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(REVIEW ARTICLE)

A mini-review on influence of physical exercise in remodeling the immune mechanism

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Abstract

Exercising on a regular basis has been associated with delay in onset of many lifestyle disorders and chronic conditions. Different types of exercise have varied effects on our innate immune cells, both positively and negatively. Low-intensity exercises like yoga or brisk walking, medium-intensity exercises like swimming or cycling, and long-term high-intensity exercises like playing sports like volleyball or working out in the gym are some examples. The immune system's function is impacted differently by exercise training depending on the type, duration, intensity, and other factors. Exercise training is a double-edged sword that helps the body's immune system by changing the immune cells' post-exercise reaction mechanisms. Regular physical exercise is one of the lifestyle adjustments aimed at minimizing morbidity and mortality associated with contemporary illnesses such as obesity, diabetes, cardiovascular disease, and cancer. Regular leisure exercise training is regarded to be beneficial, but extreme exercise, such as that performed by professional athletes, is thought to have possibly detrimental consequences. This review summarizes current information in the field of exercise-associated alterations of infection susceptibility and indicates knowledge gaps for further investigation. It highlights that long term effects of physical activity shows a positive association with longevity and exercise.

Keywords: Physical activity; Immunity; Infections; Immuno-suppressions; Exercise training intensity

1. Introduction

The term 'immunity' is derived from the Latin phrase '*immunis*', which means exempt, and hence refers to protection against any illness or ailment. The immune system has two responses: innate and adaptive. The innate immune response is comprised of the body's physical and chemical defense barriers, as well as the actions of macrophages, dendritic cells, natural killer cells, neutrophils, cytokines, interleukins, and many more. T and B lymphocyte cells, as well as their products such as antibodies and cytokines, are responsible for adaptive immunity.

Physical exercise is critical for maintaining body health and preventing the emergence of conditions like diabetes, cardiovascular disease, and other lifestyle conditions. It also minimizes the likelihood of developing inflammatory disorders in the body and boosts cellular immunity. Moderate-intensity exercise has been proven to boost immunization responses, reduce inflammation, and minimize death rates in people with co-morbidities. Exercise can range from mild to severe in intensity, duration, and timing, resulting in a variety of stimulatory or inhibitory responses. A moderate intensity workout stimulates cellular immunity, whereas higher intensity leads to a decline in cellular immunity, leaving the person more susceptible to infectious illnesses. Table 1 lists the various cells involved in the two branches of the immune system and their levels with respect to intensities of physical exercise.

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Table 1 Various cells involved in the immune system and their response to levels of physical exercises

Cytokines	These are anti-inflammatory & pro-inflammatory molecules and their production can be influenced by physical exercise; their levels are influenced by duration and intensity of exercise.
Neutrophils	During physical activity, muscle fibres get activated, leading to release of calcium and pro-inflammatory cytokines that recruit selectins and in turn neutrophils to the site in the activation pathways.
Leukocytes	Increase in physical activity increases circulating leukocytes. The concentration of leukocytes peaks within 1-2 hrs of activity. This may be due to shearing of blood vessels and release of immune cells in liver, spleen and lungs.
Antigen-presenting cells (APC)	An aggravated exercise may induce a decrease of expression of toll-like receptors (TLSRs) in macrophages that cause failure in presentation of antigens to T cells. This leads to inflammatory damages and also increases susceptibility to damage and infection by microorganisms.
Natural killer cells	Cellular stress due to physical activity leads to increased blood flow that would recruit natural killer cells
Lymphocytes	Concentration of lymphocytes increases during moderate levels of activity.

More number of immune system cells are recruited against infections related to physical exercise. It involves increase in activity of macrophages, elevation in circulation of immune cells, immunoglobulins and anti-inflammatory cytokines and such a movement would decrease pathogen burden on the body viscera. **Figure 1** depicts the relationships between immunosurveillance, levels of activity and sensitivity to infection of individuals. As we are living in the era of technology where everything can be accomplished at the touch of a button, physical inactivity and sedentary lifestyle is the biggest threat to the current generation.

