Review Article

A review and update of pathogenesis and treatment of inflammatory disorders and auto-inflammatory diseases

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Abstract

Inflammatory disorders and auto-inflammatory diseases are multifaceted ailments marked by dysregulated immune responses and chronic inflammation. Understanding the pathophysiology of these disorders and creating successful treatment techniques are major areas of research and clinical interest. This review article gives an updated summary of the pathophysiology of inflammatory illnesses and auto-inflammatory diseases, as well as current therapeutic techniques. These diseases are caused by a complex interaction of genetic predisposition, environmental stimuli, and immune system dysregulation. Abnormal cytokine signaling, immune cell malfunction, and tissue damage induced by chronic inflammation are all important mechanisms. Insights into the pathogenic processes that underpin disease have paved the way for the development of specific treatment approaches. Non-steroidal anti-inflammatory medications (NSAIDs), corticosteroids, biologic therapy, targeted therapies, and immunomodulatory therapies are all used to treat inflammatory disorders and auto-inflammatory diseases. Traditional treatments alleviate symptoms, whereas newer biologic and targeted medications selectively target immune system components to control the inflammatory response. Immunomodulatory medicines attempt to rebalance the immune system and control abnormal immunological activity. This review focuses on the most recent developments in treatment techniques, such as the use of biologics that target specific cytokines and cellular pathways, as well as targeted therapies that target key molecular targets implicated in inflammation and autoimmune. Furthermore, the ability of immunomodulatory medicines to modify immune response is explored.

Key words

Inflammation, Inflammatory disorders, Auto-inflammatory diseases, Pathogenesis, Treatment.

Introduction

Inflammation is the immune system's response to damaging stimuli such as pathogens, damaged cells, poisonous substances, or irradiation [1], and it works by removing the harmful stimuli and starting the healing process [2]. Inflammation is thus a vital health-protective process [3]. Typically, during acute inflammatory reactions, cellular and molecular activities and interactions successfully minimize impending harm or infection. This procedure helps to restore tissue homeostasis and resolve acute inflammation. Uncontrolled acute inflammation, on the other hand, can develop chronic, contributing to a number of chronic inflammatory illnesses [4].

Inflammatory ailments and auto-inflammatory diseases have made tremendous advances in recent years. Rapid advances in molecular biology, immunology, and genetics have resulted in a better knowledge of the underlying mechanisms behind many diseases. The purpose of this study is to provide a complete and up-to-date overview of the pathophysiology and therapy options for inflammatory disorders and auto-inflammatory diseases. Inflammatory illnesses are caused by a complex combination of genetic, environmental, and immunological variables. Chronic inflammation and tissue damage are exacerbated by abnormal immunological responses, such as dysregulated cytokine synthesis and excessive immune cell activation. Breakthrough research in recent years has uncovered critical molecules and signaling pathways involved in the pathophysiology of a variety of inflammatory illnesses. These breakthroughs have paved the way for novel targeted medicines and personalized treatment approaches.

Auto-inflammatory disorders, on the other hand, are distinguished by dysregulated innate immune responses in the absence of autoreactive cell participation. Genetic abnormalities affecting

molecules involved in the regulation of inflammation, such as inflammasomes, cytokines, and receptors, are predominantly responsible for these disorders. Understanding the genetic underpinnings and molecular mechanisms of auto-inflammatory illnesses has changed the way they are diagnosed and treated. With the advent of genetic testing and tailored medicines, patient outcomes in many illnesses have greatly improved.

The treatment landscape for inflammatory illnesses and auto-inflammatory diseases has changed dramatically. Traditional treatments, such as non-steroidal anti-inflammatory medications (NSAIDs) and corticosteroids, continue to play a role in symptom management and inflammation reduction. However, the introduction of tailored biologic treatments has transformed the management of a variety of inflammatory illnesses. Monoclonal antibodies directed against certain cytokines or their receptors have shown significant success in reducing disease activity and improving patient outcomes. In addition, small molecule inhibitors targeting critical signaling pathways have demonstrated promising outcomes in auto-inflammatory disorders. These tailored medicines provide the promise of more precise and personalized therapeutic options. Furthermore, the discovery of new therapeutic targets and the investigation of immunomodulatory methods show promise for the future therapy of these diseases.

