Physical and immunological aspects of exercise in chronic diseases

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Running Title: Exercise to boost immunity

Background: Physical inactivity and sedentary lifestyles are believed to be independent risk factors for the occurrence of numerous diseases, including, obesity, type-2 diabetes, metabolic syndrome, cardiovascular disease, cancer and mental health, all leading to substantial morbidity and/or premature death. It has been found that regular exercise, is associated with better quality of life and health outcomes, and reduces the risk of cardiovascular disease and cancer. Here, we review the effects regular exercise has on mental health and well-being, on the immune system and in cancer, cardiovascular disease, autoimmunity and metabolic syndrome. Is exercise the new immunotherapy to treat diseases?

KEYWORDS: cancer . chronic diseases . exercise . immune status . immunity, immunotherapy . inflammation . physical activity

Introduction

Physical inactivity is ranked just behind cigarette smoking as a contributing factor of lifestyle health issues and conditions [1]. Physical inactivity is a 'health hazard'. Physical activity and exercise, on the otherhand, appears to be a cost-effective immunotherapeutic approach with few known side effects. Most importantly, people with greater levels of physical activity report improvements in mental and physical health, as well as quality-of-life [2-5]. Such improvements can even be achieved with low intensity aerobic activity, such as walking and dancing [6]. According to the Global Recommendations on physical activity for health, released by the World Health Organisation in 2011, 150 minutes a week of moderate physical activity can reduce the risk of breast and colon cancers, diabetes and heart disease [7]. However, this was recently updated (06 February 2014) by the Department of Health, Australia. This suggests that we should accumulate 150-300 minutes a week of moderate intensity physical activity, or 75-150 minutes of vigorous intensity physical activity to be undertaken per week for health. In addition, strength training should be included at least 2 days per week [8], in order to build bone and muscle strength, aid in body fat burn and increase in metabolism, for 18-64 year olds [8].

The benefits of exercise to health

As early as the 5th century BC, exercise was recognized to be the best medicine for health and wellbeing. Hippocrates stated…, "All parts of the body, if used in moderation and exercised in labors to which each is accustomed, become thereby healthy and well developed and age slowly; but if they are unused and left idle, they become liable to disease, defective in growth and age quickly". However, the importance of physical activity waned with the decline of ancient civilization and until a decade ago, physical activity was predominantly used in military, sports and athletics. The important observational studies of Jerry Morris et al, in the 1940s-1950s, changed modern views of exercise, fitness and health, even though the scientific community did not readily accept these [9]. In 1949, Morris and colleagues noticed that double decker bus drivers had higher rates of cardiovascular disease compared to the conductors who climbed the stairs of the bus [10]. Overall the conductors had lower blood pressure and wore smaller uniform sizes as compared to the drivers. In addition, postmen that rode their bike, had lower incidence of heart attacks compared to those who worked at sedentary jobs, such as clerks or telephone receptionists [11]. Further studies demonstrated that gardening did not have the same effects on heart disease as did exercise or more vigorous physical activity [12]. These studies led to the importance of physical activity with a link to health outcomes. With the exponential number of publications and correlations of physical activity in health and disease prevention in the last decade, a new era has evolved between the relationship of exercise and health and wellbeing.

