Review Article:
Evaluation of Health and Social Inequalities in the Occurrence of Different Types of Chronic Stress and Their Effect on Immunoregulation

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ABSTRACT

Inequality in health and its multiple dimensions is an essential aspect of social injustice. Several studies have shown that mental and physical health in adulthood is not a phenomenon independent of one's childhood. Those from lower socioeconomic status have higher mortality and shorter life expectancy. Individualism and utilitarianism in social relationships have led to a wide range of social instability, poverty, deprivation, and inequality in societies. In addition to widespread social effects, they have made harmful consequences on the basic vital systems and organs through interference with multiple biological processes. In modern societies, people live in highly stressful situations, and several studies have pointed a strong relationship between the higher prevalence of diseases and social and physiological stresses. Studies of normal and experimental situations also showed their significant effects on the immune response. Accordingly, increased incidence of invasive behaviors has been associated with increased cytokines and immune-cellular activity in animal studies. According to the stimulus type and contact duration, chronic stress influences both innate and acquired immune factors. Stress affects the immune system via activation of the hypothalamus-pituitary-adrenal axis and affects the innate immune agents such as monocytes, macrophages, and proinflammatory cytokines, causing the increase of stress hormones (glucocorticoid-catecholamines). Chronic stress influences the acquired immune components by changing the immune cell population and altering the balance between immune cells and their secreted cytokine levels.

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1. Introduction

The issue of inequality and its various aspects has received considerable attention from planners and researchers in health in recent years. For this reason, this topic has been the subject of numerous research papers and has drawn the attention of renowned scientists and scholars. It can be explicitly acknowledged that reducing inequity in health has a special place in international health policy affairs. The reason is the presence of inequalities between countries, and even inside the world's advanced countries.

The achievement of social justice is one of the most critical goals in social planning. Theoretically, justice is a universal value and conceptual goal consistent with the human nature that various societies are trying to accomplish. Inequality in health and its multiple dimensions are an essential presentation of social injustice. Several studies have shown that the mental and physical health of individuals in adulthood is not a phenomenon independent of their childhood. An influential part of childhood experiences is related to the socioeconomic status of parents. The level of literacy, the amount of income, the living environment, including the physical environment of the home, the neighborhood, the city, communication with neighbors, parents' addiction, family disputes, the available health services, and their use are all factors that affect the individual's socioeconomic situation in the adulthood [1]. In other words, the deep inequalities in wealth and resources create a defect circle that imposes irreparable damages on health.

For this reason, those with lower socioeconomic status in society have higher rates of mortality and shorter life expectancy. The term, known as social gradient in health, is studied in different age groups and with different indicators of socioeconomic situation in various societies [2, 3]. Cruelty and injustice with the escalation of class divisions undermine the lives of the poor classes, depriving them of ordinary life. Various environmental stresses undermine the survival of poor people and induce early disability. This condition is not the result of the natural process of life but rather the accumulation of harmful effects of various stressors due to injustice imposed upon them [4].

Individualism and utilitarianism in social relations have led to the formation of a wide range of social instability, poverty, deprivation, and inequality in societies. In addition to widespread social effects, they create harmful effects on critical systems and organs through interference with multiple biological systems. Social stress can lead to a wide range of organic disorders and psychopathological disorders such as depression and anxiety. Today, people live in stressful societies, and studies show a relationship between the increased prevalence of diseases like depression with social and physiological stresses. According to the World Health Organization report, the complications associated with depression, an essential mental illness, have risen 3% to 10% annually [5].

Poverty

About one billion people in the world are affected by extreme poverty [6]. Malnutrition, illiteracy, and low quality of life are the main characteristics of the poor, in which there are sometimes no apparent signs of human dignity. In most societies, the life expectancy and well-being of poor people are shorter than those of prosperous people. In the contemporary world, out of every four people, one suffers from poverty [7]. Poverty is sustainable social stress that activates chronic stress-related mechanisms in the body. Based on the existing evidence, it has long-term effects on tissues and organs, including the Hypothalamic-Pituitary-Adrenal (HPA) axis (through disturbances in the secretion of cortisol and Dehydroepiandrosterone [DHEA], and cortisol escape phenomenon) and the inflammatory system (through impaired C-Reactive Protein [CRP] and Interleukin[IL]-6 and other immune modulators). These effects cause sustained damage to biological systems in the body, leading to health disorders, increased illnesses, vulnerability to infections, cell proliferation disorders, and cancers, and ultimately shorter life expectancy [8]. Recent studies have shown that injustice is more deadly than most of today's known dangerous illnesses. The present century has widened the class gap and the intensified injustice among the social strata [4]. Most studies have indicated the role of poverty in reducing health as "reduced access". This condition means that malnutrition, lack of access to health facilities, illiteracy and low culture, and multiple negative social factors created by poverty and deprivation cause more illness or lack of necessary care and treatment. Accordingly, the health of poor people is at risk. However, the direct effects of poverty and social inequalities have been less critical on physiological cycles [9].

