabolic cytokines and matrix degrading enzymes. The aberrant behavior of OA chondrocytes is reflected in the appearance of fibrillations, matrix depletion, cell cluster, and changes in quantity, distribution or composition of matrix protein.[1,7]

The clinical signs of inflammation in OA are usually not prominent, but modest synovial swelling, tenderness, and joint effusion, indicating presence of inflammation. The analysis of human OA cartilage in a number of laboratories has shown an up-regulation of mRNA of several pro-inflammatory cytokines, several MMPs, inducible nitric oxide synthetase (iNOS), cylooxygenase (COX)-2, interleukin (IL)-8, and TGF-β. 1 A large number of pro - inflammatory cytokines, antagonists, growth factors are likely to be involved in OA. In particularly, IL-1β released by fibroblast- and macrophage-like cells of the synovium and tumor necrosis factor (TNF)-α seem prominent and of major importance to cartilage destruction (**Figure 1**).[1,5]

The interleukin-1β and TNF-α can stimulate their own production and induce chondrocytes and synovial cells to produce other cytokines, such as IL-8, IL-6, IL-17 and IL-18 (increasing the expression of IL-1β, IL-6, stromelysin, iNOS, and COX-2), leukemia inhibitory factor (LIF), as well as stimulate proteases production and prostaglandin (PG) E2 production by stimulating the gene expression or activities of COX-2, microsomal PGE synthetase-1 (mPGES-1), and soluble phospholipase (sPL) A2, matrix metalloproteinases (MMPs), insulin like growth factor-1 (IGF-1), transforming growth factor (TGF)-β or bone morphogenetic protein (BMP)-2, and they up-regulate the production of nitric oxide via iNOS or NOS2 which may inhibit actin polymerization, matrix synthesis, and promotes apoptosis of chondrocytes.[5,8,9] Prostaglandin E2

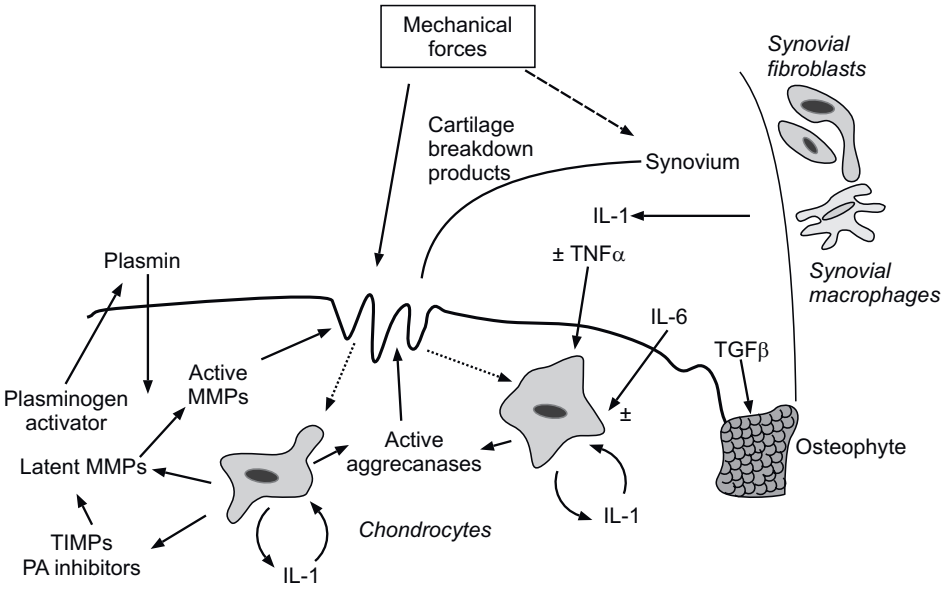

Figure 1. Schematic representation of the cells and mediators involved in the pathogenesis of OA. Mechanical stress initiates the cartilage lesion by altering chondrocyte-matrix interactions and inducing synthesis of catabolic cytokines and matrix-degrading proteinases by chondrocytes. The povital role of Il-1 released by fibroblast-and macrophage-like cells of the synovium in response to cartilage breakdown products, and possibly to direct mechanical stimulation is represented. Amplification by TNF-α and modulation by other cytokines may also be important in the inducing and maintenance of cartilage destruction.[1]