Physical inactivity and sedentary lifestyles are believed to be independent risk factors for the occurrence of obesity, type-2 diabetes and metabolic syndrome [13]. Visceral fat activates a range of inflammatory pathways that leads to insulin resistance and atherosclerosis. These diseases are commonly referred to as, ‘sedentariness’. As such, lifelong physical activity, or beginning physical activity at any stage of life, results in significant cardiovascular health benefits [14]. Modern lifestyles, have forced people to be less active, as much time is spent watching television, searching the internet, electronic game playing and reading. The amount of time spent being physically inactive predicts ill health [15]. For instance, a large longitudinal Canadian study of 17,013 people over 12 years, demonstrated that those who were inactive for a longer block of time were 50% more likely to die prematurely compared to those who sat for shorter periods of time [16]. Interestingly, there was a dose response relationship between total sitting time and ill health, ie. the longer one sat, the more likely they were to experience ill health, independently of the amount of physical activity. Hence, the time we spend sitting and its distribution throughout the day, rather than being less or more physically active, is associated with increased morbidity and mortality. In fact, the Department of Health Australia, suggests to, ‘minimise the amount of time spent in prolonged sitting’, and to ‘break up long periods of sitting as often as possible’ [8]. In the last 2 decades, there has been an explosion in diseases associated with inactivity. A dose response relationship exists indicating that people with high physical activity have the lowest risk factor for premature death. Regular exercise, either as part of a lifestyle or as part of a disease intervention program are associated with better physical and mental health outcomes, to chronic diseases, such as, cancer, obesity, osteoporosis, stroke, coronary heart disease (CHD), cardiovascular disease (CVD), blood pressure, type-2 diabetes, cognitive functioning and mental health and well-being [17-20]. However, high physical activity increases the risk of injury, hence, extra care should be taken when increasing physical activity.

Exercise, the immune system and disease

Exercising on a regular basis is one of the pillars of leading a healthy lifestyle. Regular exercise is known to improve cardiovascular health [21], lowers blood pressure [22], helps control body weight, and protects against a variety of diseases. But does it help maintain a healthy immune system? Just like a healthy diet, exercise can contribute to general good health and therefore to a healthy immune system. Indeed, western diet, stress, smoking, sleep deprivation and inactivity, have all been linked to immune system disorders and chronic inflammation [23]. Hence, it is conceivable to include exercise in daily routines for immunological health benefit.

a. Exercise and immune cells

Brief exercise is known to induce a stress response and increases inflammatory cells in the circulation, including monocytes [24]. Exercise affects monocyte (CD14+) phenotype, cell surface markers, cytokine secretion, increases the number of circulatory monocytes of up to 4.8 fold, and cortisol released during exercise up-regulates monocyte CCR2 expression and migration activity [25]. Dendritic cells (DC) (MHC class II expression, mixed lymphocyte reaction and IL-12 production) and neutrophils are also increased in the circulation during exercise [26]. In addition, during brief exercise, natural killer (NK) cells are increased up to 5-fold in blood, which play a role in defense against pathogens and cancer immunosurveilance [27]. However, after prolonged exercise, the number of NK cells are reduced [26]. NK cells are the most sensitive population of immune cells to exercise stress. A short bout of 30 minutes of cycling increases the expression of cytokines of, T-cells (TNF-alpha, IL-6, IL-4), of monocytes (IFN-gamma, IL-4), and, of B-cells (GH, IGF-I) [28]. At the molecular level, it is becoming clear that exercise does not change cell surface markers, but instead selectively mobilises subsets of cells that have pre-determined levels of these markers [29, 30].

A study consisting of 12 healthy males aged in their 20s underwent 10 x 2 minute bouts of cycle ergometer exercise (high intensity exercise training or HIT) equivalent to 82% of peak VO_2 consumption followed by a 1 minute rest [24]. Immediately following exercise peripheral blood mononuclear cells (PBMC) were isolated and using gene arrays, gene alterations were noted which were likely to direct monocytes into an anti-inflammatory pathway [24]. Down-regulation of monocyte tumor necrosis factor (TNF), toll-like receptor-4 (TLR4) and CD36 genes and up-regulation of EREG and CXCR4 were noted, which influence vascular health. Hence, despite the stress response induced by HIT exercise, this stress response has a positive outcome that appears to promote cardiovascular health. Likewise, TLR-2 and HLA-DR expression were down-regulated, which may have implications for modulation of post-exercise immune surveillance [31]. In addition, in patients with high blood pressure, exercise increases the expression of monocyte CD62L and CXCR2. However, the clinical implications of this response need to be further examined [32]. In a similar study, consisting of 13 healthy males aged in their 20s underwent a similar HIT exercise regime, 10 x 2 minute bouts of cycle ergometer exercise equivalent to 77% of VO_2max followed by a 1 minute rest [27]. NK cells isolated from PBMC and using gene arrays, it was found that 986 genes and gene pathways were altered, predominantly those involved with cancer, (melanoma, glioma, prostate cancer), p53 signaling pathway, cell to cell communication, focal adhesion and adherens junction [27]. This data supports that even brief bouts of high intensity exercise alters the expression of NK cell genes and this could alter health through the innate immune system. A similar exercise regime was applied to 11 healthy males aged in their 20s who performed 10 x 2 minute bouts of cycle ergometer exercise equivalent to 76% of VO_2max followed by a 1 minute rest [24]. Immediately following exercise, neutrophils were isolated and using gene arrays and in silico analysis, 4,724 genes and 3 pathways were altered; Ubiquitin-mediated proteolysis, Jak-STAT signaling pathway and Hedgehog signaling pathway [24]. These pathways are known to play a role in inflammation in humans. Similarly, pro-inflammatory (IL-32, TNFSF8 and CCR5), anti-inflammatory (ANXA1), growth and repair genes (AREG and FGF2, involved in angiogenesis) and genes known to be involved in asthma and arthritis, were altered following exercise [33]. In sedentary women, a single bout of cycling, for 1 hour, increased the phagocytic and oxygen-dependent microbial capacity of neutrophils [34]. It is clear that in particular aerobic exercise of different durations and intensities has a direct impact on immune cells. These responses appear to have beneficial outcomes to disease.