Improper socioeconomic conditions in the early years can increase the risk of developing cardiovascular diseases, respiratory illness, and some cancers in the future. There are several justifications for explaining the relationship between the socioeconomic status of people and their health. One of the mechanisms that have drawn

particular attention in recent years is stress. Laboratory studies on social and health communication in the context of stress indicate that animals belonging to different social classes experience different patterns of stress [10].

Stress

The term stress was first introduced in 1936 and had many definitions. Stress is defined as a physical, social, or psychological event due to an actual or mental stimulus that triggers the physiologic responses of multiple biological mechanisms to overcome abnormal states. It ultimately results in the appearance of general and specific responses in the individual. According to psychoneuroimmunological expertise, stress is an environmental event (real or perceived) that stimulates physiological and psychological homeostasis and balance [11]. A stressor is defined as a threat to the body's homeostasis, and the responses to it are different based on the nature of the stressor (type, severity, and repetition) and individual factors (such as vulnerability, emotional stability, and coping methods).

Accordingly, stress is classified into acute and chronic. Chronic stress is defined as the stress that takes several hours a day or days and months, and the person is in a prolonged and repeated call with stimuli [12, 13]. Chronic stress is considered a key risk factor for various diseases in humans, especially anxiety and depression [14]. Chronic stress affects different parts of the brain, such as the hippocampus, amygdala, and prefrontal cortex [15, 16], and presents in various forms such as social stress, social isolation, anxiety, depression, social failure, conflict and war, violence, etc., in different individuals. Social interactions are one of the essential sources of chronic stress for social populations, including humans and animal communities [4, 11, 17].

Stress and animal models of inequalities

Our previous studies have argued that animals, like humans, understand the difference in social status, and feelings of inequality represent a far more severe disorder than food poverty in tissues such as the heart [18, 19], liver [5], brain [20-23], sexual organs and reproductive system [24, 25], retina and vision systems [18, 26]. Also, feelings of inequality change the level of pain reception and vital activity in peritoneal macrophages and spleen lymphocytes, serum levels of proinflammatory cytokines such as Interleukin (IL)-6, IL-1, and Tumor Necrosis Factor (TNF)-α in the immune system [27-30]. A relationship between food poverty and food inequality with oxidative stress is also shown in other studies [5, 21, 26, 29, 30]. In particular, it is believed that poverty, feeling inequality, and the difference in social status with interfering the Hypothalamus-Pituitary-Adrenal (HPA) axis and the creation of chronic stress stimulates the psycho-neuro-endocrine pathway [29].

Dr. Sarah Broussen studied ten male and female monkeys and showed that if a group of animals was given a specific prize in the event of a particular action and the prize is repeated, in a study by Dr. Sarah Broussen on ten male and female monkeys, it was shown that monkeys refused to participate if they witnessed a conspecific obtain a more attractive reward for equal effort, an effect amplified if the partner received such a reward without any effort at all. These reactions support an early evolutionary origin of inequity aversion [31].

In a study by Carol Shively on monkeys, it was found that coronary artery atherosclerosis in monkeys that were socially subordinate was higher than dominant monkeys [32]. Also, a study that examined the impact of the social environment on the progression of atherosclerosis in rabbits has shown that in rabbits with genetically deficient lipoprotein clearance, environmental stress can exacerbate the atherosclerosis process [33]. Studies show that social subordination affects inflammatory immune processes, such as the levels of proinflammatory cytokines (IL-6 and IL-1) in the blood, lungs, spleen, and brain [34].

In examining memory in the dominant social mice, the rate of anxiety was found greater than that in subordinate mice. This finding indicates that the same exposure affects the animals based on their social class [30].

Immunology

Some empirical and clinical studies have shown that natural and induced stresses in laboratory studies significantly affect immune response [35-37]. Accordingly, increased incidence of invasive behaviors has been associated with increased cytokine production and the activity of immune cells in animal studies [38]. In some studies, spleen cells in subordinate animals produce high levels of proinflammatory cytokines such as IL-6 and TNF-α in the presence of Lipopolysaccharide (LPS) stimulants [39-41].