In this review, we will examine the present state of knowledge about the pathophysiology and therapeutic options for inflammatory illnesses and auto-inflammatory diseases. We will look at the molecular and immunological pathways that underpin these diseases, highlighting the most recent research discoveries. Furthermore, we will present an overview of the therapy alternatives accessible, including standard medicines, biologic drugs, and new therapeutic modalities.

Pathogenic factors of inflammation

Inflammation can be caused by a variety of pathogenic reasons, including infection, tissue injury, or myocardial infarction. Inflammation can have infectious or non-infectious causes (**Table - 1**).

Table - 1: Pathological factors contributing to inflammatory process.

Infectious factors	• Microorganisms such as bacteria, viruses
Non-infectious factors	• Psychological factors: excitement • Biological factors: damaged cells • Chemical factors: glucose, fatty acids, toxins, alcohol, chemical irritants (including fluoride, nickel and other trace elements) • Physical factors: burn, frostbite, physical injury, foreign bodies, trauma, lionizing radiation

Inflammation and hypertension

Inflammation in vascular walls is a major leading factor of hypertension and of many other diseases. Essential hypertension is that which results from increased resistance in peripheral vessels to blood flow. Resistance in arteries play key role in development of hypertension and also leads to complications. When lumen of arteries become narrow, resistance will increase significantly. In the decreased and narrowing lumen of arteries inflammation and extracellular matrix are major responsible factor. When arteries remain constricted for prolonged period of time it seems hard to return to their normal state of vasodilation. In some cases, hypertension (isolated systolic hypertension) is age related. With advanced age usually vessels become narrow due to many other factors. Proper mechanism of age-related hypertension or diseases related vasoconstriction is not fully understood but it is suggested that changes occur

due to the gene expression which is associated with arterial stiffness and constriction. Increased blood pressure induces pro-inflammatory response.

Hypertension accentuates the atherosclerosis progression which has inflammatory components. Indeed, inflammation is considered as the central mechanism of cardiovascular diseases which induce hypertension, diabetes, obesity and many others. Inflammatory components and inflammatory markers both increase in the presence of cardiovascular diseases. The components and markers that increase in demonstrated hypertension are C reactive protein, chemokines, monocyte chemokine attraction protein-1, vascular cell adhesion molecule-1, anti-fibrinolytic agents, intracellular adhesion molecule-1, plasminogen activator inhibitoe-1, adhesion molecules, nuclear factor kB and activator proteins [5].

Hypertension is a demonstration of underlying cardiovascular disorders and vascular damage in which present inflammation induce narrowing of vessels by increasing resistance to blood flow cause hypertension. From the recent prospective studies it has been shown that inflammation and hypertension linked with each other because circulatory inflammatory molecules have been founded increase in hypertensive patients. Patients having high blood pressure have high level of inflammatory markers. Angiotensin two also exerts pro-inflammatory stress on the arterial walls. Basically, angiotensin two induce activation of nuclear factor kB which trigger the production of inflammatory cytokines promote the NADPH oxidase activation which release from super-oxides causing impairment in endothelial by reducing nitric oxide which induce vasodilation. By inhibiting angiotensin two through angiotensin two receptor blockers endothelial will be normal in functioning by reversing all bas changes. Humoral factor and mechanical stress also provide important stimulus for cellular element resident activation in the wall of artery. It became clear from the recent studies that inflammation and hypertension interact with each other in bi-directional manner. Presence of chronic Inflammation anticipates the further development of hypertension [6].

Inflammation and cancer

Our body does not have unique mechanism and does not behave differently in case of cancer; it behaves parallel to other processes such as wound healing and inflammation. Recent studied expanded that role of inflammation in cancer progression is very critical because many cancers develop from the site of infection and inflammation. It has become clear from many data that inflammation provides indispensable micro-environment for tumor. The local environment of tumor is developed from cellular effectors and inflammatory mediators. Be the malignant changes to happen generally inflammation is present at that site. Inflammation is said to be the tumor promotor because it helps in progression, proliferation, survival of tumor cell, angiogenesis promotor, induce mutation, alter the response of body to hormonal responses and chemotherapeutic changes [7]. Generally, it has proven that longer the inflammation persists, higher the chances of cancer.

