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PHYSICAL EXERCISE AND IMMUNITY

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ABSTRACTS
Epidemiological evidence suggests a link between the intensity of the exercise and the occurrence of infections and diseases. The innate immune system appears to respond to chronic stress of intensive exercise by increased natural killer cell activity and suppressed neutrophil function. The measured effects of exercise on the innate immune system are complex and depend on several factors: the type of exercise, intensity and duration of exercise, the timing of measurement in relation to the exercise session, the dose and type of immune modulator used to stimulate the cell in vitro or in vivo, and the site of cellular origin. When comparing immune function in trained and non-active persons, the adaptive immune system is largely unaffected by exercise. Physical activity in combination with infections is usually associated with certain medical risks, partly for the person who is infected and partly for the other athletes who may be infected. The risk of infection is greatest in team sports, but also in other sports where athletes have close physical contact before, during and after training and competitions. This chapter starts with a short introduction of the immune system followed by a description of free radicals' and antioxidants' role in the immune system and how they are affected by physical activity. The chapter will also focus on need of antioxidant supplementation in combination with physical activity. The different theories regarding the effect of physical activity on the immune system will be discussed, along with advantages and disadvantages of being active, and finally effects of physical activity on the immune system are described.

KEYWORDS: Exercise, immunology, cancer, rehabilitation, survival.

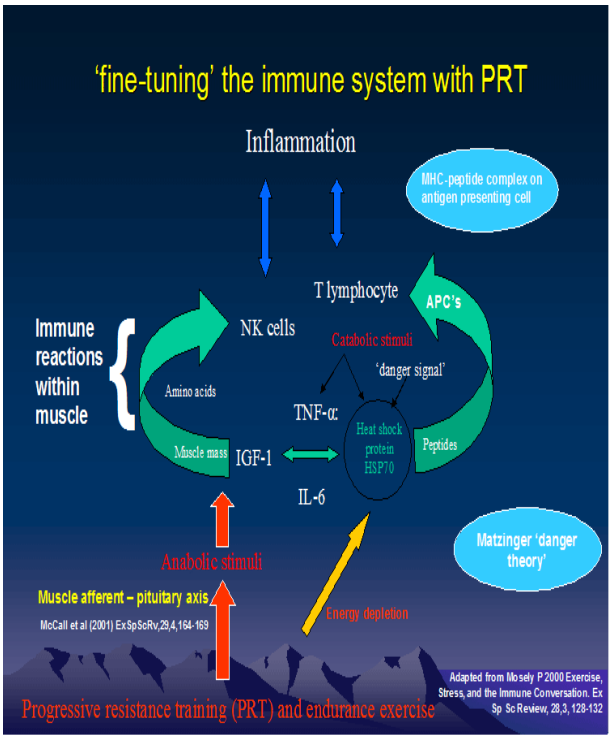

Figure-1.

INTRODUCTION

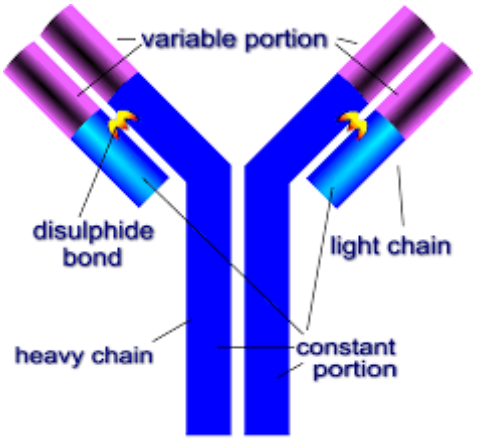

Figure-2.