Stressful conditions can directly increase cytokines, especially IL-1 and IL-6 [42]. Stress can also worsen inflammatory and autoimmune diseases, asthma, and allergies, although these diseases recover with immunosuppression. The fight-or-flight stress response that oc-

curs in situations like confronting an aggressive behavior leads to immunosuppression. Therefore, these findings suggest that some stresses, unlike some others, cause immunosuppression [43, 44].

Stress is an essential factor in the organism's susceptibility and the onset of various neuro-cognitive, metabolic, and immunological diseases [45]. Chronic stress, proportional to the type of stimulus and contact duration, affects natural and acquired immune factors. Stress affects the immune system through activation of the HPA axis and impacts the innate immune agents, such as monocyte, macrophage, and proinflammatory cytokines, through the increase of stress hormones (glucocorticoid-catecholamines). Chronic stress influences the acquired immune components such as T helper1 (Th1) and T helper2 (Th2) cells by the change of immune cell population and the alteration of the balance between immune cells and their secreted cytokines [27, 46-49].

Cytokines are soluble proteins that maintain homeostasis and cellular processes. These proteins, in addition to the connections between the immune system components, interact with cells and tissues, including the nervous system, and play an essential role in normal and pathologic processes in the body. Their essential roles include neurogenesis and synaptic plasticity [50].

Studies have shown that stress-induced mental disorders, including depression, are related to the activity of intrinsic and acquired immune systems, such as changes in immune system cytokines [51]. The most critical activities pertained to the inflammatory activity of the IL1, IL6, and TNF-α inflammatory cytokines. These proinflammatory cytokines, with a direct effect on the immune system, disrupt body hemostasis, increase the susceptibility to various diseases, and impair the cognitive and reactive function of the brain [50, 51]. Different studies have reported the effect of chronic social stress on the number and function of Natural Killer (NK) cells. According to Andrew's study, an increase in the number and activity of NK cells in the social stress model has been observed [52]. In contrast, Houdiandong showed that the number and function of NK in chronic stress have decreased [53].

Our study in 2013 showed an increase in serum concentrations of proinflammatory cytokines in dominant and subordinate mice (especially in subordinate mice). Increasing circulating levels of inflammatory cytokines are associated with increased glucocorticoid resistance. In other words, elevated levels of glucocorticoids in a feedback loop decrease the production of inflammatory cytokines such as IL-6 [54]. If the circulating levels of corticosteroids are high in stressed groups, glucocorticoid resistance is likely to inhibit the effect of corticosterone on reducing the production of these cytokines. The study of Meagher also showed that long-term social stress through increased glucocorticoid resistance increases IL-6 production [55]. Social stress not only increases the activity of proinflammatory cytokines but also changes the tuning of such a response. High cortisol levels typically inhibit the production and expression of the gene for proinflammatory cytokines [56]. Although social stresses in humans and animals increase glucocorticoids, certain types of stress may contradict the inhibitory function of glucocorticoids and thus lead to the simultaneous increase in glucocorticoid and proinflammatory cytokines [30].

In other words, social stressors can reduce the ability of glucocorticoids to prevent inflammatory responses. Such a response can result from decreased glucocorticoid receptors in immune cells producing anti-inflammatory cytokines and increasing these cytokines [40]. In addition, glucocorticoids seem to act as inflammatory mediators in the central nervous system. Evidently, the effects of glucocorticoids in the brain are different from their effects. Evidently, that the effects glucocorticoids in the brain are different from their effects in the environment. In the central nervous system, long-term high levels of glucocorticoids can have pro-inflammatory effects, while insignificant glucocorticoid levels have anti-inflammatory effects, and this response is different from their effects in the environment [57]. In animals that experience social subordination, the level of proinflammatory cytokines production is higher than that in other types of stress, in animals that experience social subordinate, the level of pro-inflammatory cytokines production is higher than other types of stress such as social dominance stress, and decreased glucocorticoid susceptibility has been associated with social dominance stress, and other stresses do not make such a big change in the immune system [56]. Therefore, the study of glucocorticoid resistance can be another of our future goals in relation to social stress.