Acute inflammation occurs due to presence of infection and some damage etc. so does not play any role in cancer development but chronic inflammation lead to cancer formation by providing a suitable environment for development of cancer. Chronic inflammation mostly occurs as a result of damage from free radicals which causes oxidative stress and induce inflammation. Chronic inflammation further lead to diseases e.g. cancer, pulmonary diseases, cardiovascular diseases, diabetes and neurological problems [8].

Inflammation associated cancer develop due the solubility factor provided by inflammatory cytokines including macrophages, neutrophils,

eosinophils and monocytes thought to be that it is mediator of it. Chronic exposure of inflammatory mediators (arachidonic acid, free radicles, cytokines and chemokines) increases proliferation of cell and induce mutagenic changes. As the result of proliferation and mutagenic changes cell loss the ability to grow normally. Some medical conditions in which chronic inflammation lead to cancer are inflammatory bowel diseases risk of colon carcinoma, skin infection risk of skin cancer, bacterial infection helicon bacter pylori risk of gastric ulcer, chronic schistosomiasis risk of fibrosis and cystitis, HIV risk of non-Hodgkin lymphoma, untreated hepatitis risk of liver cell carcinoma [9]. Oxidative stresses by activating the inflammatory pathway lead the transformation of normal cell into the cancerous cell [8]. Nuclear factor kb is considered the hallmark of inflammation which is detected in cancer calls. Nuclear factor kb by upregulating the tumor necrosis factor Induce inflammation which ultimately lead to cancer [9]. By inducing polymorphism of Inflammatory cytokine and inhibition or deletion of inflammatory cytokines may result in the suppression of cancerous cell growth [10].

Inflammation and depression

Major depressive disorder is highly prevalent neuro-psychiatric condition characterized by broad range of symptoms including alter mood and cognitive function. This complex disorder has multi-factorial etiology originating from genetic factors and environmental interaction. Many hypotheses have been proposed to clear its etiology [11]. One of them is inflammation hypothesis which is recently known as malaise theory of depression or cytokine theory of inflammation [12, 13]. This hypothesis expanded the psycho-neurological dysfunction from the immune system activation [14, 15]. Alteration in immune system increase the pro-inflammatory cytokines level which results in alteration in behavior, mood change, insomnia, fatigue, cognitive disorder and anxiety [16].

In major depressive disorder many inflammatory biomarkers have been measured, most frequent of them are cytokines (interleukin-1, interleukin-6 and tumor necrosis factor). C reactive protein also present which produce in response to interleukin-6. Major depressive disordered persons also have elevated level of chemokines, E selectin, adhesion molecules and plasminogen [17]. In major depressive disorder endotoxin and lipopolysaccharides induce symptoms by peripheral activation of immune system [18]. Toll like receptors activate the nuclear factor kB which induce the inflammatory response by the release of pro-inflammatory cytokines [17, 18, 19]. Cytokines reach to brain through leaky blood brain barrier, because blood brain barrier impaired in major depressive disorder and allows the extravasation of leukocytes by up regulating intracellular adhesion molecules.

Inflammation and atherosclerosis

Atherosclerosis is a disease in which lipid storage and bland plaque formation occur inside the arteries, and arteries due to the deposition give inflammatory response. Injured endothelial lead to the aggregation of platelets and release platelet factors. Platelet factors trigger the proliferation of smooth muscle cells in the intima of arteries. Multi-factorial evidences suggested that inflammation play key role for regulation of many pathways leading to the development and complication of atherosclerosis [20].

Recent studies expanded that inflammation proceed the all steps of atherosclerosis including initiation, progression and occurrence of thrombotic complications. By the new finding's inflammation is considered as risk factor for atherosclerosis mechanism. Increases level of c reactive protein and presence of low-grade chronic inflammation is an important ant leading causes of atherosclerosis [21].

According to the oxidation hypothesis, low density lipoproteins and inflammation are the main cause of the development of

atherosclerosis. Lipid causes adhesion of pro-inflammatory cytokine, chemokine and other inflammatory mediators in vascular cell wall and macrophages. Low density lipoproteins undergo oxidation and sometimes cause the activation of inflammatory mediators in endothelial cell. In myocardial infarction, level of inflammatory markers rises. C reactive protein's level increases in cardiovascular diseases which Is a major indication of underlying inflammation or any disease [22, 23, 24].