b. Exercise and anti-inflammatory effects

Low-grade chronic inflammation is involved in atherosclerosis, diabetes and chronic pathological diseases. Regular physical activity reduces the risk of chronic diseases, partly due to the anti-inflammatory effects of exercise [35]. These effects may be mediated via reduction in visceral fat mass and decreased adipokines secretion, and an altered inflammatory milieu following exercise [35]. Physical activity reduces IL-6, IL-8 and IL-15 cytokines and during muscle contractions, IL-1 receptor antagonists and TNF-receptor molecules are released which have anti-inflammatory affects [36]. Inflammatory cytokines are also associated with age and diseases related to inactivity. In a group of 65-80 year old females, those assigned to exercise training for 12 weeks were associated with lower levels of monocytes and TNF-alpha production [37]. In addition, moderate to high intensity training, reduces systemic cytokines (TNF-alpha, IL-6, IL-1beta) in an inflammatory milieu in elderly women [38], and in obesity [39]. Further, CRP is significantly decreased in physically active subjects [40], and growth hormone secretagogue receptor-1a is increased which has high anti-inflammatory properties [41]. These studies suggest that exercise has anti-inflammatory effects.

In animal models, rats subjected to treadmill exercise decreases oxidative stress (malondialdehyde), CRP and proteinuria [42]. Further, increase in antioxidant enzyme (superoxide dismutase), Cu/Zn superoxide dismutase protein in renal proximal tubules, nuclear levels of Nrf2 transcription factor D1 receptor function and IL-10 cytokines are noted in rats undergoing exercise as compared to sedentary rats [42]. Exercise may therefore be beneficial in preventing oxidative stress, inflammation and preserving kidney function. Interesting, moderate aerobic exercise of mice, decreases Th2 responses and Th cell migration within the lungs of an ovalbumin (OVA)-sensitised murine allergic asthma model [43], as well as decreasing leukocyte infiltration and activation of nfκB [44]. In addition, forced treadmill running exacerbates inflammation, by increasing diarrhea, IL-6, IL-1beta, IL-17, however, voluntary treadmill running attenuated symptoms of inflammation in a colitis mouse model [45]. Further, intense aerobic treadmill exercise increases pro-TNF-alpha and anti-IL-10 and pro-apoptotic protein (caspase 3), indicating an overall anti-inflammatory effect as a result of wheel running in healthy mice [46]. Likewise, exhaustive exercise reduces TNF-alpha and IFN-alpha concentrations and this reduction is via TLR-7 and elevation of systemic catecholamines [47]. Further, hepatic inflammation and fibrosis is reduced by reduction of TNF-alpha, macrophage infiltration and tissue inhibitor of matrix metalloproteinase-1 mRNA [48]. It is clear that factors released by exercise, such as IL-6 and decreasing levels of TNF-alpha production, lead to a decreased inflammatory state.