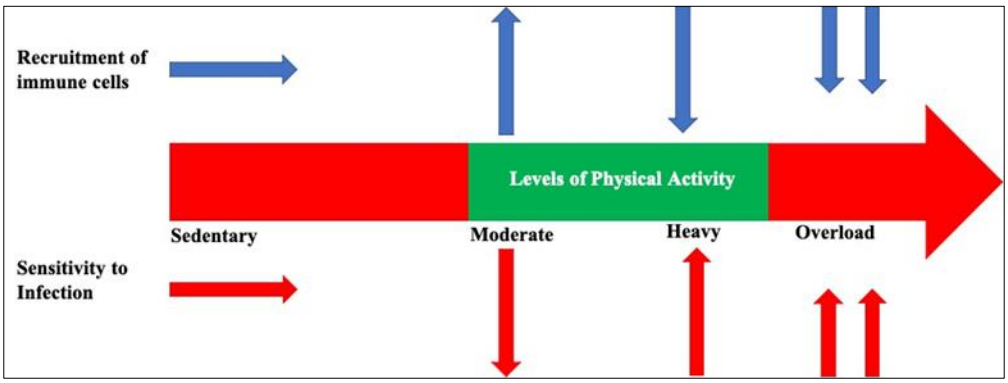

Figure 1 Relationship between levels of physical workout, proneness to infection and immunosurveillance [adapted from Simpson et al 2020]

Decrease in physical activity has been instrumental in increasing cases of obesity which could impact the cardiorespiratory fitness of an individual. Running is one of the best physical activities and has been linked to high levels of cardiorespiratory fitness. It helps in prevention of diabetes, osteoarthritis, respiratory diseases and several disabilities. Another side to this coin is that high performance athletes are very prone to high risk of acquiring infections as they surpass the guidelines of physical activity as well. This leads to suppression of immune response and lead to many challenges as well decreased cellular immunity, impaired responses to vaccines and novel antigens.

1.1. Physical Exercise & Immune Responses to Infection

Physical activity is regarded as one of the most important aspects of healthy life. Aside from the functions associated to the control of excess body weight, systemic inflammation, and chronic noncommunicable illnesses, physical exercise may have a potential benefit in lowering communicable infections, particularly viral pathologies **(Figure 2).** The most contagious illness in humans, acute respiratory infections (ARIs) are brought on by respiratory viruses and bacteria.