Inflammation and pain

In the development of pain and persistent of any pathological state of pain in CNs and PNS inflammatory responses play key role [25]. Inflammatory cytokines in dorsal root ganglion, spinal cord, injured skin and nerve are thought to be associated with pain with the production of abnormal activity from injured or inflamed nerve. Cytokine is a common name of small secreted protein including chemokine, lymphokines, interleukins, and mono-kines released from the cells having particular effect on interaction and communication between cells. Act of cytokines not only remain on cells from which they are released but also put act on distant and nearby cells. Different cytokines perform similar action that's why they are called redundant in activity.

Cytokines are predominantly produced by macrophages, helper T cells and from the herniated nucleus pulposus present inside the spinal cord [26, 27, 28]. In the injured site cytokines released. Pro-inflammatory cytokines released in injured site produced from macrophages up regulate the inflammatory reaction. In the process 0f pathological pain, pro-inflammatory cytokines such as interleukin-1 alpha, interleukin-6, interleukin-1 beta and tumor necrosis factor alpha are included. Inter leukin- 1 beeta primarily, released from monocytes. Non-immune cell (fibroblast etc.) and macrophages during infection, inflammation, cell injury and invasion. In nociceptive diagnosed related group interleukin-1 beeta is overexpressed [29]. Its expression increases in astrocytes of CNS and microglia in crush nerve injury [30].

Production of prostaglandin E2 and substance P is enhanced by interleukin-1 beeta in neuronal cell [31, 32]. Interleukin-6 also play key role in injury reaction and for the development of therapeutic pain it contributes [33 34]. Cachetin also known as tumor necrosis factor alpha is also inflammatory mediator which play central role in pain. By acting on many signaling pathways through its receptors, activates pathway of inflammation and induce apoptosis. It has equal role in hyperalgesia and inflammation. Chemokines, the inflammatory mediators are structurally related to cytokines induce chemotaxis. These low molecular weight families of proteins activate the leukocyte migration. Inflammatory mediators not only induce pain but also play role in the persistence of pain [35].

Inflammation and metabolic disorders

During last decade, incidence of obesity has increased drastically. Consequently, obesity is considered as major threat to health for all population. WHO estimated obesity incidence and according to WHO about one billion individuals are overweight world widely and more than three hundred million of them are obese clinically. Obesity is defined as body mass index more than or equal to 30kg meter per square [36].

Obesity has association for causing many other diseases including cardiovascular problems, diabetes mellitus (type 2) degenerative disorders, fatty liver, come cancers, atherosclerosis and diseases of airway. In the past decade, obesity is cleared as key feature of diabetes mellitus and obesity. As inflammation is protective response of body with many hallmarks by its symptoms exploring the underlying disease but the long-term presence of it is not beneficial. The long-term presence of inflammation is known as low

grade inflammation, chronic inflammation and in the case of metabolic disorder it is known as meta inflammation. Obesity and type-2 diabetes are closely related with chronic inflammation which is characterized by production of abnormal cytokines and other inflammatory mediators [37]. Among all of inflammatory mediator's tumor necrosis factor alpha firstly described the link between obesity, diabetes and inflammation because it was found overexpressed in obese persons [38].

Tumor necrosis factor alpha is defined as pro-inflammatory cytokine which activates the signaling pathway of inflammation. Over expression of tumor necrosis factor alpha cause insulin resistance [39, 40]. If over expressed tumor necrosis factor alpha is treated by anti-TNF alpha they will reduce the inflammatory condition and provide clearer evident to express the link between inflammation and diabetes (insulin resistance) [41, 42]. It became clear from the past published studies that not only tumor necrosis factor alpha over expressed in obesity but also many other inflammatory mediators elevated. In obesity, inflammatory response is triggered predominantly in adipose tissue and later in other sites such as liver [43].

Insulin receptors belong to the tyrosine kinase receptor kinase family and to mediate it signaling pathway use docking proteins. Among the large number of substrates, insulin receptor substrate proteins are used to bind with receptors of insulin [43, 44, 45]. Insulin by stimulating tyrosine phosphorylation of insulin receptor substrate protein mediates its pathway. Tumor necrosis factor alpha cause defection in insulin pathway by inducing resistance through inhibitory serine phosphorylation of insulin receptor substrate. Serine residues phosphorylate insulin receptor substrate-1 by kinases which interfere with the ability of protein to engage in insulin receptor signalling and cause alteration of action [46, 47].

