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CIRCADIAN RHYTHMS IN ARTHRITIS: A REVIEW

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Abstract

Arthritis is a severe disease of joints that is affecting a large portion of population. The symptoms of arthritis show a circadian variation in which joint stiffness and pain are more prominent in the early morning and during winters. Dysfunctioning of the hypothalamic–pituitary–adrenal axis (cortisol) and pineal gland (melatonin) seems to be important factors in the perpetuation and clinical circadian symptoms of arthritis. The occurrence of circadian rhythms of the inflammatory reaction suggested the activities of daily living activities for measurements in clinical trials. The present review deals with the signs and symptoms of various types of arthrits, its dependence upon circadian rhythm in terms of hormonal and pain threshold and different treatments to overcome its occurrence. From this review it can be concluded that a better understanding of circadian cycle will help to evaluate new modes of drug targeting in a more effective manner and with fewer side effects.

Key Words: Circadian rhythms, Arthritis, Morning- stiffness, Cortisol, Melatonin

Introduction

It is a well-known phenomenon that the patients with chronic inflammatory diseases exhibit circadian rhythms. This has been mostly seen in patients with arthritis disease.¹⁻⁷ Morning stiffness is the main marker in the arthritis so the arthritis patients particularly experience joint pain, morning stiffness, and functional disability in the early morning hours due to the effect of cytokines, mainly, TNF-alpha and IL-6. This shows that the diurnal variations causes larger amplitudes of arthritis pain with the patient's condition being poor in the early morning and being mild or moderate in the early evening. The mechanism of diurnal cycle causes the changes in symptoms with a maximum peak of pain in the morning time and is relevant to the patho physiology of arthritis disease.^{8,9} Since circadian rhythm is generated solely in the brain centers of the hypothalamus, neuro endocrine immunologic

pathways are relevant to arthritis. Sex hormones like progesterone and estrogen seems to be involved in the circadian rhythm of the arthritis. Single cells in the human body can generate circadian rhythms like cardiomyocytes, natural killer cells, liver cells and other cells. These activities are controlled by the supra chiasmatic nuclear cells situated in the midline of the brain just above the optic chiasma. All the circadian rhythms i.e., disease related or not are originated from the SCN. So the SCN is the main source of the origination of the circadian rhythms. Most of the anti inflammatory agents in arthritis disease are originate from the site of the SCN nucleus because the arthritis symptoms are mainly occur due to the variations in the hypo thalamic pituitary adrenal axis (cortisol) and pineal gland (melatonin) the involvement of various cytokines like TNF alpha, IL-6, IL-1 shows the diurnal rhythm variation. Such coupling phenomena are important in the treatment of arthritis symptoms.

The term ‘Arthritis’ comes from the Greek word *arthron* means “joint” and Latin word *itis* means “inflammation”. Arthritis affects the muco skeletal systems, especially joints. Arthritis is not a single disease or a condition it is a term that covers over 100 medical conditions. A joint is a place where two bones are meeting. Ligaments hold the two bones together. The ligaments are like elastic bands, while they keep the bones in place your muscles relax or contract to make the joints moveable. The covering of cartilage allows the joints to work smoothly and painlessly. A capsule surrounds the joint contain the synovial fluid which nourishes the joint and the cartilage. The synovial fluid is produced by the synovium or synovial membrane which lines the joint cavity. There are over 100 types of arthritis. Here is a description of some common ones:

Osteoarthritis

In this type of arthritis the cartilage loses its elasticity and joint damaged easily because it becomes stiff. Due to this the ligaments and tendons become stretched this causes the severe pain in the joints.

Rheumatoid arthritis

The synovial membrane is affected badly this resulting in swelling and pain. This type of arthritis is significantly more common in women than men .It mainly the affected the patient aged between 40 and 60. However, children and much older people may also be affected.

Infectious arthritis (septic arthritis)

In this type of arthritis the synovial fluid and tissues of a joint are affected. It usually caused by bacteria, fungi or viruses which may be spread through the bloodstream from infected tissue of the joint of the patient. Most susceptible people develop an infection through the bloodstream.

Juvenile rheumatoid arthritis (JRA)

The arthritis that affects a person aged 16 or less. So it is called as juvenile type of arthritis.

Signs and symptoms of arthritis

The symptoms of arthritis depend on the type of arthritis:

Osteoarthritis

In this type of arthritis there is a pain in a joint either during or after the movement of joint. When

pressure is applied on the joint this causes the tenderness on the joint and the joint loses its flexibility. In the morning the joints becomes stiffer this causes the grating sensation in the joint of the patient. Hard lumps or bone spurs appear around the joints and it might swell. The most common affected joints are in the hips, hands, knees and spine.