c. Keeping the metabolic balance through exercise

An increase in sedentary lifestyles with decreasing physical activity has led to obesity, type-2 diabetes, hypertension, hypercholesterimea and metabolic syndrome factors [49]. These constitute the metabolic syndrome, leading to atherosclerosis and other cardiovascular related diseases. It is believed that high calorie intake plays a role, however, there is evidence supporting that, adequate physical activity reduces the risks without the need to modify caloric intake to keep a metabolic balance. In fact, exercise has been shown to reverse the risk of developing metabolic syndrome in those with high-fat diets [50]. In addition, the Amish community, which has maintained a physically active lifestyle, has much lower prevalence of type-2 diabetes and obesity despite high calorie intake [51]. Further, a few days of bed-rest (inactivity) in healthy individuals results in decreased effects of insulin and glucose utilization, despite normal diet [52]. A 28 year study, from 1970-1998, involving 2,501 healthy males demonstrated that physical activity (daily walking, gardening or cycling) inversely correlated to weight gain [53], and those with high intensity activity had greater health benefits.

Wild animals do not suffer from metabolic diseases due to their 'continuous' physically active state. Physical activity and exercise, attenuates high blood pressure, insulin resistance, glucose intolerance, cholesterol, triglyceride and obesity [54]. In a 12 week trial of obese middle-aged women taking part in a 1 hour resistance and aerobic exercise, 3 days per week clearly demonstrated that metabolic syndrome factors (blood pressure, percent body fat, fasting glucose levels, triglyceride and cholesterol levels) and, visfatin levels, were significantly lowered [55]. Blood pressure is lower in physically active women compared to healthy sedentary women [56], and, resistance training for 12 weeks improves heart rate, blood pressure and cholesterol levels [57]. In addition, aerobic exercise improves metabolic syndrome factors such as, blood pressure, waist circumference, and fasting glucose levels [58], and, protects against obesity related low-grade inflammation and beta-adrenergic receptor desensitization [59]. In addition, Bikram yoga 3 times per week, improves glucose tolerance in older obese adults [60], improves arterial stiffness and insulin resistance in adults [61], and, resistance exercise significantly decreases triglyceride values [62]. Furthermore, a 10 year study, involving 4,100 males and 963 females, indicated that the ones that were involved in walking, running, jogging, treadmill type exercises, were associated with lower body mass index and triglyceride levels as compared to the ones that did not undertake regular exercise over the 10 year period [63].

Several chronic conditions, including those related to the metabolic syndrome are orchestrated by inflammatory cytokines. As such, TNF-alpha is increased in chronic conditions such as type-2 diabetes, obesity and atherosclerosis (reviewed in [44]). TNF-alpha plays a role in insulin resistance and has been suggested as an intermediary link between obesity and inflammatory diseases including heart disease and type-2 diabetes [44]. Numerous studies suggest that increasing physical activity is effective in reducing low-level inflammation. For example, diabetic or metabolic syndrome males put on a 3-week daily exercise program showed significant reductions in body mass index, serum lipids and cholesterol, fasting glucose, insulin, macrophage inflammatory protein-1alpha, matrix metalloproteinase-9 and C-reactive protein (CRP) [64, 65]. Moreover, voluntary habitual exercise augments the innate immune system, through increases in stress-evoked heat shock protein 72 (Hsp72), MCP-1, IL-6 and IL-10 and decreases inflammatory cytokines IL-1 beta and TNF-alpha [66]. In addition, soluble intercellular adhesion molecule-1 (sICAM-1) levels are significantly improved in physically active type-2 diabetic patients [67]. Exercise also up-regulates peroxisome proliferator-activated receptor-gamma (PPAP-gamma) in the plasma and on monocytes [68]. Myokines, such as IL-6 are released by muscle cells during exercise, which further have anti-inflammatory effects [69]. Hence, exercise reduces oxidative stress, inflammation and monocyte-endothelial interactions, and increases PPAP-gamma and myokines, all of which have been linked to have anti-diabetic and anti-metabolic syndrome effects. Major lifestyle changes like increasing physical activity habits, may therefore improve patients with diabetes or metabolic syndrome factors and in patients with coronary arterial disease risk factors. Even in those who feel too ill to exercise, decreasing sedentariness is clearly a positive start. In postmenopausal women for example, cardiovascular disease is increased, and this risk is significantly lowered in physically active women [56], by improving antioxidant capacity and decreasing body iron burden [70]. Physical activity plays a pivotal role in maintaining health and metabolic balance. Indeed, the National and Nutrition Examinations Study (NHANES III) [71, 72], concluded that physical activity is the primary element to prevent and treat metabolic syndrome.