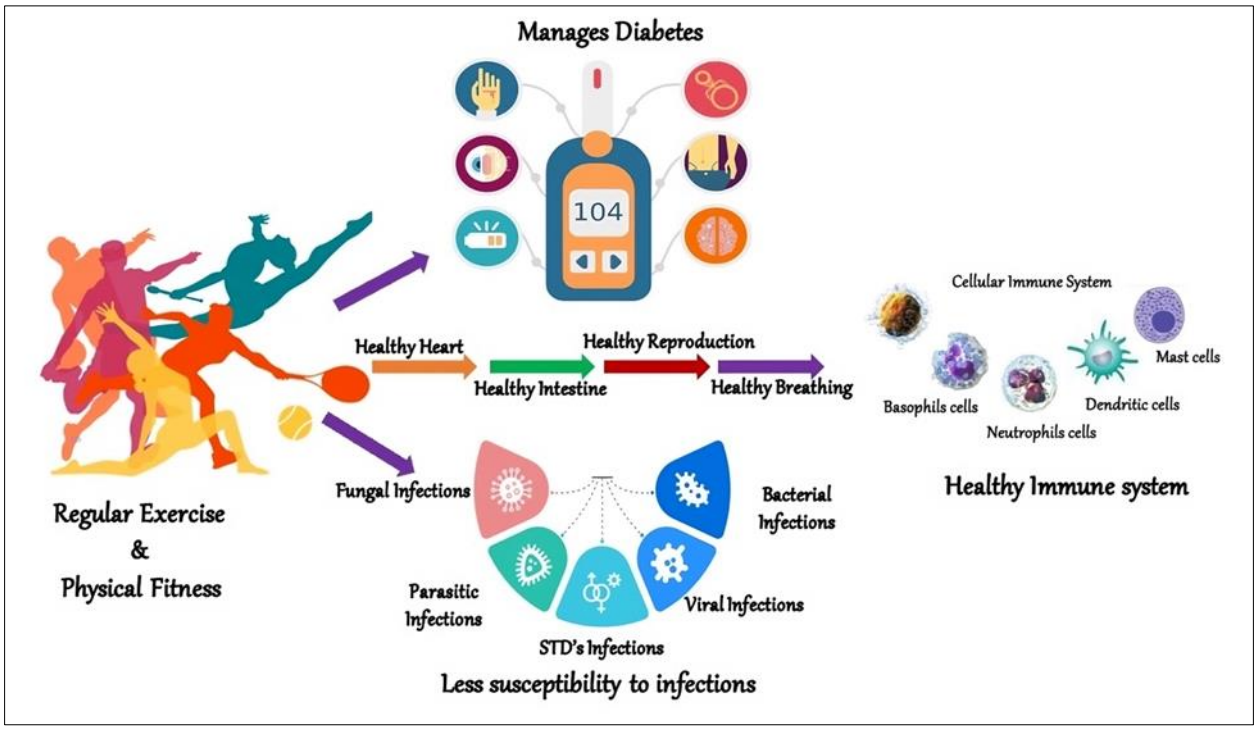

Figure 2 An overview highlighting the significance of Physical Exercise

There are several examples which show that regular exercise improves the body's response to the infection. Regular exercise lessens the severity of sickness in hosts infected with *Leishmania* major and *Trypanosoma cruzi* parasites. An exercise programme on a treadmill for 4 weeks produced a reduction in cardiac fibrosis in the study carried by Pedra-Rezende and co-workers, 2021 (1). Their data demonstrated that exercise can enhance quality of life and stop the progression of Chagas Disease, despite the fact that no reduction in parasite load or inflammatory markers was seen with exercise.

1.2. Exercise Effect on fungal, viral and bacterial infections

Apart from managing systemic inflammation, and chronic non-communicable diseases, physical activity is also beneficial in preventing communicable diseases, such as viral, bacterial and fungal pathologies (2). Moderate levels of exercise are also seen to lower rates of ARI incidence, length and intensity of symptoms, and risk of mortality from infectious respiratory infections. Additionally, numerous studies indicate a direct connection between regular physical activity and benefits in cardiorespiratory health, vaccination response, glucose, cholesterol, and insulin metabolism, as well as a reduction in the death rate from influenza and pneumonia (2) Increased immune surveillance against infections has been proposed as a method for improving the immunological response to exercise. During moderate-intensity exercise, by increasing macrophage anti-pathogenic activity and increasing the circulation of immune cells, immunoglobulins, and anti-inflammatory cytokines, one can reduce the burden of pathogens on organs such as the lung and protect against lung damage caused by the influx of inflammatory cells. Routine physical exercise reduces inflammatory responses and stress hormones while increasing lymphocytes, NK cells, immature B cells, and monocytes. As a result, there is an improvement in immunovigilance and a decrease in the systemic inflammatory process, which are indicators that regular exercise strengthens the immune system while preventing respiratory diseases and thereby defending against infections like COVID-19 (3).

1.3. Effects of Different Intensity of Exercise and Sports Training on Immune Cells

Sports professionals have known for a long time that participating in a single extremely intense activity, like a marathon run, or participating in extended periods of intense training can temporarily suppress the immune system, making one more susceptible to infections. While moderate physical exercise stimulates a number of immune functions, more strenuous activity and extended periods of intense training lower a number of immune response parameters. Studies show that characteristics including frequency, intensity, duration, and kind of effort used affect how the immune system reacts to exercise (2). As mentioned earlier, lengthy or high-intensity workouts without adequate rest might cause lower cellular immunity, raising the risk for infectious illnesses, moderate-intensity physical activity stimulates cellular

immunity (4). The immune system deteriorates after engaging in extended physical activity, or 90 minutes of moderate- to high-intensity physical activity, according to the International Society for Exercise and Immunology (ISEI).