Bacteria and viruses can do harm to our body and make us sick. The immune system does a great job in keeping people healthy and preventing infections, but problems with the immune system can still lead to illness and infections. The immune system is separated in two functional divisions: the innate immunity, referred to as the first line of defense, and the acquired immunity, which, when activated, produces a specific reaction and

immunological memory to each infectious agent. As the quadrennial sporting jamboree that is the summer Olympic Games fast approaches, athletes from all over the world will be training hard towards achieving a lifetime's ambition. While we at home marvel at athletes' abilities to perform faster, higher and stronger than ever before, what many will not realize is that intense exercise has dramatic effects on the host immune system. Indeed, strenuous exercise elicits immunological changes similar to many clinical stresses such as trauma, burns, surgery and sepsis. Specifically, a substantial body of work accumulated over the last 20 years has shown that intense endurance exercise, such as running, swimming, cycling or rowing, results in a profound leukocytosis[3] due to increases in the numbers of neutrophils, T and B lymphocytes, and NK cells in the systemic circulation.[1,2] Furthermore, in the post-exercise recovery period a marked alteration in the proportions of circulating immune cells is observed, with several immune cell populations decreasing to below pre-exercise levels.[4] Additionally, the functions of many of these immune cell types are also altered following exercise.[1,2] These changes have led to the idea that this recovery period from intense exercise presents a window of opportunity for infectious agents to gain a foothold, although convincing epidemiological data for this are lacking.

Innate immune system

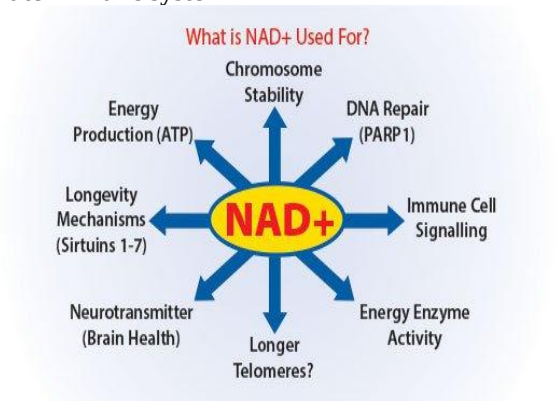

Figure: 4.

The innate immune system consists of anatomic and physiological barriers (skin, mucous membranes, body temperature, low pH and special chemical mediators such as complement and interferon) and specialized cells (natural killer cells and phagocytes, including neutrophils, monocytes and macrophages.[1] When the innate immune system fails to effectively combat an invading pathogen, the body produces a learned immune response. Leukocytes (also known as white blood cells) form a component of the blood. They are mainly produced in the bone marrow and help to defend the body against infectious disease and foreign materials as part of the immune system.[4] There are two basic types of leukocytes; the phagocytes, which are cells that chew up invading organ- isms, and the lymphocytes, which allow the body to remember and recognize previous invaders.[1] Granulocytes along with monocytes protect us against bacteria and other invading organisms, a process that is called phagocytosis (ingestion). Only cells participating in the phagocytosis are called phagocytes. The granulocytes are short lived.

After they are released from the bone marrow they can circulate in the blood for 4 to 8 hours. Then they leave the blood and enter into the tissues and can live there for 3 to 4 days.[11] If the body is exposed for serious infections, they live even shorter. The numbers of granulocytes in the blood depends on the release of mature granulocytes from the bone marrow and the body's need for an increased number of granulocytes (i.e. during infection). If a bacterial infection occurs, the neutrophils travel to the infected area and neutralize the invading bacteria.[7] In those cases, the total number of neutrophil granulocytes is high. The eosinophil granulocytes do not phagocytize and are more important in allergic reactions. The same is the case with the basophil granulocytes; they contain histamine and heparin and are also involved in allergic reactions. The eosinophil granulocytes do not phagocytize and are more important in allergic reactions. The same is the case with the basophil granulocytes; they contain histamine and heparin and are also involved in allergic reactions. The eosinophil granulocytes do not phagocytize and are more important in allergic reactions.[6] The same is the case with the basophil granulocytes; they contain histamine and heparin and are also involved in allergic reactions. Monocytes (another type of white blood cell) are produced by the bone marrow from hematopoietic stem cell precursors called monoblasts.[8] When the monocytes leave the blood barrier, they differentiate in the tissues and their size and characteristics change. These cells are named macrophages.