and IL-8 have neutrophil chemotactic activity into the tissues. The IL-8, TNF-α, platelet activating factor, leukotriene B4, and lipopolysaccharide which may enchance neutrophils for greater respons to agonist.[10,11] Moreover, TNF-α has also been shown to induce osteoclastic bone resorption in vitro, a phenomenon that may be involved in the remodeling of OA subchondral bone (**Figure 2**).[1,5]

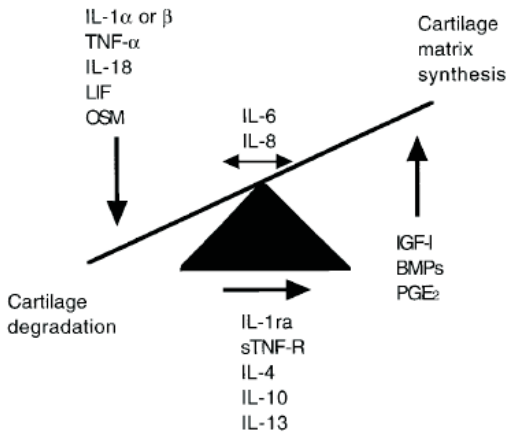

Figure 2. The cytokines balance in OA. Both catabolic and inhibitory cytokines are present in OA joint tissues, but it is the balance among these cytokines and with anabolic factors that determines the severity of cartilage damage.[1]

The involvement of chondrocyte-derived matrix MMPs in the degradation of cartilage collagens and proteoglycans in OA is well established. The development of antibodies that detect specific cleavage epitopes has permitted the analysis of degradation products of type II collagen and aggrecan in synovial fluid and cartilage of OA patients.[1] The proteolytic enzymes involved in this process ate matrix metalloproteinase 1 (MMP 1 or collagenase) and matrix metalloproteinase 3 (MMP-3 or stromelisin) and controlled by endogenous inhibitor called by tissue inhibitor of metalloproteinase (TIMP). The balance of MMPs and TIMP depends on interleukine-1 (IL-1).[12,13]

The pathological process of OA will continue since there is dysregulation mechanism or up regulation of MMPs genetic expression by synovium and chondocyte. Several MMPs will produce in large amount, such as MMP-1 (collagenase-1), MMP-3 (stromelysin), MMP-2 and MMP-9 (gelatinase), MMP-8 (neutrophil collagenase), MMP-13 (collagenase-13), MMP-7 (matrylisin), aggrecanase, lysosomal hydralase, and cathepsin-B.[13] The ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) or aggrecanase also involved in the degradation process of the cartilage. There are 2 types of aggrecanases or ADAMTS: ADAMTS-4 (aggrecanase-1) and ADAMTS-5 (aggrecanase-2), which cleavage the proteoglycan (aggrecan) in matrix cartilage.[8,14,15]

The IGF-1 and members of TGF-β or BMP-2 have been implicated as important regulators of cartilage-specific gene expression during development, growth, and differentiation. The IGF-1 is more appropriately categorized as a differentiation factor and has a limited mitogenic activity which depends on basic fibroblast growth factor (bFGF) as the most potent chondrocyte mitogen.[15,16] The TGF-β or BMP-2 regulates the early commitment of mesenchymal cell to chondrogenic and osteogenic lineages during cartilage development and endochondral bone formation, stimulates proteoglycan synthesis, and osteophyte formation.[17,18]

