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PHYSICAL ACTIVITY AND THE IMMUNE SYSTEM

BY DR PAUL BATMAN

As we learn to live with the after-effects of the COVID-19 pandemic, there has been a shift in people's expectations about exercise and fitness. While body image and weight loss were often the main reasons for starting an exercise programme, there is now a move to improving mental health as well as developing a strong immune system.

The COVID-19 pandemic has made us more aware of how vulnerable we are to infectious diseases, as well as the need to move to improve and maintain our health and wellbeing. Quarantining and self-isolation has also taught us how inactivity and a sedentary lifestyle can decrease immune resistance against both infectious and chronic disease, as well as contributing to mental health issues.

Conversely, since 1990, physical activity has been regarded as a key player in improving the function of the immune system. Many epidemiological studies have reported that moderate to vigorous exercise for up to 60 minutes can stimulate the movement of immune cells between tissues and the circulation.

Physical activity can enhance the surveillance of the macrophages that are the first responders of the innate immune system as they work in concert with anti-inflammatory cytokines, neutrophils, natural killer cells, T cells and immature B cells, all contributing to an improved immune resistance to invading viruses and bacteria.

To understand the relationship between the immune system and physical activity, it is important to identify its components. There are five different types of white blood cells responsible for immune responses. These include basophils, eosinophils, lymphocytes, monocytes/macrophages and neutrophils, which comprise both the innate immune system and the more powerful adaptive immune system.

Macrophages and neutrophils are key components of the innate immune system that initially chase an invader, engulf it and break it down. Neutrophils travel rapidly to the infected site and begin the inflammation process. The macrophages release proteins that are responsible for sending signals between cells and systems that are also seen in the blood. To maintain successful immune function, it is important to create a balance between the pro and anti-inflammatory cytokines.

T cells, B cells, helper T cells and killer T cells are part of the adaptive immune system and are regarded as super cells that support and co-ordinate the first responding innate immune system. T cells direct the immune response for killing cells infected with viruses or other pathogens. B cells produce antibodies that fight the infection and killer T cells destroy the host cells that contain the infection.

During muscle contractions and for approximately three hours after, these important immune cells circulate throughout the body at a faster rate than normal. The most effective are neutrophils (situated in bone marrow and lung), natural killer cells (located in spleen) and macrophages, all part of the front line of immune defence.

Physical activity brings these cells out from the lymphoid tissue and into the blood compartments to roam throughout the body. After three hours of recovery from exercise, everything returns to nearby tissue. Significantly, the immune system receives no long-term effect from a single bout of physical activity. The results are purely from the accumulation of the acute effects of one bout of physical activity building upon another bout, indicating the immune responses are frequency dependent. Physical activity is the only stimulus that permits the transient surge of important immune cells, as it releases the front line of defence and improves pathogen surveillance by moving immune cells from the circulation to the tissues.

Daily intermittent muscle contractions are key to immune protection, as they have the potential to exceed the levels beyond that of any other method, including medications and supplements. If the pathogen gets through the slower acting immune cells, the T cells and B cells of the adaptive immune system are then brought into action.

While physical activity can prevent infection or disease, it cannot be therapeutic as it does not help once the virus has been contracted. Where this does occur, it is important to rest for a full recovery.

In the aged, overweight, obese, inactive, unhealthy and unfit, low-grade chronic inflammation is always present and can become progressively more difficult to control and neutralise with the body's cells always thinking that they are under attack. This causes the immune system to become overworked and unable to fight legitimate infections, potentially leading to long-term chronic diseases.

The purpose of this review is to report on studies that have specifically examined the key components of both the innate and adaptive immune systems and their relationship to workload, vaccine response, immunosenescence and chronic conditions.

RESEARCH REVIEW 1

Title: *Exercise after influenza or COVID-19 vaccination increases serum body antibody without an increase in side effects*

Authors: J Hallam, T Jones, J Alley, M Kohut (2022)

Source: Brain, Behaviour and Immunity, 102: 1-10

Introduction

An increase in immune response has been reported when physical activity is performed around the time of vaccinations, possibly due to the stressor effect of the physical activity causing an increase in antibody response before immunisation, potentially improving vaccine efficiency.

Some studies report that eccentric muscle contractions can produce a local inflammatory response that stimulates an immune response, placing the immune system on alert. While this is a possibility, the results are still inconsistent across all studies, mainly due to the dose of exercise.

The purpose of this study was to examine the immune response to 90 minutes of moderate-intensity aerobic exercise after immunisation to the seasonal influenza vaccine, the 2009 pandemic influenza vaccine H1N1 and the COVID-19 vaccine and compare to other studies that have focused on exercise prior to vaccination.

Method

A total of 20 participants comprised the 2009 pandemic influenza cohort, with 16 included in the final analysis. A further 28 subjects were used in the seasonal influenza group.

All participants were immunised with the relevant vaccines prior to the exercise session.
A further 36 subjects received the Pfizer vaccine for COVID-19.
Subjects who exercised at a moderate to vigorous intensity for two or more days per week, as well as those who didn't exercise, were included in the final analysis.

A pre-immunisation blood sample was collected before immunisation and then two to four weeks' post immunisation. In the case of Pfizer vaccine, a second dose was administered three weeks after the first dose.
In the 2009 pandemic vaccine group, subjects were randomly assigned to either a light- to moderate-intensity (60-70% HR max) exercise group for 90 minutes or a no exercise control group. The exercise was monitored by % HR max and RPE.
In the seasonal influenza group, young subjects were randomly assigned to either a 45-minute exercise session, a 90-minute exercise session or no exercise. The older group completed a 45-minute exercise session.
The COVID group was assigned to a 90-minute exercise session or to go about their daily routine of activity.

Results

There were no differences in heart rate, RPE and exercise heart rate between the non-exerciser and the exercise treatment groups or within each vaccine experiment. There was also no difference in the side effects of the vaccines between the non-exercise group and exercise groups.