The acquired immune system

Adaptive immunity involves the lymphocytes and develops from early childhood. Adults are exposed to diseases or are immunized against diseases through vaccination. The main cells involved in acquired immunity are the lymphocytes, and there are two kinds of them: B lymphocytes and T lymphocytes; both are capable of secreting a large variety of specialized molecules antibodies and cytokines) to regulate the immune response.

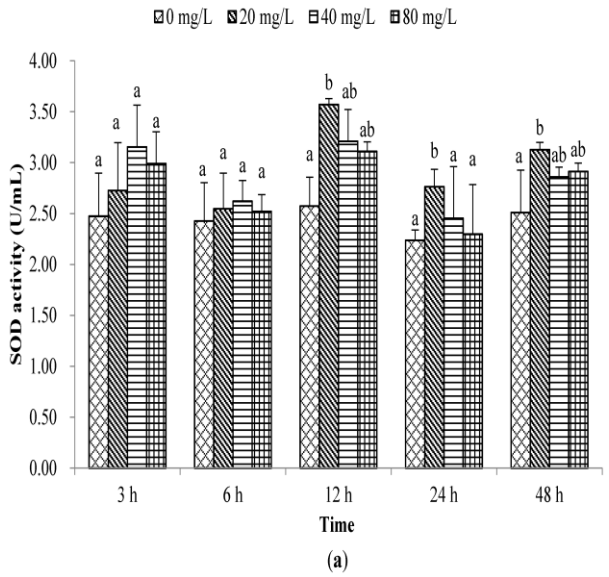

Figure-3.

C - reactive protein (CRP)

C-reactive protein (CRP) is an acute phase protein presented in the blood and rises in response to inflammation. Its physiological role is to bind to phosphocholine[9] expressed on the surface of dead or dying cells to activate the complement system. The complement system is the name of a group of plasma proteins, which are produced by the liver, and is an important part of the innate immune system. The complement system has an important role in the fight against bacteria and virus infections. A blood test is commonly used in the diagnosis of infections.[12] The level of CRP rises when an inflammatory reaction starts in the body. Blood for analysis may be taken by a finger prick and can be analyzed quickly. The level of CRP increases in many types of inflammatory reactions, both infections, autoimmune diseases and after cellular damage. After an infection, it takes almost half a day before the CRP increase becomes measurable. During the healing process the level of CRP decreases in a relatively short time (½h ~ 12-24 hours in the blood). Bacterial infection can increase CRP to over 100 mg/L, while during viral infections the values are usually below 50 mg/L.[8] This distinction between bacteria and viruses are often useful because antibiotics (such as penicillin) have no effect on viral infections, but can often be very useful in bacterial infections. Recent investigations suggest that physical activity reduce CRP levels. Higher levels of physical activity and cardiorespiratory fitness are consistently associated with 6 to 35% lower CRP levels.[3] Longitudinal training studies have demonstrated reductions in CRP concen- tration from 16 to 41%, an effect that may be independent of baseline levels of CRP, body composition, and weight loss[3]

Anticancer Therapy and the Immune System

In Cancer Survivors Cancer treatments have been shown to have dramatic effects on several immune system components in cancer survivors. In general, although the results are not entirely consistent, cancer therapies tend to be immunosuppressive. For example, Head et al. reported that breast carcinoma survivors who received chemotherapy demonstrated significantly impaired T and B cell response to mitogenic stimulation.18 In addition, Haku et al. reported that platinum-containing systemic chemotherapy significantly reduced the number of alveolar macrophages in survivors with lung carcinoma.[1,9] Fludarabine, a nucleoside drug used in hematologic cancers, produces a profound and persistent depletion in T cell (CD4) populations.[2,10]

Immune System Response to Tumors

The immune system protects against destructive forces either from outside the body (e.g., bacteria, viruses, and parasites) or from within (e.g., malignant and autoreactive cells). It comprises two functional divisions that work together in a coordinated manner. The innate immune system consists of cellular components, soluble factors, physical barriers, and the reticuloendothelial system.[6] It provides a first line of defense against foreign pathogens while an acquired immune response is activated.[7] The acquired immune system produces a specific reaction and immunologic memory to each pathogen and comprises cellular components and soluble factors.[6] The innate and acquired immune systems are illustrated in Figures 2 and 3, respectively.