The treatment of inflammatory disorders and autoimmune diseases

Inflammatory and autoimmune disease treatment is a difficult and growing field. These illnesses include a wide spectrum of ailments characterized by an aberrant immune response that causes inflammation and tissue damage in the body. To improve the patient's quality of life, the therapeutic approach for these illnesses tries to inhibit the immune response, reduce inflammation, and manage symptoms.

NSAIDs (non-steroidal anti-inflammatory drugs)

NSAIDs are frequently used to treat inflammation and discomfort caused by inflammatory diseases. They function by preventing the formation of prostaglandins, which cause inflammation and pain. NSAIDs relieve symptoms but do not alter the underlying illness process.

Corticosteroids

Corticosteroids, such as prednisone, are powerful anti-inflammatory drugs that inhibit the immune system and reduce inflammation. They can be utilized for either short-term treatment during disease flare-ups or long-term therapy for chronic disorders. Long-term corticosteroid use, on the other hand, can cause weight gain, osteoporosis, and an increased susceptibility to infections.

Biologic Therapies

Biologic therapies have completely transformed the treatment of inflammatory and autoimmune diseases. These drugs are intended to directly target immune system components implicated in the illness process. TNF inhibitors, interleukin inhibitors, B-cell targeted therapies, and T-cell targeted therapies are examples of biologics. They have demonstrated extraordinary success in reducing disease activity and improving patient outcomes. Biologic therapy, on the other hand, poses the danger of some infections and must be closely monitored.

Targeted Therapies

These are medications that target specific molecular processes implicated in inflammation and autoimmune. Targeted medicines such as Janus kinase (JAK) inhibitors, phosphodiesterase-4 (PDE4) inhibitors, interleukin-6 (IL-6) inhibitors, and Bruton's tyrosine kinase (BTK) inhibitors have emerged as effective treatments for some inflammatory disorders and autoimmune diseases. These drugs use a more targeted approach by selectively inhibiting critical molecules involved in the illness process.

Conclusion

Inflammatory disorders and auto-inflammatory diseases are broad categories of ailments characterized by aberrant immune responses that result in persistent inflammation and tissue damage. These diseases have a huge impact on global health, affecting millions of people around the world. Understanding the pathophysiology of these conditions and establishing effective treatment techniques are critical to improve patient outcomes and quality of life. This review seeks to contribute to the understanding and management of inflammatory disorders and auto-inflammatory illnesses by synthesizing the most recent scientific information and therapeutic advances. This review's findings will not only aid in the creation of more effective medicines, but will also pave the way for future research endeavors and the identification of novel therapy targets. In conclusion, this study will be useful to doctors, researchers, and healthcare workers who care for patients with inflammatory illnesses and auto-inflammatory diseases. It will provide a complete summary of existing knowledge, identify gaps in understanding, and motivate additional research initiatives aimed at improving the diagnosis, treatment, and outcomes of these difficult disorders.

References

1. Medzhitov R. Inflammation 2010: new adventures of an old flame. Cell, 2010; 140: 771–776.
2. Ferrero-Miliani L, Nielsen O, Andersen P, Girardin S. Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1β generation. Clin Exp Immunol., 2007; 147: 227–235.
3. Nathan C, Ding A. Nonresolving inflammation. Cell, 2010; 140: 871–882.
4. Zhou Y, Hong Y, Huang H. Triptolide Attenuates Inflammatory Response in Membranous Glomerulo-Nephritis Rat via Downregulation of NF-κB Signaling Pathway. Kidney and Blood Pressure Res., 2016; 41: 901–910.
5. Rathod GB, Parmar P, Rathod S, Parikh A. Hazards of Free Radicals in Various Aspects of Health – A Review. J Forensic Toxicol Pharmacol, 2014; 3(2): 1-7.
6. Parmar P, Rathod GB. Interpretation of Bloodless Crime Scene in Death Due to Firearm Injury to Heart – A Case Report. Int J Cardiovasc Res, 2014; 3(3).
7. Pragnesh Parmar, Gunvanti B. Rathod, Sangita Rathod, Ashish Parikh. Nature helps to solve the crime – Diatoms study in case of drowning death. International Archives of Integrated Medicine, 2014; 1(3): 58-65.
8. Pragnesh Parmar, Gunvanti B. Rathod, Sangita Rathod, Ashish Parikh. Organophosphorus compound poisoning – Demographic profile in Gandhinagar, Gujarat. J Forensic Toxicol Pharmacol, 2014; 3:3.
9. Pragnesh Parmar, Gunvanti B. Rathod, Sangita Rathod, Ashish Parikh. Demographic profile of Aluminium phosphide poisoning in Gandhinagar, Gujarat. IAIM, 2015; 2(1): 76-82.
10. Gunvanti Rathod, Pragnesh Parmar, Sangita Rathod, Ashish Parikh. Study of dyslipidemic pattern and glycosylated