According to the repeated-bout paradigm (5) circulating cell counts, lymphocyte proliferation, and NK cytotoxicity are all altered differently by repeated exercise bouts on the same day (6) or across a number of days compared to a single exercise session.

Physically active (7), well-trained (8) or elite (9) people have been used in studies comparing the impact of one vs. two workouts on a single day. Cycling, running or rowing were the activities. The intensity and duration ranged from 15 minutes at maximum intensity to 2 hours at medium-high effort (60–75% VO2max; 56, 96). The recuperation interval between exercise bouts ranged from 45 min to 12 h with 34 h being the most frequent value.

1.4. Immune Cell Responses to Long-Term High-Intensity Exercise Training

Innate immune cell activity is impacted by long-term high-intensity training, which also decreases immune cells' capacity to handle acute exercise and raises the risk of infection (9). Shephard and Shek (10) stated that long-term high-intensity training can impair macrophage activity, thereby reducing the number of macrophages and impairing phagocytic function leading to negative consequences on immune surveillance and overall health of the body because NK cells recovered within 24 hours under such training.

Short-term high-intensity exercise training (11), on the other hand may increase the number of NK cells but decrease their toxicity. This is likely because NK cells quickly redistribute between blood and tissues after acute exercise, which favourably redistributes NK cell subsets with a well-differentiated phenotype and enhances cytotoxicity against HLA-expressing target cells. A brief exercise session changes NK cell function and number, but not cytotoxicity, and there is a positive link between exercise and NK cell count and cytotoxic activity.

The study by Simpson et al. demonstrates that regular moderate-intensity exercise is responsible for the improvement in immunity. Additionally, it has been demonstrated that frequent moderate-intensity exercise improves cardiovascular health and lowers overall disease mortality. Regular short-term, moderate-intensity exercise for up to 45 minutes is good for immunological defense (12). Exercise of moderate intensity reduces ring finger muscular spasms and reduces neutrophil infiltration into the alveolar space modifying systemic neutrophil chemokine responses.

Exercise has a variety of effects on lymphocyte and B cell concentrations, but only consistent exercise can improve a person's immune system. Long-term bed rest has a major impact on cytokine levels and immune cell populations. Immune function is inhibited, granulocyte, natural killer, T cell, hematopoietic stem cell, and CD45RA and CD25 expressing T cell numbers are raised, while monocyte numbers are considerably lowered during spaceflight and simulated weightlessness (bed rest).

The number of myeloid cells in B cells, dendritic cells, and neutrophils increases as a result of participation in various sports and exercise training. Professional and amateur distance runners have various immune cell modifications during competition. Additionally, the T cells in the body react differently to swimming and running. B cells rose by an average of 60% after a 20-minute cycling race at 80% VO2max, with immature cells showing the greatest increase, followed by memory cells, and lastly naive cells **(Figure 3)**. Similar to how exercise increased total dendritic cells by 150% during 80% VO2max exercise, mobilized plasmacytoid dendritic cells more than myeloid dendritic cells, and mobilized plasmacytoid dendritic cells preferentially, exercise enhances immune surveillance by preferentially mobilizing effector cells (13). The growth of T cells in the lungs and Peyer's patches, the body's primary defensive barrier, may improve immunological alertness in these regions as a result of vigorous running exercise, decreased lymphopenia following swimming exercise, and increased blood levels of T cells (14). Exercise-induced oxidative damage in neutrophils and the development of antioxidant defense in lymphocytes are both marginally less in women than in males. College volleyball players who trained for a month before the season (5 hours a day, 6 days a week) saw a significant increase in the number of CD56bright NK cells and CD56dim T cells (a subset with lower cytotoxicity) and a decrease in overall NK cell cytotoxicity from pretraining to post training. However, the levels of interleukin-6, interferon-gamma, and tumor necrosis factor-alpha did not change (15).