In the influenza groups, there were greater changes in the immune response in the exercise group than the non-exercise group, with the 90-minute session producing higher results than the 45-minute sessions following the vaccination.
In the COVID-19 group, the low- to moderate-intensity exercise intervention for 45 minutes and 90 minutes also increased the antibody response to the vaccine.

Discussion

This study is one of the first to report the improved vaccine response for influenza and COVID-19 caused by light- to moderate-intensity exercise several weeks after the vaccination.

This could be a significant public health finding given that those who engage in light to moderate activity (2-6 METs) can potentially improve their vaccination response even after the vaccination date. This is important for those who are unable to exercise at moderate to vigorous exercise (3-9 METs), which is the national recommendation for exercise prescription.

This study suggested that the longer duration, the greater the effect. The time course of the most effective exercise was the 90-minute session across all vaccinations. The 90-minute bout could be performed in daily physical activity in intermittent bouts of any duration. The 45-minute bout appeared to be effective for COVID-19 vaccination but less effective for the influenza vaccines.

The mechanism for the exercise enhancement of the vaccine response is still unclear. However, there is some support for exercise to stimulate the production of the cytokine IFN alpha, which is released from immune cells, stimulating the production of macrophages and natural killer cells that activate the immune system and support the vaccine.

As the immune system consists of the fast-acting innate immune system and the adaptive immune system, different levels of intensity, duration and frequency of physical activity might be required to fully activate the immune system to fight invading viruses and bacteria.

RESEARCH REVIEW 2

Title: *Effects of regular physical activity on the immune system, vaccination and risk of community acquired infectious disease in the general population: Systemic review and meta- analysis*

Authors: S Chastin, U Abaraogu, J Bourgois, P Dall, J Darnborough, E Duncan, J Dumortier, D J Pavon, J McParland, N Roberts, M Hamer (2021)

Source: Sports Medicine, 51: 1,673-1,686

Introduction

Globally, respiratory tract infections have been a major cause of death with over four million fatalities reported each year. Over the past few years, the COVID-19 pandemic has increased the awareness of how contagious these viruses are and their widespread health and economic consequences. As a means of combating the infection, numerous governments advocated lockdown and self-isolation while encouraging communities to remain physically active.

While studies have been conducted on the importance of physical activity and immune system improvements, many of the subjects in these studies were athletes and their training programmes. Little has been reported on the effects of habitual physical activity on the immune system.

The purpose of this study was to examine if habitual physical activity can reduce the risk of community-acquired infectious diseases and mortality and its effect on immunisation.

Method

Seven databases were researched between 1980 and 2020 for peer-reviewed articles published in English. Comparisons of physical activity and immune system responses were made across controlled trials and observational studies. All subjects had to be >18 years and athletes were excluded.

The physical activity component consisted of any activity performed at moderate to vigorous intensity between 15-120 minutes.
Records initially returned 16,698 records, from which 660 texts were reviewed and 551 excluded. Fifty-five studies were deemed to have met the inclusion criteria.

Results

Those subjects who participated in higher levels of habitual physical activity had a 31% reduced risk of community-acquired infectious disease and a 37% reduction in associated mortality.

Increased levels of CD4 cell (helper T cells) counts were reported compared to control groups. CD4 cells help co-ordinate the immune system by stimulating other immune cells, including the big first line of defence: macrophages from the innate immune system and the B cells from the adaptive immune system responsible for the production of antibodies.

It was also reported that habitual physical activity caused an increase in IgA, which is the most abundant antibody in the body and found mainly in saliva, and is particularly important in fighting infection in the gastro intestinal tract and respiratory tract.
Regular moderate to vigorous physical activity caused an increased vaccine response, increasing its potency.

Discussion

This study reports significant changes in immune system functioning as a result of continual habitual physical activity. The physical activity intervention cited in these studies included three to five times per week for an average of 30 minutes per session for 12 weeks. This prescription resulted in increases in CD 4 cells (helper T cells) and salivary IgA concentration and a reduction in the concentration of neutrophils. These increases also enhanced the vaccination response, further supporting physical activity as a legitimate intervention for controlling further virus transmissions.

CD4 cells (helper T cells) play an important role in controlling acute tissue inflammation while continuing to monitor the levels of pathogens and enhancing the memory of other adaptive immune cells. IgA also acts as an anti-inflammatory mediator while also strengthening the mucosal barriers and the body's first line of defence.

An anomaly to the improvement in immune system functioning is the reduced concentration of neutrophils, which are the most abundant white blood cells in the immune system. This could indicate a suppression of the immune system rather than an improvement. While the number of studies that examined neutrophils was small, it could also be interpreted that due to their strong involvement in regulating chronic inflammation the exercise bout was not severe enough to warrant such an inflammatory response. The increases in CD4 and IgA that controlled inflammation could have kept the neutrophil inflammatory response under control.

RESEARCH REVIEW 3

Title: *Habitual physical activity is associated with the maintenance of neutrophil migratory dynamics in healthy older adults*

Authors: D Bartlett, O Fox, C McNulty, H Greenwood, L Murphy, E Sapey, M Goodman, N Crabtree, C Thorgersen-Ntoumani, J Fisher, A Wagenmakers, J Lord (2016)

Source: Brain, Behaviour and Immunity, 56: 12-20

Introduction

With advanced ageing comes an increase in immunosenescence or a decrease in the functioning of the immune system leading to an increased susceptibility to infection. The first line of defence in immune system functioning is the innate immune system, with the neutrophils among the first cells to arrive at the infected site.

The neutrophil is the most abundant leukocyte in the immune system and easily one of the most potent. The neutrophils work closely with the macrophages and form the innate immune system, which are the first responders in fighting the infection. They are also called phagocytes and are also responsible for inflammation.