These cancers include non-Hodgkin lymphoma, Kaposi sarcoma, anal carcinoma, and cervical carcinoma.11 other findings, however, seem to challenge the tenets of the immune surveillance theory. For example, although individuals receiving immunosuppressive drugs show an increased incidence of immune system cancers, they do not show an increased incidence of other common cancers such as lung, breast, and colon carcinoma.[6] Although the immune surveillance theory remains controversial, it is clear that both acquired and innate immune system components are able to produce an anticancer response to tumor cells.[6]

The acquired immune system must recognize tumor antigens in order to mount an anticancer T cell response. Tumor antigens located on tumor cells are either tumor-specific transplantation antigens (TSTA) or tumor-associated transplantation antigens (TATA).[6] TSTA are unique to tumor cells and absent on normal cells. In contrast, TATA are not unique to tumor cells in that they are expressed on normal cells during fetal development, but are usually not expressed in adults.[6]

Radiotherapy

Radiotherapy can also depress several components of the immune system in cancer survivors. In particular, radiotherapy has been shown to cause significant reductions in both NK cell cytolytic activity in breast carcinoma survivors 24 and the number of NK cells (CD3–CD16CD56) in colorectal carcinoma survivors. 25 Similarly, Garzetti et al. reported that Stages I and II endometrial carcinoma survivors who received

radiotherapy demonstrated a significant reduction in NK cell cytolytic activity.[2,6] Squamous cell lung carcinoma survivors who received radiotherapy have been shown to have significant reductions in the total number of lymphocyte, T cells (CD4, CD8), and T cell proliferation in response to mitogenic stimulation.[2,7] Furthermore, radiotherapy has been shown to reduce total lymphocyte counts, T cells (CD4, CD8), T cell (CD4/CD8) ratios, and T and B cell proliferation responses to mitogenic stimulation in survivors with squamous cell carcinoma of the oral cavity.

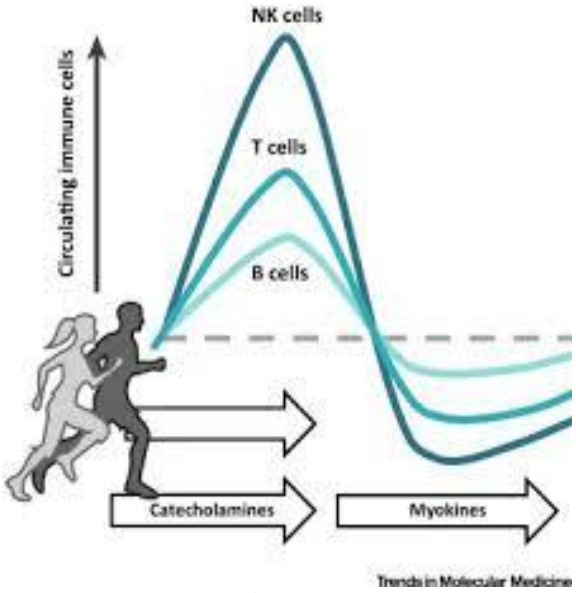

Figure-5.

Surgery

Surgery is another cancer treatment modality that has been shown to suppress immune system function. More specifically, immune system components that have been shown to be impaired after surgical interventions include monocytes phagocytosis, antigen presentation and superoxide release, B cell immunoglobulin production, T cell response to mitogen stimulation, and IL-2 production.[2,9] In addition, Uchida et al. reported that breast carcinoma survivors who received modified radical mastectomies had significantly reduced NK cell cytolytic activity that remained for more than two weeks following surgery.30 Presently, however, there is limited research linking changes in immune system function during or after anticancer therapy to important cancer outcomes such as complications and/or the risk of recurrence.[8] Nevertheless, preliminary studies indicate that the immunosuppressive effects of primary therapy may indeed be relevant. For instance, Head et al. showed that the magnitude of the decrease in the number of neutrophils and lymphocytes that occurred during chemotherapy was associated with disease relapse.