Hormones involved in the immune system

Oxytocin

Oxytocin is an amino acid hormone that is synthesized in the brain's central nervous system, the paraventricular nucleus of the hypothalamus, the uterus and ovary, the corpus luteum, prostate gland, testicles, and kidneys. This hormone facilitates parturition and reproduction

at various levels, as well as lactation, sexual, maternal, and social behaviors. This hormone also affects learning and memory [58]. In addition, oxytocin has a vital role in responding to stress. Since external oxytocin injection reduces anxiety symptoms and causes relaxation, this hormone is vital to reduce anxiety. There are oxytocin receptors all over the brain's regions that are responsible for stress response. This fact reflects the potential role of oxytocin in responding to stress [59]. Oxytocin in the brain is made by the Paraventricular Nucleus (PVN) and Supraoptic Nucleus (SON) of the hypothalamus [60]. This hormone, coupled with ACTH secretion, and through the inhibition of the activity of the HPA axis, reduces stress response in stressful conditions. The oxytocin receptors are found inherently and extensively in the bone marrow and immune tissues, such as the thymus, epithelial cells, and they are also inducible in conditions similar to stress. Oxytocin hormone has a significant influence on immune function, so inhibition of the oxytocin secretion system in a certain way affects cellular immune response and humoral immunity. Oxytocin is also an anti-inflammatory hormone. It has been shown that treatment with oxytocin and its injection in humans can reduce and even suppress the significant secretion of factors and inflammatory cytokines in response to bacterial infection [61].

Oxytocin strengthens the acquired immune system by facilitating the differentiation of thymocytes, and oxytocin receptors inhibit T cell differentiation. Oxytocin increases the production of hematopoietic cells, decreases neutrophils, and inhibits apoptosis in mesenchymal cells [62]. IL-1β is produced in conditions of inflammation and stimulates oxytocin secretion, which inhibits the production of inflammatory cytokines and ultimately suppresses inflammation and thus maintaining homeostasis. So, the oxytocin hormone is a key factor in maintaining homeostasis and regulating immune responses [63, 64].

Deprivation stress and food inequality can cause anxiety and depression in rats under stress, and treatment with oxytocin can reduce the anxiety and depressive behaviors by inhibiting the activity of the critical pathway of HPA. As a result, it has anti-anxiety and depression properties.

Leptin

Leptin is a peptide hormone secreted from the adipose tissue and the brain. It adjusts the body's energy levels, absorption of food, and immune function. Besides the central nerves, peripheral cells, including immune cells, have leptin receptors. Leptin acts in chronic stress as a regulator of the HPA pathway through its receptors in the hypothalamus, and the hippocampus can inhibit and regulate the activity of the stress pathway. Leptin, with a negative feedback effect on the brain, reduces food intake and inhibits the activity of the HPA axis. Thus, the coordination of leptin and cortisol shows the intersection of the neuroendocrine circuit, which strikes a balance between stress responses and energy balance. A path that, according to new studies, can play a role in resilience [65].

In various chronic stress models, the amount of leptin secretion decreases, and the person loses weight during stress, but later the intake of food increases as a result of lowering the level of leptin, which is collected in the form of fat in the viscose and leads to obesity, diabetes and other metabolic diseases. Some studies have also shown leptin's antidepressant effect in chronic stress. So its reduction in chronic stress exacerbates depression, and its injection decreases the symptoms [66, 67]. Leptin hormone acts as an immunomodulator and affects immune cells such as NK cells. Studies have shown that leptin is effective in the differentiation and function of NK cells, and its loss reduces the function and number of NK cells in the blood and the spleen [68, 69].

Pain

In the definition given by the International Association for the Study of Pain (IASP), pain is not only caused by biological factors such as tissue damage but also by environmental and social factors [70]. A study on chronic social stress states that these stresses, rather than hypoalgesia, cause hyperalgesia [6, 71]. However, in animal models of pain, it has been shown that exposure to stressful and scary conditions can reduce the response to pain and lead to hypoalgesia [72-76]. The effects of stress on pain response are well known. Accordingly, stress can increase or decrease the pain response depending on the parameters of the stressor. Indeed, inhibition of pain response in a frightening condition can be beneficial, while under other conditions, painful stimuli will be very effective [77]. Social subordination is the most common social behavior that leads to stress-induced hypoalgesia, in which both opioid and non-opioid mechanisms are involved [78, 79]. Under particular circumstances, the stress response that activates the HPA axis can have inhibitory effects on pain, and this effect is known as Sress-Induced Analgesia (SIA) [80]. Despite the evidence supporting the role of the endogenous opioid system, preliminary studies have shown that both opioid and non-opioid mechanisms are involved in SIA, and significant advances