The macrophages are usually the first on the scene and, when necessary, call the neutrophils into action to assist in fighting the infection. While macrophages can live up to several months, the lifespan of neutrophils is only a few hours depending on the situation. They are critical to survival and, without them, the defence against infection is seriously compromised.

Ageing can cause the neutrophils to become dysfunctional in healthy older adults. The problem can manifest itself through the neutrophils' inability to move toward the infected site or its migration ability. This delays the movement and recruitment of neutrophils and significantly reduces the immune potential of fighting infection and can increase unnecessary chronic inflammation.

It is largely unknown why ageing has such a dramatic effect on neutrophil functioning. Some suggest it could be the signalling pathways (P13 pathway) that are responsible for the migrating directional problems experienced by the ageing neutrophils.

It has been reported that increased levels of physical activity could assist in maintaining or possibly improving immune system functioning, potentially slowing down the progress of immunosenescence. It could be possible that a decrease in immune system functioning could in part be caused by the increased levels of inactivity, a feature of the ageing population.

The purpose of this study is to examine the effects of habitual physical activity on the neutrophil development and maintenance.

Method

Physical activity levels were assessed in 211 healthy older adults >66 years old (100 men and 111 women). All subjects were fitted with an accelerometer for seven days.

Measurements were taken through a battery of tests, including neutrophil migration and phagocytosis, oxidative bursts, cell receptor expression, metabolic health parameters, strength tests, blood tests and systemic inflammation.
Most active groups were compared to less active groups and results from younger participants.

Results

The most active group completed double the number of steps as the low active group and presented with lower BMIs and % body fat.
The most active group also presented with increased levels of IL8, which is a protein that is important in the recruitment and direction of neutrophils to the infected site, as well as activating macrophages. These increased levels were comparable to the younger group.
The significant differences in BMI and % body fat levels between the most active and the low active group were associated with lower insulin levels and high adiponectin levels, which also improves insulin sensitivity.

Discussion

Immunosenescence is associated with a reduction in the accuracy of neutrophil migration and the decreased clearance of bacteria. The migration of the neutrophil is critical in controlling infection, inflammation and wound repair and can cause damage to surrounding tissues by elevated protein breakdown leading to further immobility.

While neutrophil migration is slower and less accurate when compared to younger counterparts, it is now apparent that inactivity and sedentary behaviour can play a significant role in a further loss of speed and accuracy. The results of this study suggest that neutrophil performance is highly regulated and dependent upon physical activity levels. The more active the individual, the greater the improvement in neutrophil functioning. The subjects in this study did not participate in a formal exercise programme but more incidental movements. To provide more opportunities for people to improve their immune system functioning, physical activity centred around daily life activities at low- to moderate-intensity levels could improve their innate immune responses to all infections.

Regular physical activity has been prescribed in the control of glucose levels and insulin sensitivity. In this study, the most active groups reported lower blood sugar levels and improved insulin sensitivity, while also demonstrating improved neutrophil migratory accuracy and performance. This suggests a connection between metabolic health and neutrophil signalling pathways that might modify neutrophil function.

RESEARCH REVIEW 4

Title: *Salutary effects of moderate but not too high intensity aerobic exercised training on the frequency of peripheral T cells associated with immunosenescence in older women at high risk of breast cancer: A randomised controlled trial*

Authors: G Niemiro, A Colletta, N Agha, P L Mylabathula, F bBker, A Brewster, T Bevers, E Fuentes-Mattei, K Basen-Engquist, E Katsanis, S Gilchrist, R Simpson (2022)

Source: Immunity and Ageing, 19: 17

Introduction

A condition reportedly responsible for poor vaccination response, low grade chronic inflammation, increased rate of infection and cancer is immunosenescence or age-related changes in the ageing immune system.

One area of the immune system that appears particularly susceptible to ageing is the T cell. The T cell is a very important component of the adaptive immune system that has a number of varied jobs. There are different classes of T cells, including helper T cells, killer T cells and regulatory T cells, each having a specialised function. Without normal functioning T cells, there is an increased chance of dying from infection and cancers as they are the co-ordinators of the immune system. They are memory cells that can quickly recognise and produce antibodies to destroy it.

It has been reported that those people who engage in regular exercise have potentially "younger looking" T cells compared to sedentary people. With immunosenescence comes an increased risk of breast cancer. Physical activity has been reported to remove tired T cells through apoptosis or where cells commit suicide, being replaced by new T cells improving the immune profile.

The aim of this study was to examine the effects of a 12-week structured exercise programme on T cells in a group of middle-aged females who had previously been identified as being at high risk of breast cancer.

Method

Subjects in this study were post-menopausal women who were overweight and who were considered at a heightened risk of breast cancer. The subjects were exposed to either high-intensity interval training (HIIT) or moderate-intensity continuous exercise training (MICT) three times per week for the 12-week programme. The changes from the exercise interventions were correlated against muscle-derived myokines IL-6, IL-7 and IL-15, all of which play integral roles in the production and transportation of white blood cells.

Results

Helper T cells (CD4 cells) were decreased in HIIT, whereas in MICT total T cell concentration and helper T cell levels increased. When both interventions increased VO2max, there was an increase in T cell concentration.

Discussion

Decreases in T cell concentration have been reported as indicators of immunosenescence and increased all-cause mortality and cancers. There is growing evidence that immunosenescence could precede breast cancer and contribute to its development.

While exercise has been widely reported to improve immunity against most forms of cancer, there has been little information presented on the type of exercise required. This is the first study to show that MICT rather than HIIT could be more effective in creating positive changes to T cell functioning and improving immunity. After 12 weeks of training, helper T cell concentration and total T cells were increased in MICT. Apparently, HIIT decreased helper T cell concentration and reduced total T cell counts. For example, HIIT reduced T cell numbers and helper T cells by 38%, while MICT increased total T cell numbers and helper T cells by 20%.

This result is controversial, as HIIT is an effective form of training for improving VO2max and general mortality; it appears to be less effective in improving T cell concentration and functioning and might be less effective in improving the adaptive immune system performance for this older group.