d. Reducing the risk of Cardiovascular disease through exercise

CVD, a disease of the heart or blood vessels, and includes conditions such as CHD, atherosclerosis, ischemic stroke, hypertension, myocardial infarction and sudden cardiac death. Studies have demonstrated an association between physical activity with all-cause cardiovascular mortality and prevention of CHD [73]. In 1992, the American Heart Association recognised that physical inactivity to be a 'risk factor' for CHD and CVD [74], and in 1996 a report from the Surgeon general was published which indicated that 'regular physical activity decreases the risk of CHD and CVD' [75]. The US department of health and human services, issued the first physical activity guidelines in 2008 [76] which was based on published research studies between 1995-2007, on the effects of physical activity with CHD risk, and conducted in numerous countries (USA, UK, Norway, Finland, Canada, Sweden, Israel), and included over 453,000 subjects, both males and females and different racial backgrounds (reviewed in, [77]). Regular exercise training and improvements in cardiorespiratory fitness, reduces CVD risks [78].

Atherosclerosis is characterized by endothelial dysfunction, increase in oxidised stress, accumulation of lipids on blood vessel walls and inflammation. Physical activity can prevent and/or attenuate atherosclerosis by correcting and preventing endothelial dysfunction. Patients with coronary artery disease could be reversed with exercise training, by reversing endothelial dysfunction and improvement of blood flow of the coronary artery [79]. In a 5-year randomised trial of 73 males aged 70 years or less with chronic heart failure, were assigned ergometer exercise in the hospital 4-6 times per day for 2 weeks followed by 6-months at home ergometer exercise training of 20 minutes per day. After 6 months, patients in the exercise group had improvements in maximal ventilation, exercise time, resting heart rate, stroke volume at rest and reduction in cardiomegaly [80]. A recent long term 25 year study, assessing the effects of physical activity over 25 years on atherosclerosis in 101 middle aged men, demonstrated that regular high to very high physical activity had better outcomes in regards to cardiometabolic profiles (coronary artery calcification, carotid intima-media thickness and reactive hyperemia index) as compared to men with lower physical activity [81]. Similarly, 4 weeks of high intensity exercise training in coronary artery disease patients, significantly improved maximal work capacity, lipid profile, body mass index, blood pressure, fasting glucose, hemoglobin A1c and was associated with reduced CD11b and VLA-4 (CD49d) [82]. Furthermore, monocyte activation and transendothelial migration changes result after short-term exercise in an intensity-dependent manner (light, moderate, high) [83]. Moreover, aerobic exercise, but not resistance exercise, reduces CRP, IL-18 and IL-6, all markers of inflammation which are mediators associated with numerous diseases including atherosclerosis and hypertension [84, 85]. Thus, regular high intensity physical activity may protect against atherosclerosis. Indeed, it is suggested to expend at least 1,500 calories per week to halt atherosclerosis process and 2,200 calories per week for stenosis regression [86].