have been made in identifying non-opioid mechanisms [29]. Opioid analgesia is caused by the activation of opioid receptors by endogenous and exogenous opioids in the central nervous system and the environment; such analgesic effects, especially in inflammatory pain conditions, occur [81]. Chronic phase pain in response to formalin is an inflammatory pain [29]. Hypoalgesia response observed in the chronic phase of formalin test in subordinate mice is probably related to the peripheral and central activation of opioid receptors via proinflammatory cytokines. The study of Sonoda, which describes the role of social stress in reducing the sensitivity of immune cells to glucocorticoids and causing severe inflammation [82], can justify the role of environmental opioid receptors in reducing pain. Another study has shown that social stress reduces the sensitivity of immune cells to glucocorticoids [83]. Also, inflammation of the peripheral tissue leads to increased synthesis and axonal transmission of opioid receptors in the posterior root of spinal cord neurons and, consequently, increases these receptors and linking with protein G at the terminal of the peripheral nerves. In addition, the number of terminals of the pain receptors increases, and the pods around the damaged neuron will then facilitate the access of opioid agonists to these receptors. These effects produce an appropriate analgesic response by the effect of opioids on their opioid receptors during inflammation [84].

Stress can cause hyperalgesia depending on the type of stressor, its severity, and duration [85]. The invasive and dominant behavior causes an 80% reduction of serotonin relative to its basal levels in the prefrontal cortex of male rats [86]. Perhaps the observed hyperalgesia in the chronic phase may be attributed to the response of formalin in the dominant mice to low serotonin levels in these animals. Serotonin is one of the mediators involved in the neurons that inhibit the response to pain [87, 88]. The low levels of serotonin in the serum of people who experience migraine and fibromyalgia [89] and serotonin deficiency have also been observed in people with aggressive behaviors [86]. Therefore, studying the role of serotonin in social stress, such as the dominant-subordinate relationship, can be one of the essential goals in future studies.

In our study, we investigated the effects of social status on acute pain response in the formalin test and found that repeated subordination caused acute hyperalgesia in subordinate mice. This finding was different from that of the dominant mice, which felt less pain in the acute phase [90]. In another study on animals, it has been shown that repeated exposure to stressful conditions, such as social subordinate leads to acute hyperalgesia [91]. To explain this phenomenon, emphasis has been on the descending paths of induced hyperalgesia due to subordinate social status [92].

Several studies have emphasized the relationship between the socioeconomic status of individuals and the sense of pain [93-95]. There are many indications that under acute stress conditions, such as short-term food poverty, the acute pain response is suppressed [96, 97]. Studies on chronic stress show that stress causes hyperalgesia more than hypoalgesia [6]. But in examining animal pain models, increased pain responses under stress conditions have also been observed [72, 73]. Many studies have shown that social and nonsocial stress can affect the immune system [35-37, 98]. Recent research on psychoneuroimmunology states that the psychological stress associated with poverty leads to confusion in adjusting the HPA axis, thereby increasing or decreasing the activity of the inherent and specific immune system [99, 100]. It has been shown that depression and other negative emotions, as well as exposure to stressors, can also lead to increased plasma and brain concentrations of proinflammatory cytokines, in particular, IL-1 and IL-6 [42, 101]. Our studies have shown that animals, like humans, perceive the difference in social status through a neurobiopsychosocial phenomenon [4, 19].

There is little information about the relationship between long-term food deprivation and pain. A study by Walter et al. on male rats showed that long-term food deprivation affected the response to pain in the 5% formalin injection, and the pain was significantly reduced in this phase [96]. Deprivation and food inequality have a definite effect on reducing the pain of female rats in the chronic phase of response to formalin. Deprivation and food inequality, and not the stress of a roommate change, cause a significant difference in pain in the chronic phase of formalin response in female rats. This finding suggests that the stress of roommate change that indicates instability in the animal's social status has little effect on chronic pain response to formalin [29]. Studies have shown that people exposed to stress for a long time have lower pain levels [55, 78, 80, 102]. Studies conducted in the context of social exposures prove a model of stress-induced analgesia SIA [102]. Beecher et al. observed that soldiers injured in World War II usually have little pain, while similar injuries can lead to hyperalgesia in conditions without stress. These early observations made us realize that pain can be greatly affected by conditions [78]. Under particular circumstances, the stress response that activates the HPA axis can have inhibitory effects on the pain, and this effect is known as SIA. It