An improved T cell profile is reported to enhance vaccination response after a period of exercise. Evidence is mounting that newly diagnosed patients with cancer do present with immunosenescence profiles and that exercise can extend the survival rates during treatment for breast cancer and other tumours.

The mechanism responsible for these positive shifts in T cell performance is still unclear; however, it has been postulated that exercise might control infections by more effectively removing tired old T cells and replacing them with younger, better functioning cells.

RESEARCH REVIEW 5

Title: *Rejuvenation of neutrophil functions in association with reduced diabetes risk following 10 weeks of low volume, high intensity interval walking in older adults with pre-diabetes: A pilot study*

Authors: D Bartlett, C Slentz, L Willis, A Hoselton, J Huebner, V Kraus, J Moss, M Muehlbauer, G Speilmann, D Muolo, T Kovers, H Wu, K Huffman, J Lord, W Kraus (2020)

Source: Frontiers in Immunology, 11: 729

Introduction

Associated with Type 2 diabetes is neutrophil dysfunction. The neutrophil is the most abundant white cell and serves many functions in immunity against infections. Almost all the functions of the neutrophils, including cell eating, pathogen killing, and pace and direction, are impaired in Type 2 diabetes patients, creating a chronic low-grade inflammation throughout the body, with hyperglycaemia insulin resistance and increased concentration of free fatty acids resulting.

Exercise can improve metabolic health and reduce low-grade inflammation, decreasing the risk of Type 2 diabetes, with greater levels of physical activity occurring in older adults producing the best results. Moderate-intensity training has been shown to be effective in improving neutrophil speed and guidance, while neutrophil bacterial function has been improved with low-volume, high-intensity interval training.

The aim of this pilot study was to examine the effects of 10 weeks of HIIT on cardiorespiratory fitness, glucose control, systemic inflammation and neutrophil function in older adults with pre-diabetes.

Method

Ten older sedentary adults (71 +- 5 years) were recruited for this study. All women were post-menopausal, and all subjects were medication stable. A young control group was also recruited who were free of metabolic disease.

Pre- and post-testing items included glucose and insulin sensitivity, neutrophil movement, bacterial phagocytosis, reactive oxygen species (free radicals) and mitochondrial functions.

The exercise intervention included three sessions per week of 10 x 60-second intervals of low intensity at 50-60% HRR for active recovery alternated with 10 x 60-second intervals of high intensity at 80-90% HRR of treadmill walking for 10 weeks. There was a 5-minute warm-up and 5-minute cool-down included in each session.

Cardiorespiratory fitness parameters and neutrophil function were compared to subjects in the younger group.

Results

The HIIT intervention reduced fasting glucose levels and insulin levels and improved glucose control. VO2max increased considerably after HIIT, while being significantly less than the younger subjects pre training. After HIIT training, neutrophil activity, bacterial control and reactive oxygen species increased similar to levels reported in the younger group.

Neutrophil mitochondrial functions, while low pre-training, improved to levels approaching the younger subjects.

Discussion

This study demonstrated that older pre-diabetes subjects of 65-80 years can reduce risk factors associated with the development of Type 2 diabetes in a 10-week HIIT exercise intervention. Improvements were reported in aerobic fitness, neutrophil activity and performance, glucose control and insulin sensitivity.

Glucose control in Type 2 diabetes is associated with elevated neutrophil production of reactive oxygen species (free radicals) stimulating low-grade chronic inflammation. Diabetics also present with neutrophil chemotaxis, which is a neutrophil's reduced ability to detect the direction and intensity needed to move towards the infection, increasing inflammation.

This study suggests a relationship between increased glucose concentration and impaired neutrophil chemotaxis. In people with hyperglycaemia, neutrophil functions can be improved by lowering blood glucose levels with insulin indicating that insulin sensitivity could be a main regulator of neutrophil chemotaxis in pre-diabetic older adults. Improvements in aerobic capacity, glucose control and reduced body fat could be the catalyst for improvements in neutrophil functioning.

Neutrophils performance is also affected by mitochondrial functioning. Neutrophils comprise an extensive mitochondrial network and appear to be very sensitive to exercise, with neutrophils mobilising into the blood stream during movement and then leaving the blood at its conclusion.

The HIIT protocol also could have altered the metabolic functioning of adipose tissue by decreasing the production of leptin and increasing the production of adiponectin, collectively reducing the inflammatory response. Adiponectin is a fat-derived hormone whose main function is to protect against insulin resistance and diabetes, while leptin is responsible for inhibiting hunger.

Overall, the HIIT protocol improved neutrophil chemotaxis and the metabolic profile of older pre-diabetic subjects, potentially improving their innate immune system functioning against infection.

RESEARCH REVIEW 6

Title: *A systemic review of the acute effects of exercise on immune and inflammatory indices in untrained adults*

Authors: W Brown, G Davison, C McClean, M Murphy (2015)

Source: Sports Medicine, 1: 35

Introduction

Physical inactivity is regarded as an independent risk factor for cardiovascular disease, in part due to the low-grade chronic inflammation that it causes. The increased inflammation is further responsible for the release of pro-inflammatory cytokines such as Il-6, TNF alpha and CRP. Cytokines are responsible for signalling the immune system to move to the infected area and contribute to the movement of white blood cells and are important in the development of hyperglycaemia and insulin resistance.

An initial step in the development of cardiovascular disease is the reduction in the release of nitric oxide, which causes endothelial dysfunction and is the result of hyperglycemia. The reduced release of nitric oxide contributes to the arteries' inability to dilate and constrict necessarily for the movement of blood throughout the body.

Muscle contractions are a powerful stimulus for the release of anti-inflammatory cytokines called myokines. The release of myokines such as IL-6, IL-1 and IL-10 promote glucose uptake, lipid metabolism and the inhibition of pro-inflammatory cytokines, potentially reducing the incidence of cardiovascular disease. Most of the research has been conducted on trained or clinical groups and not on untrained subjects.