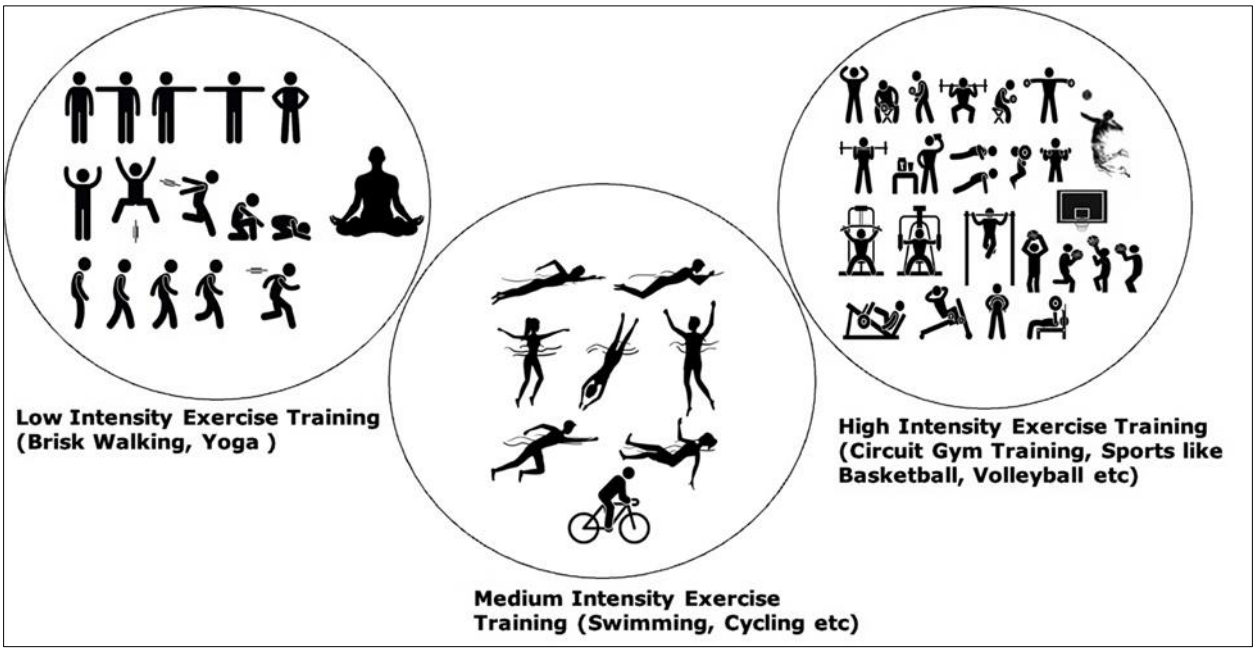

Figure 3 Different Sports representing varied exercise training intensity

1.5. Physical Inactivity & Infections

Increases in systemic inflammation, changes in the distribution of leukocyte subsets, altered T-cell IFN-production, and impaired natural killer cell activities have all been noted in human bed rest investigations. These immune system disturbances are thought to play a role in the emergence of urinary tract infections, the mild reactivation of the Epstein-Barr virus and varicella zoster virus (16) during extended periods of inactivity, and the reactivation of latent herpesviruses in astronauts during missions (17). Other situations, such as trials recruiting overweight or obese participants who are physically inactive, provide further information that could be read as supporting the idea that physical inactivity results in reduced immune function. For instance, obese individuals have inadequate immune responses to vaccination and have diminished lymphocyte proliferation after mitogenic stimulation. These immunological side effects may increase the risk of bacterial and viral infections and lengthen hospital stays as a result of more frequent and extended problems after surgery. Exercise training can, in fact, enhance immune responses to influenza and pneumococcal vaccines, speed up recovery after experimental rhinovirus infection, and lessen the frequency, severity, and duration of symptoms related to acute respiratory infections (like upper respiratory tract infections).