PROGESTERONE AND OA

Progesterone, a precursor for all steroid hormones, is produced from cholesterol in the corpus luteum of the ovaries as the major site of synthesis.[19] Primary follicles play a dual role in secreting either estrogen or progesterone. Before ovulation, granulose cells in the follicle biosynthesize and secrete estrogen. After follicle rupture an release of the ovum, these granulose cells mature to form the corpus luteum, which is responsible for secretion of progesterone and estrogen in the latter part of the cycle. In the human, if fertilization does not occure within 1-2 days followed by regression of the gland and concomitant cessation of estrogen and progesterone release. If fertilization occurs, the corpus luteul will continue to grow and function for the first 2 to 3 months of pregnancy. After this time it will slowly regress as the placenta assumes the role of hormonal biosynthesis for maintenance of pregnancy.[20] Another site of Progesterone synthesis are adrenal gland, brain, prostate gland and testis and the main souce of

progesterone synthesis in man.[21]

Once released, progesterone is carried in the blood by transcortin (corticosteroid-binding globulin) in many species including human.[20] Progesterone effects are mediated by its nuclear receptor. Progesterone receptor (PR) is a member of a large family of the ligand-activated nuclear transcription regulators, which includes receptors for steroids, retinoids, thyroid hormones, and vitamin D. The biological actions of progesterone are mediated through the PR which expressed as three isoforms, PR-A (94 kDa), PR-B (116 kDa), and PR-C (60 kDa).[20,22] The PR mRNAs are generated from a single gene by differential promoter use. The PR-B has been shown to function as a strong trans-activator of progesterone-regulated genes; when PR-A and PR-B are co-expressed, the A isoform can repress the action of PR-B. The inhibitory action of PR-A protein was suggested to be due to its inability to efficiently recruit coactivators and its increased interaction with compressor, as compared to PR-B. The third isoform, PR-C, an N-terminally truncated form of PR lacking the DNA binding domain, has been reported to be restricted primarily to the cytosolic fraction.[22,23] Given that PR-C does not have the capacity to bind DNA but is able to bind progesterone, and may inhibit PR function by sequestering available progesterone away from the PR-B isoform. The PR-C has also been found to bind the PR-B isoform, thereby reducing the capacity of PR-B to bind to PR response elements. As a result of isoform-specific functional differences, tissue responses to progesterone may be profoundly affected by changes in PR-A: PR-B: PR-C expression ratios, and they act through NF-κβ.[23]

Protein kinases that regulate signal transduction pathways in OA may induce by IL-1 and TNFα have also been proposed as therapeutic targets, including the stress-activated protein kinases, c-Jun N-terminal kinase and p38 mitogen-activated protein kinase (MAPK), as well as the Iκβ-1 and -2 kinases that release nuclear factor κβ (NF-κβ) from its inhibitor, Iκβ.1,7 The NF-κβ dependent transcriptional activation of pro-inflammatory genes, such as IL-1 or TNF-α may provide positive feedback to the pathway, self-perpetuating the inflammatory response. The transcription factor NF-κβ regulates gene expression of a variety protein induced during immune and inflammatory responses, including several cytokines.[24]

The NF-κβ is characterized as a heterodimer comprised of a 50 kDa (p50) and a 65 kDa (p65) sub-unit. In addition to the heterodimer p50-p65, homodimers also recognized the common DNA sequence binding motif. Although p50-p50 or p65-p65 homodimers both have been previously proposed to be involved in gene expression by selective activation of genes, p-65-containing complexes are the most frequently reported as initiating transcription factor.25 Such variety in dimerization may contribute to the cell type specivity of NF-κβ response. The dimer composition of NF-κβ may also affect interaction with inhibitory or regulatory proteins such as the various members of the Iκβ family of proteins (60-70 kDa).[26]

The NF-κβ activity is largely inducible, and the prototype p65/p50 NF-κβ is retained in the cytoplasm of an un-stimulated cell by its association with Iκβ. When an extracellular stimulus, such as cytokines(e.g., IL-1β, TNF-α) or oxidative stressor activates the NF-κβ-signaling pathway, Iκβ is phosphorylated at serine 32 and 36.[25] Phosphorylated Iκβ is a target for ubiquination at lysine 21 and 22, which lead to rapid removal of Iκβ via the proteosomal degradation pathway and unmasking of the p65 nuclear localization sequence and movement of the NF-κβ to the nucleus of the cell and mediating the transcriptional activation. Once activated, the NF-κβ binds to cognate NF-κβ sites in the chromatin and modulates gene expressions involved in immune response and inflammation due to the extracellular pro-inflammatory signals (**Figure 3**).[25,26]