The purpose of this study was to examine the acute effects of exercise using the current recommendations on immune and inflammatory markers in untrained adults.

Method

Ten studies reported between 1946 and 2013 that met the inclusion data were reviewed to determine the acute effects of exercise on IL-6, C Reactive Protein and neutrophil count in the 48 hours following a bout of exercise lasting less than 60 minutes. Additional information extracted included age, gender, BMI, training status and VO2max.

Results

The results of this analysis indicate that a single bout of exercise of moderate to high intensity (3-9 METs) increased the concentration of IL-6 up to 145%. IL-6 is produced by active immune cells including T cells, macrophages and endothelial cells and is an anti-inflammatory cytokine.

The moderate- to high-intensity protocol also increased neutrophil concentration up to 51% prior to and following the exercise bout. The post-exercise changes in CRP were unclear due to the small number of studies available for analysis.

Discussion

This review indicated that, post exercise, there were increases in anti-inflammatory cytokine IL-6. This could have been caused by an increase in the production of Reactive Oxygen Species (ROS) or free radicals caused by oxidative stress. Exercise that recruits the aerobic energy system increases the production of ROS, which in turn is mopped up before causing any additional side effects and creates the most effective immune response.

The intensity and duration of the exercise bout will determine the concentration of IL-6. Most studies suggest that exercise bouts lasting approximately 60 minutes and recruiting a large muscle mass produce the most effective IL-6 response. An increase in IL-6 can also increase glucose and lipid metabolism, resulting in greater metabolic control.

Neutrophils are key leukocytes that arrive at infected sites and have been reported to increase from resistance training lasting more than 30 minutes, as well as continuous aerobic training and high-intensity exercise. Neutrophils generally only remain elevated for approximately 30 to 60 minutes' post exercise. This would indicate that to receive the maximum benefit from an increase in neutrophil concentration the exercise bout would have to be performed daily as there is no accumulated effect. The lifespan of a neutrophil is only a matter of hours at best, as they are very potent weapons against infection and can cause significant harm to healthy tissue if in too great a concentration and unsupervised.

The exercise response to neutrophils could be a function of the patient's initial level of fitness. Untrained adults might gain more benefit from low-intensity muscle contractions, whereas fitter groups might require greater intensity.

Lifestyle physical activity performed throughout the day and at lower intensity could be a powerful stimulus to increase innate immune response via increased neutrophil concentration for the untrained. Without continual muscle contractions, there appears to be little need for the innate immune system to be elevated long term.

RESEARCH REVIEW 7

Title: *Human skeletal muscle macrophages increase following cycle training and are associated with adaptations that may facilitate growth*

Authors: R G Walton, K Kosmac, J Mula, C Fry, B Peck, J Groshong, B Finlin, B Zhu, P Kern, C Peterson (2019)

Source: Scientific Reports, 9: 969

Introduction

Macrophages have been given the title of "Great Eater", with one of their primary functions being phagocytosis, which occurs when the irritant is engulfed by the macrophages trapping it inside and disassembling it.

The main function of the macrophages is to eat and swallow irritants and remove them from the infected area. Macrophages have the ability to live for many months patrolling the body, disposing of any rubbish or dead cells and breaking up bacteria and releasing cytokines. They are located in all tissues of the body and are regarded as the captain of the innate immune system. They also have the ability to shut down any immune response to prevent any additional damage after the infection has been neutralised.

Both neutrophils and macrophages at the front line of the innate immune system can also initiate inflammation to protect the damaged area. The M1 macrophages are responsible for inflammation, while M2 macrophages are responsible for anti-inflammatory responses.

While the knowledge of macrophages in general is widely reported, their involvement in exercise is unclear. It is known that macrophages are activated when there is any muscle damage, especially from eccentric muscle contractions, and are responsible for promotion of muscle repair and healing.

Macrophage activity is severely curtailed in obesity, ageing and a sedentary lifestyle.

The purpose of this study was to examine whether aerobic endurance exercise and resistance training altered macrophage structure and concentration in sedentary subjects.

Method

The protocol used in this study involved three days of assessments, followed by 12 weeks of cycle ergometer training for three days per week for 45-minute bouts at approximately 65% of VO2max. The 12 weeks were then followed by a further three days of post assessments.

The responses from the cycle training were compared against resistance training data collected from one exercise bout.

Muscle biopsies of the vastus lateralis muscle in the thigh were performed as the invasive intervention for histochemistry analysis and gene expression.

Results

M2 macrophages responsible for anti-inflammatory responses, cell proliferation and tissue healing did not increase after the resistance training session but did increase in the aerobic endurance protocol. M2 macrophage increase was also apparent in fibre hypertrophy, which occurred in the 12-week programme but not the shorter resistance training session.

The positive changes in M2 macrophages from the aerobic endurance programme were associated with changes in Human Growth Factor responsible for cell growth, cell motility and tissue repair. The aerobic endurance programme also increased the release of IL-4 responsible for the activation of the T cells and B cells from the adaptive immune system.

Discussion

This study is among the first to report that aerobic training can induce increases in M2 macrophages, potentially due to the fibre hypertrophy and satellite cell proliferation that was also witnessed. This is unusual, as aerobic training does not normally cause fibre hypertrophy. In this instance, the programme was based on cycle ergometers, where the resistance was changed to induce overload, culminating in greater recruitment of type 2 fibres.

In other studies, resistance training has been reported to cause positive changes in M2 macrophage performance, mainly due to the tissue repair required after eccentric muscle contractions.

The 12-week aerobic training programme, while not causing an increase in the overall concentration of all macrophages, did cause increases in anti-inflammatory cytokines, particularly IL-4.

Given that macrophages have a relatively long life in the innate immune system, any physical activity or training protocol that continues for at least 12 weeks has the potential to produce an anti-inflammatory environment in the cells, as well as improving the patrolling and surveillance capabilities of the biggest leukocytes in the immune system.