An early indicator of atherosclerosis is the decreased nitric oxide (NO) bioactivity, which plays a role in oxidation of LDL-cholesterol. Inactivation of NO and high levels of reactive oxygen species (ROS) are present in patients with CVD, atherosclerosis and coronary arterial disease [87]. Patients with acute myocardial infarction, participating in short term low intensity exercise (use of treadmill in the hospital), have no changes in ROS, or NO, but show improved physical capacity, lower blood pressure [88], enhanced quality of life, and positive outcomes to morbidity and mortality [89]. However, the intensity of exercise impacts the oxidized-LDL (a stimulator of oxidative stress)-mediated status of monocytes. High intensity exercise increases oxidized-LDL-induced monocyte ROS production, facilitating monocyte-related atherogenesis. However this was depressed by mild to moderate exercise, indicating that lower intensity exercise may protect against suppression of anti-oxidative capacity of monocyte by oxidized-LDL [90]. It is clear that exercise has benefits for cardiovascular health with marked reductions in the long term-risk of CVD and mortality. Even in obese patients, or patients with several risk factors of CVD, regular exercise provides considerable CVD protection [91]. CVD patients frequently use the term 'I do not have enough time for exercise' or are they in fact afraid that exercise would do damage rather than good? In a HIT study in patients with chronic heart failure, it was shown to effectively reduce blood pressure and improve insulin resistance without any danger to the patient [92]. Understanding the risks and benefits of exercise to CVD patients and to the general population should be implemented for disease treatment and prevention.

e. Exercise and Psychological factors

Psychological factors can influence physical health, either indirectly, such as eating, sleeping and socializing changes, or directly, by changes in heart rate or hormones. A number of psychological factors influence the body leading to, stress, mental health problems, depression, anxiety, insomnia, alcohol and drug misuse or psychosis. Increasing data have demonstrated the role of physical activity and exercise in improving psychological risk factors and stress-related mortality [93]. In a national Canadian health survey of mental health and well-being (CCHS 1.2) representing 25 million people aged over 15 years, concluded that physical inactivity was a significant risk factor for common mental disorders, with 780,000 cases being attributed to physical inactivity [4].

An analysis based on 80 studies demonstrated a positive correlation between physical activity and clinical depression, regardless of gender, age or health status [94], and regular exercise by patients after termination of anti-depressants, had lower depression scores than those who were sedentary [2]. A study involving 950 males and 1,045 females (mean age 31.5 years) presenting with major depression, demonstrated that those that undertook physical activity improved in their depressive state overall. Males significantly improved in insomnia, fatigue and suicidality and females improved in hypersomnia, irrational guilt, vacillating thoughts and suicidality, compared to inactive control subjects [95]. On the whole regular physical activity participation results in enhanced psychological well-being. This includes improved mood, self-esteem and reduced anxiety, and stress [3], and subsequent prognosis. Even a single bout of walking induces beneficial psychological effects (tension, anxiety, anger, hostility, confusion) in elderly women [96]. In addition, in pregnant women, a single exercise class, improves the emotional state significantly [97], and no difference in mood outcomes were noted whether aqua exercise or studio gym exercise was used [98]. Increasing evidence indicates that there are various interactions between the nervous system and the immune system, and the important role the immune system plays in the pathogenesis of depression. Pro-inflammatory cytokines (IL-1, TNF-alpha) have been implicated in being involved in the neurobiological manifestations of depression. IL-6 is both a pro-inflammatory and an anti-inflammatory cytokine, which has inhibitory effects on the pro-inflammatory cytokines TNF-alpha and IL-1. Interestingly, physical activity changes the neuro-immune status in depression and depression-like behaviours. As such, during physical activity increases are noted for, IL-10, IL-6 (transiently), macrophage migration inhibitory factor, central nervous system-specific auto-reactive CD4+ T ells, M2 microglia, astrocytes, CX3CL1 and insulin-growth factor-1 [99], all of which may have beneficial neuro-immunological effects in the management of depression. However, detrimental decreases are noted for the Th1/Th2 balance, pro-inflammatory cytokines, CRP, M1 microglia and reactive astrocytes [99]. Furthermore, swimming exercise decreases depression-like behaviour by decreasing serum corticosterone, IFN-gamma, TNF-alpha, indoleamine-2,3-deoxygenase (IDO) and increasing 5-HT levels [100]. Thus, swimming may inhibit the activation of inflammation and IDO pathways induced by stress, resulting in improved depressive states. Further investigation is warranted on the neuro-immune effects during exercise in depression. In addition, the effects of T regulatory cells, CD4+ T cells, CD8+ T cells, CD200, chemokines, macrophages, monocytes, dendritic cells, TNF-alpha and other cytokines during exercise in patients with depression, would result in useful information in the use of exercise and its manipulation, in the treatment of depression.