1.6. Host Conditions: Obesity, Aging, Diabetes, Blood Pressure

Physical inactivity is a pressing global health concern in the current times. A physically active lifestyle is important in the prevention and management of several chronic conditions. Obesity is one of the leading causes of global morbidity and mortality. Hence, in order to control this ravaging epidemic, health care specialists necessarily advise physical activity, among other things like dietary restrictions. It is a well-known fact that physical activity is inversely proportional to weight gain. Low levels of physical activity are associated with an increased risk of becoming obese, according to a review of the literature (18). It should be emphasized that exercise does not greatly aid in weight loss on its own. Instead, consistent activity is essential for keeping weight off. For sustained weight reduction, 60 to 90 minutes of exercise is recommended each day at a moderate level (Hill and Holly 2005). In case of overweight or obese individuals, this time limit should be progressively increased over time in order to facilitate long-term maintenance of weight loss (19).

Another benefit of regular exercise is a more uniform and healthy body fat distribution. Exercise causes reduction of body fat but at the same time it also results in gaining lean muscle mass. In this regard, the total amount of weight lost exhibits a dose-response relation with exercise volume. On the other hand, exercise intensity is the determinant of amount of lean mass gained such as in aerobic workouts (18). Hypertension is the most major cardiovascular risk factor that is estimated to account for nearly 7.5 million deaths worldwide (Global Health Observatory, WHO). On an average estimate, a systolic blood pressure (SBP) rise of even 20mm Hg above 115, and diastolic blood pressure (DBP) rise of 10 mm Hg above 75, doubles the rate of mortality and morbidity (20). Conversely, even slight improvements in SBP and

DBP considerably enhances chances of survival. A decrease as little as 10 mm Hg could contribute to 37% decline in incidence of coronary heart disease and 56% decrease in chances of stroke (21). An inverse relationship existing between hypertension and physical activity is well documented. Evidences strongly demonstrate that increased physical activity can significantly reduce both SBP and DBP, not only in patients with hypertension, but also in normotensive and prehypertension subjects (22,23). It is noted, nonetheless, that the degree of reaction depends on things like physical activity intensity, frequency, duration, and kind. According to studies, moderately hard exercise (40–60% of maximum oxygen intake and 60–85% of projected maximal heart rate) had the most anti-hypertensive effects (24). Practically speaking, moderate intensity exercise is safe for most middle-aged and older people as well as those with severe hypertension. In this regard, brisk walking seems to be a preferred choice of most individuals. On the other hand, diabetes mellitus, primarily type 2, is a rapidly spreading global epidemic that is expected to cause up to 6.7 million fatalities in 2021 (IDF Diabetes Atlas, 10th edition). According to the study, the condition manifests phenotypically as hyperglycemia, which can be caused by either reduced insulin sensitivity or faulty insulin secretion (25,26,27). Non-insulin dependent diabetes mellitus (NIIDM), another name for type 2 diabetes, is a lifestyle illness characterized by obesity, excessive calorie consumption, insufficient physical exercise, and genetic vulnerability (28,29).

Physical activity is a lifestyle intervention that majorly contributes to management of diabetes, along with dietary modifications and weight reduction. Compromised levels of physical activity can severely contribute to pathogenesis of the condition, ultimately resulting in increased morbidity and mortality. On the contrary, augmented physical activity can considerably decrease the progression, or even reverse the condition (30). The amount of physical activity required to alleviate the risk of diabetes largely depends on an individual's level of baseline risk. For example, those with a higher baseline risk such as obese/overweight people or those with family history, need ∼300 minutes of moderately intense or 150 minutes of strongly intense physical activity per week (31). On the contrary, those with a lower risk of diabetes such as lean people without any family history of the disease, would continue to be at a low risk independent of any physical activity. Thus, physical activity strategy needs to be tailor-made on an individual basis, rather than generalizing it on a population level.