RESEARCH REVIEW 8

Title: *T-cell responses to acute cardiorespiratory or resistance exercise in cohorts of physically active or physically inactive older adults: A randomized complete crossover*

Authors: R Graff, K Jennings, E LaVoy, V E Warren, B Macdonald, Y Park, M Markofski (2021)

Source: https://doi.org/10.1101/2021.04.25.21255567

Introduction

Ageing predisposes us to many chronic diseases, including cardiovascular disease, cancer, Type 2 diabetes, arthritis and osteoporosis. Ageing also causes a down regulation of the immune system resulting in immunosenescence, which is a common underlying contributor to many of these diseases.

Lymphocytes are a type of white blood cell consisting of the T cell and B cell, which form a major part of the super-adaptive immune system often recruited after the innate immune system has played its role in fighting the infection. The T cell appears to be most affected by ageing and immunosenescence with a reduction in T cell concentration, reduction in the diversity of the types of T cells and the increase in pro-inflammatory cytokines secreted from the existing ageing T cells.

It has been reported that physical activity can alter the concentration and function of many different types of white blood cells, including neutrophils and macrophages, due to the sheer stress of blood passing through the arterial system caused by muscle contractions. T cells and CD8 cells are also increased as a result of physical activity. The effects of exercise, particularly resistance training, on the adaptive immune system are sparse, with the emphasis having been on the innate immune system.

The purpose of this study was to examine the effect of acute cardiorespiratory and acute resistance training on T cells among a group of physically active and inactive older adults.

Method

Twenty-four older adults completed one bout of cardiorespiratory exercise and one bout of resistance training exercise at moderate intensity (3-6 METs) and separated by seven days.

The cardiorespiratory exercise bout consisted of a 5-minute warm-up of walking on a treadmill at a self-selected speed, followed by an increase in either speed or gradient on the treadmill reaching an intensity of 60-70% of heart rate reserve.

The resistance training protocol included a 5-minute warm-up, followed by three sets of 8-12 repetitions at 70% 1RM with 30-120 seconds' rest between sets. Exercises included leg press, chest press, leg curl, lateral pulldown, weight calf raise, triceps extension and seated row.

Blood samples were taken pre exercise, post exercise and 60 minutes' post exercise. Samples were analysed for CD 4 (T cells) and CD 8 (natural killer cells), total T cell concentration and their status.

Results

The pre- to post-test results indicated that both cardiorespiratory and resistance-training protocols mobilised T cell subpopulations into the circulation in both the active and inactive older adult groups.

There were more T cell subpopulations mobilised in the pre to post exercise in resistance training than cardiorespiratory training in the inactive older adults.

Some T cell subpopulations stayed elevated after the exercise bout and during recovery in the inactive group. All T cells returned back to normal levels after the cardiorespiratory exercise bout in the active group.

Discussion

This was one of the first studies that used a crossover design to examine T cell response in older physically active and inactive adults after completing separate bouts of moderate-intensity cardiorespiratory exercise and resistance training.

It reported that, regardless of being physically active or inactive, moderate-intensity cardiorespiratory and resistance training caused a significant increase in the mobilisation of T cells and subpopulations, potentially improving an immune response.

In the physically inactive group, resistance training mobilised more T cell population than cardiorespiratory training.

It was also found that physically active older adults have a lower proportion of immunosenescence T cells compared to the same-aged inactive adults.➤

This further supports the emerging hypothesis that physical activity can be potentially a powerful mediator for improving immunity during the ageing process and offsetting immunosenescence. Regardless of physical activity levels, both groups experienced an increase in T cell mobilisation immediately during and after the exercise bout. The results tended to be higher in the physically active group, indicating the gains are much greater with ongoing participation in all movement experiences.

T cell mobilisation was reported to be higher at rest in the inactive group, suggesting a heightened immune response leading to long-term chronic inflammation.

The mobilisation of T cells during exercise and then a return back to normal levels as observed in the physically active group is the most favourable profile for improved immunity against infection of bacterial invasion.

Both cardiorespiratory training and resistance training can be prescribed to increase the mobilisation of the adaptive immune system through the increased mobilisation of T cells and their subpopulations.

It could be possible that multiple bouts of physical activity throughout the day could produce repeated bouts of heightened immunity to fight infection and delay the onset of immunosenescence given that, after the exercise bout and during recovery, T cell mobilisation reverts back to its normal pre-workout levels.

RESEARCH REVIEW 9

Title: *Effects of lifelong training on senescence and mobilization of T lymphocytes in response to acute exercise*

Authors: ZL Minuzzi, L Rama, M Chupel, F Rosada, J Du Santos, R Simpson, A Martinho, A Psiva, A Teixeira (2018)

Source: Exerc Immunol Rev., 72-84

Introduction

Immunosenescence during ageing is a decline in immunity in the adaptive immune system and characterised by a low number of T cells, a large number of memory T cells, poor vaccination responses and low numbers of helper T cells.

When the immune system is initially activated to fight infection, the innate immune system is the front line of defence. The macrophages race to the area and engulf all irritants, trapping them inside its borders. It then merges with another compartment filled with acid and breaks the pathogen down into basic components. The macrophages then call the neutrophils for assistance, followed by an increase in inflammation and then additional reinforcements are recruited. As the infection continues and while the innate immune system is holding its own, it becomes tired and sends out for assistance from the adaptive immune system – more specifically, the helper T cells. These cells recognise the pathogen and inform the macrophages of the action required to kill the invading bacteria. They then inform the T cells that they are now required, and so they also join the battle.

The antibodies from the T cells bring a whole new approach to the fight. They flood the area and assist the immune cells to see the pathogen much clearer and co-ordinate a much more aggressive defence.

The T cells have a much more extensive role to play in immune response, with many types of cells, including helper T cells, killer T cells and regulatory T cells, with each specialising to fight every possible combination of infections.