hemoglobin status in diabetic patients. J Hypo Hperglycemia, 2014; 2(1).
11. Pragnesh Parmar, Gunvanti B. Rathod, Sangita Rathod, Ashish Parikh. Drug abuse and illicit drug trafficking vis-à-vis human life – A review. Prensa Med Argent, 2015; 101:2.
12. Maes M, Yirmyia R, Naroberg J, Brene S, Hibbeln J, Perini G, Kubera M, Bob P, Lerer B, Maj M. The inflammation and neurodegenerative (I and ND) hypothesis of depression; lead for future research and new drug development in depression. Metab brain Dis., 2009; 24: 27-53.
13. Parmar P, Rathod S, Parikh A. Perceptions of patients' towards euthanasia – A medico-legal perspective. IAIM, 2016; 3(5): 20-23.
14. Dantzen R, O'Connor JC, Freund GG, Johnson RW, Kelly KW. From inflammation to sickness and depression: when immune system subject the brain. Nat Rev Neurosci., 2008; 9: 46-56.
15. Parmar P, Rathod GB. Knowledge and awareness among general population towards medical negligence. IAIM, 2016; 3(7): 250-254.
16. Capuran L. Miller AH. Cytokines and psychological lesson from interferon alpha. Biological psychiatric, 2004; 56: 819-824.
17. Raison CL, Capuran L, Miller AH. Cytokines sign the blues: inflammation and pathogenesis of depression. Trend Immunol, 2006; 27: 24-31.
18. Steiner J, et al. Bridging the gap between immune and glumate hypothesis of schizophrenia and major depression, potential role of glial NMDA receptor modulator and impaired blood brain barrier integrity. The World Journal of Biological Psychiatry, the official journal of the world federation of societies of biological psychiatry, 2012; 13: 482-492.
19. Dinan TG. Inflammatory markers in depression. Current opinion in psychiatry, 2009; 22: 32-6.
20. Irwin MR, Miller AH. Depressive disorder and immunity: 20 years of progress and discovery. Brain, behavior and immunity, 2007; 21: 374-383.
21. Peter libby, Paul M. Ridker, Goran K. Hansson, Leducqtranslantic network. Inflammation in atherosclerosis from pathophysiology to practice. Journal of the American college of cardiology, 2009; 54(23).
22. Parmar P, Rathod G. Study of students' perceptions regarding knowledge and attitude towards torture. IAIM, 2017; 4(1): 68-71.
23. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, Maseri A. The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. N Engl J Med., 1994; 331: 417–424.
24. Viviane Z. Rocha, Peter Libby. Obesity, inflammation and atherosclerosis. Nature review cardiology, 2009; 6: 399-402.
25. Watkins LR, Milligan ED, Maier SF. Glial proinflammatory cytokines mediate exaggerated pain states: implications for clinical pain. Adv Exp Med Biol., 2003; 521: 1–21.
26. DeLeo JA, Colburn RW. The role of cytokines in nociception and chronic pain. In: Weinstein JN, Gordon SL, editors. Low Back Pain: A scientific and clinical overview. American Academy of Orthopaedic Surgeons, 1995, p. 163–185.
27. Heijmans-Antonissen C, Wesseldijk F, Munnikes RJ, et al. Multiplex bead array assay for detection of 25 soluble cytokines in blister fluid of patients with complex regional pain syndrome type 1. Mediators Inflamm., 2006; 2006: 8398.
28. Schafers M, Svensson CI, Sommer C, et al. Tumor necrosis factor-alpha induces

mechanical allodynia after spinal nerve ligation by activation of p38 MAPK in primary sensory neurons. J Neurosci., 2003; 23: 2517–2521.