seems that certain mechanisms are implementing SIA. One of these mechanisms that play a role in stress is the function of the endogenous opioid system [80]. Despite evidence proving the role of the endogenous opioid system, early studies have shown that both opioid and non-opioid mechanisms play a role in SIA, and significant advances have been made in identifying these non-opioid mechanisms [78]. Opioids reduce the excitability of pain receptors and also reduce the release of stimulatory proinflammatory neuropeptides such as substance P, the calcitonin-dependent peptide from the terminal of central and peripheral nociceptors [84]. Some studies have shown that when the stressor is weak and short-lived, the function of the opioid system is dominant, while if the stress is severe or prolonged, the role of the non-opioid system is more pronounced in the development of analgesia [55]. Opioid analgesia is caused by the activation of opioid receptors by endogenous and exogenous opioids both in the central nervous system and in other body parts; such analgesic effects especially occur in the case of inflammatory pain. In the early stages of inflammation, both central and peripheral opioid receptors are involved in the development of analgesic effects, while in the later stages of inflammation, endogenous analgesia is mediated through peripheral opioid receptors [84].

Considering that the chronic phase of the response to formalin is inflammatory pain [103], considering that the chronic phase pain of the response to formalin is an inflammatory pain [98], it can be deduced that the analgesia created in the chronic phase of formalin test due to deprivation stress and nutritional inequalities, because of the activation of peripheral and central opioid receptors. A study by Barnes et al. indicated that food deprivation increased the opioid receptor expression in the ventromedial nucleus and arcuate nucleus of the hypothalamus [104], indicating the role of central opioid receptors in reducing pain. The study of Sonoda, which describes the role of social stress in reducing the sensitivity of immune cells to glucocorticoids and causing severe inflammation [82], can justify the role of peripheral opioid receptors in reducing pain. On this basis, probably increased proinflammatory cytokines in stress-induced mice in the present study contributed to the development of hypoalgesia. In this regard, increased circulating levels of inflammatory cytokines are associated with increased glucocorticoid resistance. In other words, as stated above, increasing glucocorticoid levels in a feedback cycle can reduce the production of inflammatory cytokines such as IL-6 [54]. In our study [29], it has been verified that if circulating levels of corticosteroids are high in stressed groups, glucocorticoid resistance may prevent the effect of corticosterone on reducing the production of these cytokines. The study of Meagher also indicated that long-term social stress induces an increase in IL-6 production through glucocorticoid resistance [55]. Social stress not only increases the activity of proinflammatory cytokines but also changes the regulation of such responses. High cortisol levels typically inhibit the production and expression of the gene for coding proinflammatory cytokines [56].

Although social stresses in humans and animals increase glucocorticoids, certain types of stress may interfere with the inhibitory function of glucocorticoids and, as a result, increase glucocorticoids and proinflammatory cytokines together [30]. In other words, social stressors can reduce the ability of glucocorticoids to prevent inflammatory responses; such an answer could be the result of a decrease in glucocorticoid receptors in immune cells that produce proinflammatory cytokines, which will increase these cytokines [40]. In addition, glucocorticoids may act as inflammatory mediators in the central nervous system. It is stated that the effects of glucocorticoids in the brain are different from their effects in the other body parts. In the central nervous system, long-term high glucocorticoids can have anti-inflammatory effects, in the central nervous system, long-term high levels of glucocorticoids can have pro-inflammatory effects, while insignificant glucocorticoid levels have anti-inflammatory effects, and this response is different from their effects in the environment [57]. Therefore, it is argued that glucocorticoids may influence both the central nervous system and the peripheral nervous system, leading to an increase in inflammatory cytokines, and this increase is associated with an increase in the receptors and opioid agonists. The potential effects of stressful events on the immune system have been widely studied. However, many studies have focused on physical stresses, and less talked about social stress [105].

It is generally believed that stress suppresses immune function and predisposes a person to various illnesses. However, stress-dependent suppression of the immune function does not always happen. When an organism is in a stressful condition, it needs a strong immune response, which contradicts the fact that immune function is suppressed in these situations. On the other hand, it is thought that stress causes immunosuppression and increased susceptibility to infections and cancer, and inflammatory diseases such as psoriasis worsen asthma and arthritis. Considering these contradictions and based on early studies on the effects of stress and corticosterone on circadian rhythm and the patterns of migration and leukocyte implantation, it is assumed that stress can have a reciprocal effect on the immune system's per-

formance. Accordingly, under some conditions, stress increases and, in some others, suppresses immune function. Firdauss study was found that acute stress reduces the relative levels of B and T cells, as well as natural lethal cells and monocytes in the blood and spleen. In contrast, chronic stress increased the level of T cells in the brachial lymphocyte, and also T and B cells, natural lethal and monocytes in bone marrow [44]. Considering the patterns of migration and implantation of leukocytes to the spleen, it should be noted that, in contrast to acute stress, chronic stress, or glucocorticoid treatment increases the accumulation of leukocytes in the spleen. The spleen, with large amounts of corticosteroid-binding globulin, plays an important role in buffering leukocytes from high levels of stress hormones. Various mechanisms that can contribute to increasing the immune function under stress are not known, just as the unknown mechanisms associated with suppression of immunity in chronic stress [43].