These cells are critical in co-ordinating the immune system throughout the body and directly activate the key immune cells; without them, there is an increased chance of disease or dying. They are critical to health maintenance and improvement throughout life.

Following the activation of the T cells is the recruitment of the very powerful B cells, whose main responsibility is the production of the most potent weapon: an extensive number of antibodies.

In ageing, as the T cells reduce in number and change their composition, they become more pro inflammatory, contributing to the chronic low-grade inflammation that redisposes many chronic diseases.

Some studies have reported that ageing decreases helper T cells by 10% and 10.2% in T cells per decade, while subjects who had an above average VO2max presented with fewer senescent T cells. This could indicate that aerobic fitness might be a more predictable determinant of senescent T cells than merely ageing.

The purpose of this study was to investigate the effects of lifelong training on the senescence and mobilisation of T cells after acute exercise.

Method

The subjects in this study consisted of 19 athletes who had been training and participating in competitions for over 20 years. A control was also formed, consisting of 10 healthy adults with no extensive training age.

All subjects undertook a cycle ergometer test to exhaustion with blood samples to determine T cell variations were taken pre-test, 10 minutes after the test and 60 minutes after the test.

Results

The results indicated that subjects with a long training history presented with fewer senescent T cells and helper T cells than those with a low training age.

Those with a higher V02max had a positive effect on the helper T cells but little effect on total T cell count.

No difference was found for helper T cells and T cell concentration between those with a long training history and those with low history of activity.

Discussion

This study reports that lifelong training and maintaining a high level of aerobic fitness during normal ageing could reduce the accumulation and development of senescent helper T cells and T cells.

Little difference was found in the concentration of T cells between the lifelong group and the control group, indicating that training age did not affect the total volume of T cells. ➤

The preservation of helper T cells and the reduced accumulation of lower functioning senescent T cells are characteristics of a stronger immune system in ageing.

The changes in senescent T cells in lifelong training could be caused by many of these older exhausted cells being mobilised into the blood during the physical activity and then directed to inflamed tissue one to two hours' post exercise and during recovery, where they are exposed to voluntary cell destruction reducing their number. This can create more space for a potential increase in the number of helper T cells in the vacant space and increase the T cell immunity.

RESEARCH REVIEW 10

Title: *Frequent participation in high volume exercise throughout life is associated with a more differentiated adaptive immune response*

Authors: A Moro-Garcia, B Fernqdez-Garcia, A echeveria, M Rodriguez-Alonso, F Suraez-Garcia, J Solano-Jaurrieta, C Lopez-Larrea, R Alonso-Arias (2014)

Source: Brain, Behaviour and Immunity, 39: 61-74

Introduction

The success of any exercise programme revolves around the interaction of intensity, frequency and duration performed long term. It is well known that exercise of different intensities can improve immune function with muscle contractions releasing anti-inflammatory cytokines, reducing the low-grade chronic inflammation responsible for many chronic diseases.

A controversial area of epidemiology study is the differences between high-intensity exercise compared to light- to moderate-intensity on overall immunity. The relationship between physical activity and immunity has been reported in some papers as a J curve, where moderate-intensity exercise improves immunity, while high-intensity exercise has the potential to cause an immunosuppression response possibly due to the interaction of hormonal, nutritional and inflammatory factors.

Some suggest that intense exercise performed repeatedly without adequate recovery can cause transient inflammatory responses in the exercising muscles, potentially altering immune capacity.

There are similarities between sedentary older individuals and a high volume of intense workout performed without recovery. Older sedentary people experience a low-grade chronic inflammation, which is regarded as the root cause of many chronic conditions, possibly to the presence of a greater number of senescent cells that no longer contribute to immunity.

Over a lifetime, the immune system is subjected to a plethora of antigens and pathogens that fatigue the T cells, neutrophils and macrophages and the thyroid gland which is so important in training T cells and B cells about antigens and irritants.

The purpose of this study was to assess the effects of a high volume of exercise over a lifetime on specific aspects of immunity by comparing immunological features of 27 young and 12 elderly athletes and 30 young and 26 elderly non athletes.

Method

Ninety-five subjects volunteered for this study. The young athletes were rowers that trained by on-water rowing, resistance training and running. Their intensity proportions were 60% low-moderate, 30% intense and 10% very intense. They had been training six days per week for 90-120 minutes per day for approximately four years. The inactive young group were selected from those who did not perform the national recommendations of 150 minutes of moderate intensity or 75 minutes of vigorous intensity per week.

The elderly athletes were over 65 years old and had trained for five days per week for 30-80 minutes per day for between 35-50 years at an easy-to-moderate intensity. The elderly inactive or non-athlete group were selected from those living in a nursing home but were still judged physically fit.

All subjects were screened by a physical examination and subjected to a variety of functional tests and blood tests that could affect immune function. Blood samples were taken with leukocyte and lymphocyte subpopulations analysed.

Results

This is the first study to show that participation in high-volume physical activity over a lifetime produces different responses across the spectrum of the immune system.

This study reported that a high volume of physical activity reduced the number of leukocytes, neutrophils and lymphocytes in both the innate and adaptive immune systems. Highly active individuals presented with a decrease in helper T cells and an increase in natural killer cells.

The functionality of the helper T cell and natural killer cells was significantly impaired in the young, but not the elderly, athletes. However, the increased capacity of the natural killer cell might represent a compensatory mechanism to maintain a strong immune response.

Discussion

In the young athletic group, there was a decrease in the immune response from the T cell subpopulations, largely compensated by an increase in the activity of the natural killer cells.