29. Copray JC, Mantingh I, Brouwer N, et al. Expression of interleukin-1 beta in rat dorsal root ganglia. J Neuroimmunol., 2001; 118: 203–211.
30. Yan HQ, Banos MA, Herregodts P, et al. Expression of interleukin (IL)-1 beta, IL-6 and their respective receptors in the normal rat brain and after injury. Eur J Immunol., 1992; 22: 2963–2971.
31. Jeanjean AP, Moussaoui SM, Maloteaux JM, et al. Interleukin-1 beta induces long-term increase of axonally transported opiate receptors and substance P. Neuroscience, 1995; 68: 151–157.
32. Schweizer A, Feige U, Fontana A, et al. Interleukin-1 enhances pain reflexes. Mediation through increased prostaglandin E2 levels. Agents & Actions, 1988; 25: 246–251.
33. Ramer MS, Murphy PG, Richardson PM, et al. Spinal nerve lesion-induced mechanoallodynia and adrenergic sprouting in sensory ganglia are attenuated in interleukin-6 knockout mice. Pain, 1998; 78: 115–121.
34. DeLeo JA, Colburn RW, Nichols M, et al. Interleukin-6-mediated hyperalgesia/ allodynia and increased spinal IL-6 expression in a rat mononeuropathy model. J Interferon Cytokine Res., 1996; 16: 695–700.
35. Parmar PB, Bharpoda K, Bhensdadia V, Bhokan P, Bhut P, Chaudhary B. Study of undergraduate students' perceptions towards organ donation. J Indian Acad Forensic Med., 2016; 38(4): 437-440.
36. Rathod GB, Parmar P. Study of association of thrombocytopenia with plasmodium vivax infection. Indian J of Med Sciences, 2017; 69: 33-35.
37. Wellen K. E., Hotamisligil G. S. Inflammation, stress, and diabetes. J. Clin. Invest., 2005; 115: 1111–1119.
38. Hotamisligil G. S., Shargill N. S., Spiegelman B. M. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science, 1993; 259: 87–91.
39. Hotamisligil G. S., Arner P., Caro J. F., Atkinson R. L., Spiegelman B. M. Increased adipose tissue expression of tumor necrosis factor-α in human obesity and insulin resistance. J. Clin. Invest., 1995; 95: 2409–2415.
40. Krogh-Madsen R., Plomgaard P., Moller K., Mittendorfer B., Pedersen B. K. Influence of TNF-α and IL-6 infusions on insulin sensitivity and expression of IL-18 in humans. Am. J. Physiol. Endocrinol. Metab., 2006; 291: E108–E114.
41. Kiortsis D. N., Mavridis A. K., Vasakos S., Nikas S. N., Drosos A. A. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. Ann. Rheum. Dis., 2005; 64: 765–766.
42. Gonzalez-Gay M. A., et al. Anti-tumor necrosis factor-α blockade improves insulin resistance in patients with rheumatoid arthritis. Clin. Exp. Rheumatol., 2006; 24: 83–86.
43. Shoelson S. E., Lee J., Goldfine A. B. Inflammation and insulin resistance. J. Clin. Invest., 2006; 116: 1793–1801.
44. Taniguchi C. M., Emanuelli B., Kahn C. R. Critical nodes in signaling pathways: insights into insulin action. Nature Rev. Mol. Cell Biol., 2006; 7: 85–96.
45. White M. F. IRS proteins and the common path to diabetes. Am. J. Physiol. Endocrinol. Metab., 2002; 283: E413–E422.
46. Aguirre V., Uchida T., Yenush L., Davis R., White M. F. The c-Jun NH2-terminal kinase promotes insulin resistance during

association with insulin receptor substrate-1 and phosphorylation of Ser307. J. Biol. Chem., 2000; 275: 9047–9054.

47. Paz K., et al. Elevated serine/ threonine phosphorylation of IRS-1 and IRS-2 inhibits their binding to the juxtamembrane region of the insulin receptor and impairs their ability to undergo insulin-induced tyrosine phosphorylation. J. Biol. Chem., 1997; 272: 29911–29918.