1.7. Immunosuppression and Exercise

Immunosuppression is the loss or reduction of body' s ability to fight off foreign antigen, virus, viral particles including surface antigen on tumor cells. It may be the result of killing off of effector cells or blockage of intracellular pathway (32). Individuals infected with oncogenic virus are at the risk of developing cancer when in the continued state of immunosuppression. The neoplastic cells which have arisen spontaneously or due to genotoxicity in an immunosuppressed person will thus escape the immunosurveillance and divide without check to form tumor (33).

Diseases that are associated with immunodeficiency are a heterogeneous group. However, an attempt has been made to classify them into primary and secondary immunodeficiencies. Any failure of the B-cell system, B-cells, T-cell system or T- cells fall under the former category. These are hereditary in nature and manifest early in life. Secondary immunodeficiency arises when its initiation is due to a non-immune element like environment (34).

Immunosuppression could also be the adverse effect of another treatment the patient is undergoing (35). Interest on effect of exercise on the white blood count dates back to more than 100 years but exercise immunology became a formal discipline of science only in the latter part of the twentieth century. Physical fitness has been gaining importance in past few years especially due to the pandemic COVID 19. Moderate exercise has been seen to improve the overall immune response in an individual reducing the risk of non-communicable diseases. But can physical activity bring about immunosuppression was a question long explored by army hospitals and sports physician (36). It has now been found that intense level of exercise can compromise both the innate and acquired immunity. Immunosuppression in such individuals is also co-dependent on the genetics, stress, nutrition intake psychological condition, environment or any other underlying health condition which promotes inflammatory responses (12). Acute bout of exercise invokes an immune response similar to one post infection. This can be evaluated by checking for increased level of circulating cellular immune elements like neutrophils, monocytes and natural killer (NK) cells, a catecholamine-mediated lymphocytosis and a higher plasma concentration of several hormones (37). Heavy training schedule and endurance training compromises the immunity making them susceptible to upper respiratory tract infection (URTI) post work out. Between 1980s and 1990s several studies were carried out to investigate these incidences. Peter and Bateman in 1983 studied the incidence of URTI on marathon runners (56 km). The subjects were 150 random marathon participants and they were compared to 124 age-matched controls. Post two weeks of marathon 33.3% of the participants reported URTI in comparison to 15.3% from control group (38). Infact, a J shaped curve has been proposed by Nieman in 1997 reflecting the relationship between upper respiratory tract infection risk and exercise load (39). According to this curve

moderate level exercise lowers the risk of URTI and intense workout results in transient immune suppression increasing the risk of URTI **(Figure 4).**

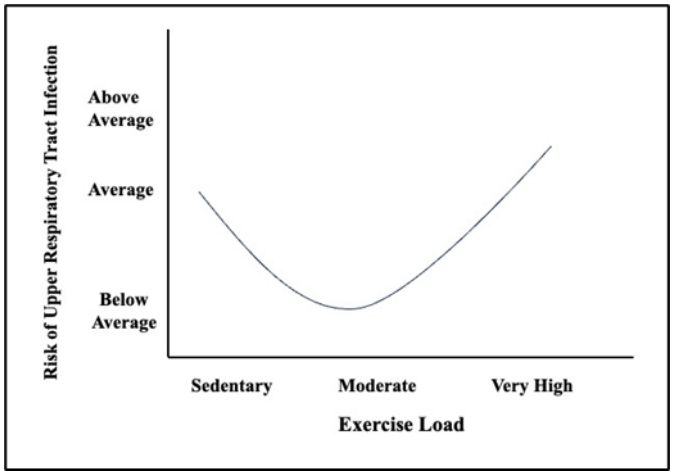

Figure 4 The J shaped model showing the relationship depicted by Niemann,1997, between upper respiratory tract infection risk and exercise load

The exercise induced immunosuppression though transient is of great importance in exercise immunology since acute respiratory infection, flu like symptoms hamper the scheduled training session for the athletes.