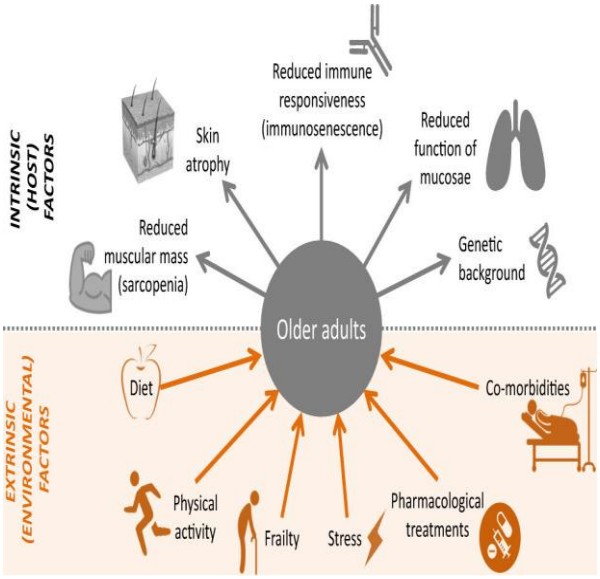

Figure-6.

Intervention

Physical exercise interventions several physical exercise interventions were utilized. All six studies initiated exercise that was consistent with current guidelines recommended for the development of physical fitness in cancer survivors.42 The frequency of the exercise was five times per week for two studies[8,9] and three or four times per week for an additional two studies.40,41 Other studies reported an exercise training frequency of seven times per week36 and 10 times per week.37 The intensity of the exercise was between 60% and 80% of each subjects' maximum heart rate in five out of six studies.[3–4]

RESULTS

RESULTS In general, the studies that examined the effect of physical exercise training on immune system function in cancer survivors reported favorable outcomes. The subjects assigned to the physical exercise training group had lower heart rates during a fixed sub maximal load, increased 16-minute walk distances, and increased leg strength compared to the control group after the exercise intervention.40 In addition, trained subjects had a decreased loss of physical performance36 and increased aerobic power41 compared to untrained subjects. Three studies did not report changes in cardiorespiratory fitness and/or muscular strength.[3] Similarly, the studies reported favorable immune system outcomes. More specifically, four out of six studies reported statistically significant improvements in immune system function as a result of exercise. The immunologic benefits that have been shown include improvements in NK cell cytolytic activity,[7] monocytes function,[9] proportion of circulating granulocytes, 39 and duration of neutropenia.[3,6] Notably, these statistically significant results occurred in the studies despite the fact that they had an average of only 28 participants each. In contrast, two studies found no statistically significant improvements in immune function as a result of exercise. In fact, Nieman et al. found no statistically significant

change in NK cell cytolytic activity or the proportion of T and NK cells,40 while Shore and Shephard reported non-significant decreases in T cell populations as a result of exercise.[4,1] Limitations of Past Research and Directions for Future Research Although the extant literature suggests that physical exercise training may have a positive influence on several immune system components important in cancer defense, there are several limitations that should be considered when interpreting the results and planning future research. Moreover, there are many unexplored issues due to the nascency of this field that warrant further investigation. Some limitations of past research and directions for future studies are presented below.[8]

CONCLUSIONS

A strong rationale exists for examining physical exercise and cancer recurrence/survival through effecting immune system function in cancer survivors. To our knowledge, six studies have examined this issue to date. The results of these studies suggest that physical exercise training may improve a number of immune system parameters that may be important in cancer defense. However, these studies have limitations in sample size, study design, physical exercise interventions, physical fitness assessments, and immunologic assessments. Moreover, many unanswered questions remain. Additional research is needed to determine if exercise in cancer survivors may reduce the risk of recurrence and/or secondary malignancies and increase survival times.

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