Progesterone shows its anti-inflammatory effects in OA by suppressing IL-1β mRNA and TNF-α mRNA productions and expressions, inhibits inducible nitric oxide synthase gene expression and nitric oxide production, MMPs production which involved in the type II collagen cleavage, IL-6 production, IL-12 and PLA2 production, IL-8 and other cytokines productions and expressions, also COX-2 mRNA expression and PGE2 production.[27-30] These effects may be

explained by the negative interaction between NF-κβ p65 sub-unit and the progesterone receptor and/or the progesterone –induced increase of Iκβ protein translocation to the nucleus.[25]

Progesterone may indirectly regulate bone remodeling, fascilitated by the ability of progesterone to act as ligand for the glucocorticoid receptor. Glucocorticoid have been implicated in the process of bone loss through their ability to block 1,25(OH)2-vitamin D-induced osteocalcin synthesis and to prevent attachment of osteoblast to matrix proteins, including osteonectin, possibly through down-regulation of β1-integrin and other cell surface attachment factors. Glucocorticoid may also increase bone sialoprotein mRNA levels contributed to acceleration in maturation of pro-osteoblast which contribute to bone loss, that can be blocked by 1,25(OH)2-vitamin D. Progesterone may also play a role in the development and maintenance of cartilage since it has effect on reducing the production of MMP family as tissue-degrading proteinases.[20,31]

TRANDERMAL BIO-IDENTICAL PROGESTERONE CREAM AS SUGGESTED HORMONAL TREATMENT FOR OA

The transdermal delivery of progesterone is the administration of the progesterone through intact skin for systemic effect that will avoid progesterone from the hepatic first pass metabolism, give ability to discontinue administration by removal of the system, control the progesterone delivery for a longer time than the usual gastrointestinal transit or oral dosage form, and modify the properties of the biological barrier to absorption.32,33 Progesterone is very lipophilic (hydrophobic) and is non-polar. As a result, after it is well absorbed through the skin, it will be stored in fat tissues and after reaching a saturation level that is sufficiently high so that the fatty tissue diffuses them into the capillaries for the uptake by blood circulation.[34] Entering the blood circulation, the progesterone will seek out a similar, or non-polar, environment, such as the fatty membrane of red blood cells, and not by absorption into plasma. Since red blood cells are the major cellular components of the blood, it is reasonable that progesterone is transported in the blood in this way. When progesterone is added directly to whole blood, about 80% of it is taken up by red blood cells. Furthermore, progesterone bound to red blood cells can dissociate within milliseconds, allowing rapid transport into target tissues.[34,35]

The progesterone cream used in the treatment of OA is bio-identical progesterone, usually extracted from wild yams which contain many steroid hormones with some components