The changes in immune response to exercise load is also age, sex and puberty related. Studies have shown that young boys and girls (12 years) recover from immune changes much more rapidly after strenuous cycling than their older counterparts (14 years). Also, the age-related immunologic response to exercise during childhood are more pronounced in the older girls than younger ones (40).

Though moderate exercise may have beneficial effects, regular and vigorous exercise have been seen to reduce mucosal immunological markers. The most typical secretion employed for measuring secretory antibodies in the evaluation of mucosal immune status is saliva. Immediately following a period of vigorous exercise, salivary IgA and IgM concentrations decrease; however, they typically increase within 24 hours. Chronic suppression of salivary immunoglobulin levels might occur as a result of years of hard training. The intensity of exercise and the length or volume of training are related to immune suppression levels and rates of recovery after exercise. There is a higher risk of respiratory infection in athletes who have low levels of salivary IgM and IgA, particularly the IgA1 subclass (41).

1.8. Molecular Underpinnings of Exercises

The immune response is coordinated, regulated, and directly impacted by CD4 T cells. As part of immunosurveillance, CD4 T cells are always on the lookout for infections. They both control the early inflammatory response and chronic inflammation, which helps to mount a quicker and stronger immune response. They not only help other immune cells respond and remember things better, but they also directly contribute to the removal of pathogens. This meta-analysis's finding of an increased concentration of CD4 T cells indicates that regular exercise enhances these immune system activities and expedites the response. A considerate relationship has been established between regular physical exercise and immunological markers. Overall, there was a decrease in neutrophil concentration and a rise in CD4 T cell helpers and salivary immunoglobulin IgA concentration after the physical activity interventions, which lasted a median of 12 weeks and included aerobic (walking, running, cycling) or resistance or combined aerobic and resistance activity delivered 3–5 times per week for an average of 30 min at moderate to vigorous intensity (42).

2. Conclusion

The WHO recommends that asymptomatic, healthy adults exercise for at least 150 minutes per week, while children and adolescents exercise for 300 minutes per week. Walking is the most beneficial type of exercise for obese people since it reduces the risk of musculoskeletal injury, requires no skills or training, and is practicable in most conditions. Weight training, on the other hand, is suggested for people of all ages since it includes long-term weight control and the preservation of metabolically active tissue. Thus, the amount of weight lost by exercise is proportional to its intensity, duration, and kind. Physical exercise has been significantly reduced in today's society as technology and innovation

have advanced. Experts recommend the primary type of exercise for prevention and management of hypertension to be endurance activities such as aerobic exercise, supplemented by dynamic resistance training. Benefits of exercise for management of type 1 diabetes and prevention and management of type 2 diabetes is multi-factorial. Firstly, physical activity contributes to weight loss, reducing percentage of body fat and thus prevention of obesity, consequently leading to decreased chances of diabetes. Secondly, exercise promotes a host of beneficial physiological changes that contribute to better prognosis of the condition. Regular exercise improves insulin sensitivity, glucose uptake and utilization, glycemic management, blood pressure, and lipid profile. Furthermore, long-term diabetic consequences such neuropathy, nephropathy, and retinopathy may be averted or postponed. It is important to note here that benefits are maximal when physical activity is regular and consistent throughout the week. Walking is considered as the best moderately intense aerobic exercise that is capable of inducing major benefits in a diabetic condition and is also negatively associated with the risk of developing the disease. Another crucial factor that a diabetic should consider before beginning any physical activity plan is exercise testing by a health professional. Many underlying cardiovascular diseases may be disguised in the person, but they may become apparent during or after activity. The immune system's potency and effectiveness cannot be entirely determined by immune cell count and antibody concentration on their own. However, it is logical to consider appropriate levels of physical activity can significantly contribute to the development of the overall fitness and health.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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