Rheumatoid arthritis

It is severe type of arthritis form. The symptoms include joints pain, inflammation and stiffness. The joint is tender when touched and the fingers, arms, legs and wrists are mostly affected. Symptoms are usually worst in the morning. The morning stiffness can last for 30 min. Hands may be red and puffy. There may be nodules or bumps of tissue under the skin of the patient's arms are formed. Many patients with rheumatoid arthritis feeling tired and fatigue most of the time. Weight loss is common.

The smaller joints are usually affected. As the arthritis progresses it spreads from the smaller joints in our hands, wrists, ankles and feet to our elbows, knees, hips, neck, shoulders and jaw.

Infectious arthritis

The patient suffering from fever, joint inflammation and swelling, will feel tenderness or a sharp pain. These symptoms are linked to an injury or another illness. Mostly affected areas are the knee, shoulder, elbow, wrist and finger. In the majority of cases, only one joint is affected.

Juvenile rheumatoid arthritis

The patient experiences an intermittent fever which tends to peak in the evening and then suddenly disappear. The appetite will be poor and the patient will lose weight. Anemia is also common. The patient experiences a stiff neck, hips or some other joint.

Circadian rhythms in arthritis

In the early 1970s, brain lesion experiments and metabolic indicated that in mammals the central circadian oscillator is located in the hypothalamic suprachiasmatic nucleus (SCN).¹⁰⁻¹⁶ Lesions in this area of the brain led to complete loss of circadian rhythm, and SCN restored the diurnal rhythmicity.^{17,18} The neurons of the SCN contain a genetically driven clock mechanism.^{19,20} Circadian rhythm also occurs in living entities fungi, bacteria, algae, worms, plants, and other organisms, with a similar period. Even single cells in the human body

such as peripheral blood mononuclear cells, natural killer cells, liver cells, and most other cells, generate a circadian rhythm of 24 h, which is controlled by super ordinate SCN activities via hormones and neurotransmitters released into the blood and locally into the vicinity of nerve terminals.²¹⁻²⁴ The cells of the body including immune cells are controlled by the SCN leading to coupled cell and organ activities in the periphery with a 24 h daily cycle.²⁵ Such coupling phenomena may be important for the anti inflammatory action of hormones and neurotransmitters in arthritis has been demonstrated for cortisol and for norepinephrine.²⁶ Arthritis is based on:

- Immune cells like T cells, B cells, dendritic cells
- Cell migration and proliferation activity include monocytes, macrophages, neutrophils
- Cytokines, chemokines production /release
- Cell-cell interactions like fibroblasts, osteoclasts

Since arthritis associated symptoms undergo a similar 24 h cycle leading to large variations in disease activity and the super ordinate neuroendocrine center in the hypothalamus is of great importance with regard to arthritis. Rhythms can be highly disturbed in arthritis patients leading to a flattening of the response curve and two peaks appear in the morning and in the afternoon.^{27,28} The loss of circadian variation was confirmed in the adjuvant-induced arthritis.²⁹⁻³¹ In arthritic patients with high disease activity have elevated serum cortisol levels, which are, inadequately low in relation to ongoing inflammation.^{32,33} Since cortisol is the strongest endogenous anti inflammatory substance, its up-regulation in the early morning is most probably related to inhibition of inflammation during the day and its down-regulation during the evening and night is linked to an increase of inflammation during the early morning. Adenosine suppresses the release of TNF-alpha and IL-6 which may contribute the anti inflammatory action. Besides cortisol, two other hormones melatonin and prolactin, demonstrate a perfect 24 h rhythm. Both hormones have been linked to stimulation of the immune system, which would lead to an increase in pro inflammatory conditions in arthritis.³⁴⁻³⁹ The typical circadian rhythm of melatonin exhibits a maximum at 3:00 AM, which is quite similar to that of prolactin. The rhythms of these 2 hormones are not shown to be markedly different in patients with arthritis as compared with healthy controls. However, the serum levels of melatonin reached a

peak two hours earlier in arthritic patients than in controls. In arthritic patients, melatonin levels exhibit a wide plateau lasting 2–3 h, an effect not observed in healthy controls. After the peak was reached, melatonin levels decreased similarly in arthritic patients.⁴⁰ Both elevated melatonin and elevated prolactin will probably establish a more pro inflammatory environment.⁴¹ Sex hormones also have some local effects in the modulation of cell proliferation and cytokine production like TNF alpha and IL-1. At the point when cortisol and TNF alpha levels are lowest the ratio of prolactin and melatonin peaks at 2:00 AM because the pineal gland is sensitive to external light/dark cycles and it also influences the other body's biological functioning in arthritic patients.⁴² Both hormones, i.e., prolactin and melatonin induce a Th1 immune response and may thus lead to an unwanted increase in related cellular immune phenomena in arthritic patients.⁴³ Since arthritis prevalence and incidence are higher in women than in men, whether neuroendocrine mechanisms are different in women and men, and this may contribute to sex differences, might be important.⁴⁴ The circadian rhythm of cortisol levels is similar in women as compared with men⁴⁵ a sex difference for prolactin and melatonin has not been found.