Despite the adaptability of the stress response, chronic stress can be pathogenic. It is believed that chronic stress leads to adrenal evacuation from epinephrine and glucocorticoids. Accordingly, stimulating the immune system in response to stress over a short period results in immunosuppression and low resistance to illness. An initial study that emphasized the relationship between stress and the immune system was posed by Hansley and stated that chronic stress leads to immunosuppression, especially inherent immunity [106]. The effects of chronic social stress on rats were investigated in the Klein study. In this study, it was found that despite enlargement of the adrenal gland and increasing corticosterone levels, the activity of NK cells and the response of lymphocytes to mitogen did not change, indicating that increased levels of corticosterone due to social stress of the immune system was not affected [107]. However, in some studies, it has been proven that social stress causes splenomegaly and changes the phenotype and function of the immune cells derived from the spleen. This stress increases the number of CD11B+ cells in the spleen and effectively led to glucocorticoid resistance in mononuclear cells. In addition, splenocytes secreted high levels of proinflammatory cytokines, such as IL-6 and TNF-α, in the presence of LPS [40]. As previously mentioned in our study, the social stresses of food inequality and roommate change were higher in the vital activity of the spleen lymphocytes than in the control group of female mice in response to ConA mitogen. In addition, the level of proinflammatory cytokines in the serum of stressed groups in male and female rats was higher than that in the control group. It has been shown that severe stress disrupts the anti-inflammatory function of glucocorticoid hormones. Previous studies have shown that repeated and prolonged social stress reduces the glucocorticoid sensitivity of immune cells and increases inflammation [108]. For example, splenocytes of mice that were repeatedly exposed to a stressful agent showed more vital activity in the presence of corticosterone. In addition, the proinflammatory cytokines produced from the cell culture of lymphocytes in these mice were more than control groups [109]. Reduced glucocorticoid response of the spleen was observed only in the presence of the mitogenic stimulus, while cells that did not stimulate with stimulus did not differ from the control group [110]. Studies using social stress have shown that the effect of these stressors on the number of lymphocytes in the mice and rats depends on the patterns of migration and altered implantation of leukocytes in lymphoid and skin organs [109]. accordingly, the above-mentioned social stresses increase the vital activity of the lymphocytes of the spleen by creating glucocorticoid resistance in the spleen lymphocytes [55]. In general, exposure to social conditions of poverty and inequality, and not roommate change, leads to chronic SIA. At the same time, all stresses lead to reduced vital activity of the peritoneal macrophages, increase the vital activity of the spleen lymphocytes and create a proinflammatory stress design [29].

Recent research in the field of justice in health emphasizes the effects of stressful social conditions on the health level. It seems that the stressful nature of social exposures can cause hyperalgesia and analgesia in humans and rodents and can also affect the immune response. Stress through proinflammatory cytokines has led to the release of endogenous opioid peptides and thus reduced chronic pain response in subordinate mice, but, despite the increased production of these cytokines, chronic pain response in dominant mice has been increased.

2. Conclusion

Inequality in health and its multiple aspects is an essential part of social injustice. Several studies have shown that the mental and physical health of individuals in adulthood is not a phenomenon independent of childhood. For this reason, those with a lower socioeconomic level in society have higher mortality and lower life expectancy. Accordingly, justice in health is one of today's most important challenges in health. Recent studies have shown that injustice is more deadly than most of today's known dangerous illnesses. The advances of the present century have led to a widening of the class gap and the intensification of injustice among the social strata. At the same time, it has been

proven that the feeling of injustice has a devastating effect on the soul and body of the community.