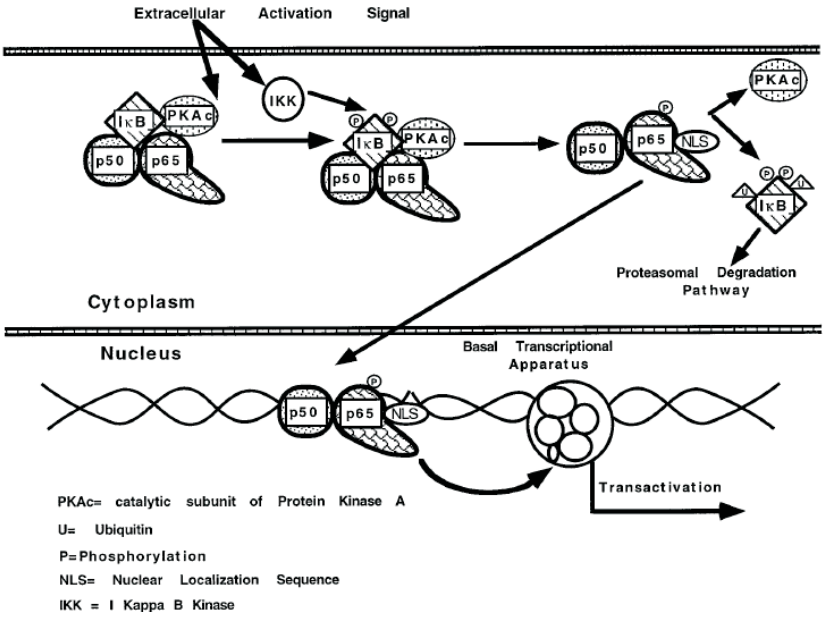

Figure 3. The general mechanism of NF-κβ activation. Unactivated NF-κβ heterodimers are retained in the cytoplasma by the inhibitory NF-κβ sub-unit Iαβ.[25]

molecularly identical to what a human female makes. In order for a hormone to be labeled "natural", its source must exist somewhere in the nature, either plants or animals. Natural hormones are not created in a lab. The bio-identical hormones can be manufactured in a lab or extracted from nature; the source does not matter as long as the actual product is molecularly identical to what the body makes.[36] The synthetic progesterone hormones, such as dydrogestrone, medroxyprogesterone, and norethisterone, are progesterone hormones with the molecule structure is not identical to what is produced in the human body. The synthetic progesterone acts at many on the same receptor sites as bio-identical hormones, thereby triggering a similar response in many areas of the body. However, the similarity is limited, as synthetic progesterone has many un-wanted and un-controlled effects, such as fatigue, dizziness, weight gain, light periods or absent periods, headaches, nipple tenderness, and mental fogginess.[36,38,39] These side effects are rarely happened with bio-identical progesterone, and may be handled by adjusting the dose.[33,37] Since the OA is a degenerative process during post-menopause and andropause period, so there is a possibility that the deficiency of progesterone may play a role in its pathogenesis. Beside as anti-inflammation and play a role in the development and maintenance of cartilage, natural progesterone may also give benefits, such as natural anti-depressant, enchances mood and create a calming effect, provides healthiness to skin, hair, and nails and helps prevent hair loss, regulates fluid balance by acting as natural diuretic, helps burn fat for energy and provides necessary control for insulin regulation, protects against endometrial cancer, fibrocystic breasts and probably breast cancer, helps support the thyroid, regulates body temperature, and controls monthly bleeding by normalizing blood clothing.[37,38]

The bio-identical progesterone cream used in the treatment should contain at least 450 mg of progesterone per 28 grams (1 ounce), with the recommended physiological dose is 15-20 mg of progesterone daily (1.6% or 2.0% cream) and may be increased to 10%. It may be applied directly on the joint or tissue that hurts and do not wash the skin for at least an hour after applying. There are reports of significant joint and muscular mobility after 2 years on bio-identical progesterone and many have reported remission with no further progression 3 years on, suggested that the bio-identical progesterone may slow down or even stop the inflammation and degradation process in OA.[33]

The bio-identical progesterone cream should be avoided in patients who take contraceptive pill, synthetic prednisolone or prednisone, cortisone acetate, combination of hormone replacing treatment patches combining estrogen and progestogens, synthetic progesterone hormones, injections of cortisone based analgesics, and other unknown drugs. The bio-identical progesterone cream should not be used by those who have severe active liver diseases, history of herpes gestationis, jaundice of the pregnancy, and known sensitivity to progesterone creams or any of their individual components.[33,39]

CONCLUSION

The OA is a slowly and continuously progressive degenerative disease characterized by gradual loss of articular cartilage. There are clinical signs of inflammation in OA such as synovial swelling, tenderness, and joint effusion, indicating presence of inflammation. The IL-1β and TNF-α seem prominent and of major importance to cartilage destruction and may induce the activation of NF-κβ. The bio-identical progesterone cream may be used in the treatment of OA by producing negative interaction between NF-κβ p65 sub-unit and the progesterone receptor and/or the progesterone –induced increase of Iκβ protein translocation to the nucleus. There are reports on bio-identical progesterone cream about the significant joint and muscular mobility and remission of the disease with no further progression. The transdermal bio-identical progesterone cream may be used as suggested treatment of OA.

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