The helper T cells are responsible for planning and decision making, while the killer cells are aggressive and at the front engaging the pathogen. To overcome the lack of commitment by the helper T cells, the killer cells assume a more aggressive and powerful stance against any invaders, helping them maintain their health and performance. The changes in T cell subpopulations could be caused by the stress hormones released during the intense activity and changes in the ratio of pro-inflammatory to anti-inflammatory cytokines. ➤

The same response was not seen in the elderly athletes. There was no down regulation of the T cells in the adaptive immune system of the elderly group, possibly due to the reduced intensity they trained at. They were trained at moderate intensity rather than the 40% intensity and high-intensity protocols followed by the young group.

The adaptive immune system of the elderly group may have benefited by the long-term moderate-intensity training offsetting some of the problems experienced with the general increase in senescent T cells associated with ageing. If the elderly group had been subjected to more intense workouts, they may have experienced the same changes as the younger group. The T cell response in young athletes could be due to the increased need to maintain higher levels of physical activity for long periods.

Both the young and the old athletic groups also presented with a decline in neutrophil activity and total white cell number when compared to the non-athletic groups. This appears to be caused by an initial increase in neutrophil activity at the beginning of the exercise, followed by a decrease caused by a redistribution of the neutrophil to improve the immune response against pathogens in the skin, lungs, gastrointestinal tract, mucosal surfaces and lymph nodes.

Intense training protocols will induce different changes in the adaptive immune system, according to age and length of ageing. Younger athletes can maintain their immune status when compromised by intense training by increasing the activity of the natural killer cells, even though the surveillance helper T cells become less functional. This appears not to be the case with elderly athletes.

If the aim long term is to maintain a functioning innate immune and adaptive immune system, a focus on low- to moderate-intense physical activity will reduce the number of senescent cells and maintain neutrophil concentration, and increase the patrolling and guidance capabilities of the helper T cells as well as increase the performance of natural killer cells to recognise and destroy infected cells.

THE BOTTOM LINE

1 Vaccine response to influenza and COVID-19 can be improved by light- to moderate-intensity exercise several weeks after the vaccination. This could be a significant public health finding given that those who engage in light- to moderate-intensity activity (2-6 METs) can potentially improve their vaccination response even after the vaccination date. This is important for those who are unable to exercise at a moderate to vigorous intensity (3-9 METs), which is the nationally recommended exercise prescription.

2 Significant changes in immune system functioning can occur as a result of continual habitual physical activity. The physical activity intervention of three to five times per week for an average of 30-60 minutes per session for 12 weeks can result in increases in CD4 cells (helper T cells) and salivary IgA concentration. These increases also enhance the vaccination response, further supporting physical activity as a legitimate intervention for controlling further virus transmissions.

3 Immunosenescence is associated with a reduction in the accuracy of neutrophil migration and the decreased clearance of bacteria. The migration of the neutrophil is critical in controlling infection, inflammation and wound repair and can cause damage to surrounding tissues by elevated protein breakdown leading to further immobility. While neutrophil migration is slower and less accurate when compared to younger groups, inactivity and sedentary behaviour can play a significant role in a further loss of speed and accuracy. Neutrophil performance is highly regulated and dependent upon physical activity levels. The more active the individual, the greater the improvement in neutrophil functioning.

4 While exercise is widely reported to improve immunity in the adaptive immune system, there has been little information presented on the type of exercise required. Moderate-intensity continuous training (MICT) rather than HIIT could be more effective in creating positive changes to T cell functioning and improving immunity. Apparently, HIIT can decrease helper T cell concentration and reduce total T cell counts. HIIT reduced T cell numbers and helper T cells by 38%, while MICT increased total T cell numbers and helper T cells by 20%.

5 A relationship exists between increased glucose concentration and impaired neutrophil chemotaxis. In people with hyperglycaemia, neutrophil functions can be improved by lowering blood glucose levels with insulin, suggesting that insulin sensitivity could be a main regulator of neutrophil chemotaxis in pre-diabetic older adults. Improvements in aerobic capacity, glucose control and reduced body fat could be the catalyst for improvements in neutrophil functioning.

6 Neutrophils, the key leukocytes that arrive at infected sites, can increase from resistance training lasting more than 30 minutes, as well as continuous aerobic training and high-intensity exercise. Neutrophils only remain elevated for approximately 30-60 minutes' post exercise, indicating that to receive the maximum benefit from an increase in neutrophil concentration the exercise bout would have to be performed daily as there is no accumulated effect. The lifespan of a neutrophil is only a matter of hours at best, as they are very potent weapons against infection and can cause significant harm to healthy tissue if in too great a concentration and unsupervised.

7 Aerobic training can induce increases in M2 macrophages (anti-inflammatory response), potentially due to the fibre hypertrophy and satellite cell proliferation. This is unusual, as aerobic training does not normally cause fibre hypertrophy. In this instance, the programme was based on cycle ergometers where the resistance was changed to induce overload, culminating in greater recruitment of type 2 fibres.

8 Physical activity is a powerful mediator for improving immunity during the ageing process and offsetting immunosenescence. There is an increase in T cell mobilisation immediately during and after an exercise bout that tends to be higher in the more physically active older adults, indicating the gains are much greater with ongoing participation in all movement.

9 Changes in senescent T cells from lifelong training could be caused by older exhausted cells being mobilised into the blood during the physical activity and then directed to inflamed tissue one to two hours' post exercise and during recovery, where they are exposed to voluntary cell destruction reducing their number. This can create more space for a potential increase in the number of helper T cells in the vacant space and increase the T cell immunity.

10 In young athletic groups exercising at high intensities, a decrease in the immune response from the T cell subpopulations has been observed largely compensated by an increase in the activity of the natural killer cells. The helper T cells are responsible for planning and decision making while the killer cells are aggressive and at the front engaging the pathogen. To overcome the lack of commitment by the helper T cells, the natural killer cells assume a more aggressive and powerful stance against any invaders helping them maintain their health and performance. The changes in T cell subpopulations can be caused by the stress hormones released during the intense activity and changes in the ratio of pro-inflammatory to anti-inflammatory cytokines. The same response is generally not seen in the elderly athletes, possibly due to the reduced intensity of their training programmes.