Circadian Rhythms of Pain Thresholds in Arthritis

Patients with arthritis exhibit maximum stiffness at 6:00 AM and maximum pain at 8:00 AM and maximum functional disability at 6:00 AM. Grip strength has been found to reach a minimum at 6:00–8:00 AM.⁴⁶ It is interesting that there is a time shift between healthy subjects and patients with arthritis with respect to pain whereas pain levels demonstrate a maximum at 8:00 AM in arthritis patients and lowest at 3:00 AM (lag phase of 5 h). At present, the circadian rhythm of disease such as stiffness, pain, functional disability with arthritis might be a factor in the greater severity of the problems in female patients. Similar to arthritis, in other diseases such as myocardial infarction, angina pectoris, and renal colic, the peak frequency of painful attacks lies between 4:00 AM and 8:00 AM.⁴⁷⁻⁴⁹ In patients with arthritis the peak level of TNF alpha has been reported to appear at 6:00 AM and that of IL-6 at 7:00 AM. Thus, for both cytokines, a time shift of the peak value appears towards the morning. In healthy peoples, serum TNF alpha and IL-6 levels are low whereas in arthritic patients these levels are elevated. In healthy subjects the serum levels of

TNF alpha and IL-6 have already begun to decrease at 6:00 AM and 9:00 AM respectively, whereas in arthritic patients these levels remain elevated until 10:00 AM and 11:00 AM respectively. The broadness of these pro inflammatory cytokines in arthritic patients versus healthy peoples despite the similarity of the circadian rhythms for serum cortisol, within similar amplitude and shape indicates inadequate cortisol secretion in relation to inflammation in arthritis as mirrored by TNF alpha and IL-6 release. It is found that serum levels of IL-2 and interferon demonstrate the peak levels at midnight 2:00 AM in healthy subjects.⁵⁰⁻⁵² These two cytokines induce a Th1 immune response, as growth hormone and prolactin particularly during the night; Th1 immune responses develop the cellular immunity.⁵³ Since cortisol and IL-6-dependent secretion of fibrinogen with maximum fibrinogen levels at 10:00 AM causes the elevation in pain threshold.⁵⁴ The circadian rhythm exists for immunoglobulins in arthritis which has been demonstrated for IgA rheumatoid factor which peak at 8:00 AM and IgM rheumatoid factor was peak at 2:00 AM.⁵⁵ Circulating immune complexes exhibit circadian rhythms in arthritis with a peak between 6:00 AM and 9:00 AM. When biological rhythm get out of sync in the arthritic patients it is possible to synchronize them.^{56,57} Since IL-17 shows its synergistic effect in the treatment of disease because it is a potent inducer of various cytokines like TNF alpha and IL-1.

Treatment of arthritis

Generally, the medicines are used in reducing the arthritis pain and swelling using the drugs like Sulfasalazine, Leflunomide, Oxaprozin, and Cyclosporin. If severe pain and swelling occur in the joints different types of NSAID's are administered like Naprosyn, Relafen, Indocid, Voltaren, Feldene or Clinoril. These medications sometimes cause stomach pain diarrhea and abdominal pain. For the treatment of these symptoms disease modifying anti rheumatic drug's are used along with the NSAID's to reduce arthritic pain, stiffness and swelling because DMARD's are act as chronotherapeutics agents are mainly used to suppress the immune system of the human body. TNF-alpha and IL-1 increase the inflammation and stiffness in the joints of the patient so the formulations are used to block the effects of these anti inflammatory agents are known as biologics. Some biologics are Rituxan, Remicade, Kineret, Cimiza, Enbrel, Orencia, Humira and Simponi.

They suppress the immune system which makes the body to fight against the infection. Non steroidal anti-inflammatory drugs are much effective in the treatment of the morning stiffness and pain. The treatment of the arthritis based on the type of the arthritis and it also includes the physical exercise, life style, medications and dietary supplements.

Conclusion

Since circadian rhythms represents an entire new field of arthritis management. Future studies in this direction will demonstrate whether timed release also leads to the ability to reduce drug dosages frequency. Since circadian rhythmicity is completely depend on central nervous mechanisms (the SCN) and downstream hormonal and neuronal pathways and study of circadian coupling and uncoupling phenomena demonstrate that neuroendocrine factors which play a critical role in the pathophysiology of chronic inflammatory disease of arthritis.

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Declaration of Interest

It is hereby declared that this paper does not have any conflict of interest.

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