Recent research in the field of justice in health emphasizes the effects of stressful social conditions on the health level. Recent research in justice in health emphasizes that repeated exposure to social stressors will have adverse outcomes on the health level. A person's social class has a lot of effects on his stress level so that exposure to the same situation has different effects on the animals based on their social class. Changes in social status significantly affect the emotional-behavioral and physiological responses of individuals in different species. Several structures have been proposed to explain the relationship between the socioeconomic status of individuals and their health. One of these issues, which has been specially considered in recent years, is the biological effects of chronic social stress. The different socioeconomic conditions, the feeling of inequality, and the lack of justice and instability in the social situation create a level of sustained chronic stress in the body. Unlike acute stresses that its biological effects end with the stressful condition, in chronic stress, the organism confronts with long-term levels of hormone disturbances and stress mediators, which also have biological effects. Accordingly, the search for long-term biological effects of chronic stress on organs of the body as a link between socioeconomic status and health is the subject of modern research. People with lower socioeconomic status have reported more exposure to stressful life events. Compared to those with a more favorable socioeconomic status, people without power and adequate resources to respond to stress and adapt to them report more stressful events in their lives.

Studies have shown that the social environment with inequality has left persistent biological effects in different organs. The emergence of reactive oxygen species due to oxidative stress has been suggested as a basis for explaining the mechanisms of biological and tissue damage caused by social inequalities.

Among the biological effects of inequalities is the accumulation of lipofuscin lesions in various organs such as the brain, heart, and liver as an aging factor. Studies have shown that the effect of food deprivation on the amount of lipofuscin in the brain has increased. So that the increase in the rate of formation of lipofuscin over time potentially reduces the cell's potential for survival. Therefore, one of the leading indicators of the aging of accumulation of pigmentary granules of lipofuscin is considered. Food deprivation enhances the oxidative stress factors, such as lipid peroxidases and hydrogen peroxide, in brain tissue and reduces the antioxidant properties of glutathione, Superoxide Dismutase (SOD), and vitamin E.

Inequity in food intake and social instability has led to increased lipofuscin accumulation (as an indicator of oxidative stress and premature aging) in the hippocampal pyramidal cells, thus increasing the probability of their apoptotic death.

Cardiovascular problems are the first and most important cause of death and illness in advanced societies and some developing countries. Among the biological effects of inequalities is heart disease. As coronary artery atherosclerosis is increased in groups that are under stress inequality, and the presence of lipofuscin pigments in the heart suggests oxidative stress and aging. Also, in the brown atrophy of heart, the presence of these granules is clearly seen with high levels.

Stress in all periods of life can threaten an individual's health, but there are periods in life that are considered sensitive and critical periods. The period of intrauterine life is among the most sensitive ones. Much evidence suggests that disease and health talent are determined by the dynamic interaction between genetics and the environment, especially in the prenatal period and the beginning of life. The stresses and the challenging conditions of the environment within the uterus and the period of onset of growth induce long-term changes in the nervous system of the individual, which can remain even until the end of their life.

Food deprivation with exposure has led to an increase in testicular tissue cell death. Regarding the effect of melatonin on deprivation conditions with inequality and decreasing cell death, oxidative stress mechanisms have been implicated in the stress of "food deprivation with inequality." Also, oxidative stress, by affecting the DNA of sperm, affects ovum growth and development, leading to ovum cell failure or abortion.

Deprivation stress and food inequality can cause anxiety and depression in rats that are under stress, and treatment with oxytocin can reduce the anxiety and depressive behaviors by inhibiting the activity of the vital pathway of HPA. As a result, it has anti-anxiety and depression properties. Also, leptin in chronic stress as a regulator of the pathway of HPA through its receptors in the hypothalamus and the hippocampus can inhibit and regulate the activity of the stress pathway. Exposure to long-term stress leads to shrinking the hippocampus, which is the main focus of memory in the brain.

The stress of inequality (social subordinate) leads to hypoalgesia, which is associated with activating the peripheral and central opioid receptors through proinflammatory cytokines. Also, stress can cause hyperalgesia, depending on the type of stressor and its severity and duration. The invasive and dominant behavior causes an 80% reduction of serotonin relative to its basal levels in the prefrontal cortex of male rats. Studies on chronic stress show that stress causes hyperalgesia more than hypoalgesia.

Stress has a reciprocal effect on the function of the immune system. Severe stress disrupts the anti-inflammatory function of glucocorticoid hormones. It is generally believed that stress suppresses immune function and predisposes a person to various illnesses. However, stress-dependent suppression of the immune function does not always happen. It seems that when an organism is in a stress condition, it needs a strong immune response, which is contradictory to the fact that immune function is suppressed in these situations. On the other hand, it is thought that stress causes immunosuppression and increased susceptibility to infections and cancer, and inflammatory diseases such as psoriasis worsen asthma and arthritis.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest

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