An important question with regard to physical activity, immunological factors and mental health is that of causality. Prospective epidemiological evidence suggests that depression is associated with low levels of physical activity and reduced cardiorespiratory fitness. In addition, physical inactivity is a predictor of sustained depression. That is, low physical activity levels precede the response to depression whereas individuals who maintain physically active are less likely to develop depression [101]. However, the role of the immune system in this needs further research. Hence, it is unclear what the protective factors to decreased mental health are in physically active and inactive individuals.

f. Autoimmunity

The incidence of autoimmune diseases has increased 3-fold in the last few decades. This includes diseases such as, lupus, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, Sjogren’s syndrome, fibromyalgia, psoriasis and hypothyroidism. Autoimmunity is a condition where the body’s immune system destroys itself causing chronic systemic inflammation and subsequent tissue destruction. For example, in multiple sclerosis high levels of IFN-gamma, TNF-alpha and IL-17 are present, whilst, the anti-inflammatory cytokines IL-6 and IL-10 are associated with remission periods of the disease [102]. In a combined (stretch, aerobic, resistance) exercise program in multiple sclerosis patients for 8 weeks, resulted in increased muscle strength and balance, and decrease in IL-17 and IFN-gamma levels [103]. Furthermore, people presenting with an autoimmune disorder are commonly faced with issues of muscle weakness, fatigue, and painful joints. However, with a structured exercise training regime, one does not only increase physical fitness but also quality of life. Indeed, in a 12 week resistance training program, in 42 multiple sclerosis (MS) patients, improved voluntary isometric contraction and muscle power were noted in those undergoing the training program as compared to those who did not [104]. Further, improvements to physical and psychological functioning, fatigue and quality of life are noted [105, 106], in addition to, improved ambulatory function and mood status [107], in MS patients taking part in exercise activity. A 2 year blind, parallel-group, randomized controlled trial is currently being assessed in 240 multiple sclerosis patients, to determine the effects of exercise to reduce disability and to promote health [108].

In rheumatoid arthritis, excess levels (up to 100 times excess) of TNF-alpha, IL-6, IL-1beta, CRP and leukotriene B4 are known to contribute to the inflammatory state that ultimately destroys joint cartilage and synovial fluid. In addition, rheumatoid arthritis patients have an increased CVD risk factor profile, accounting for nearly 40% of their mortality, and a 2-fold increase in myocardial infarction and stroke, which may be attributed to being less physically active with poor aerobic fitness. Indeed, physically inactive rheumatoid arthritis patients have higher systolic blood pressure and elevated total cholesterol and LDL levels, as compared to physically active rheumatoid arthritis patients [109]. In addition, the chronic state of inflammation in rheumatoid arthritis patients enhances the development of atherosclerosis and may be a contributing factor for the increased CVD risk. Importantly, many patients don't participate in exercise programs, as they do not feel safe, and there are no 'specialist' programs tailored to such patients, hence, such programs should be included in studies. The benefits of exercise in autoimmune diseases and the subsequent immunological changes and their role in disease management requires further research, and a clearer understanding is necessary for the inclusion of exercise as a prescription in their treatment and management program.

g. Cancer

The cancer council Victoria, Australia, recommends up to one hour moderate or 30 minutes of vigorous physical activity daily to reduce the risk of cancer [110]. Sedentary lifestyle is responsible for at least one-third of deaths due to colon and other cancers [111]. Indeed, in a case control study with 1,130 breast cancer patients and 1,142 control subjects demonstrated a significant decreased risk of breast cancer in women with lower body mass index and those that were involved in regular physical activity [112]. Thirty to 60 minutes per day of physical activity reduces the risk of colon cancer by 30-40% in a dose response relationship, and breast cancer risk is decreased by 25-30% in physically active women compared to inactive women. It is clear that exercise may help prevent the development of certain cancers, notably colon and breast cancers, with prostate cancer having inconclusive evidence, lung cancer only having a few studies published, and there is little information on the role of exercise in preventing other cancers [113]. Interestingly, a review assessing the relationship between physical activity and risk of gastric cancer, in 1,535,006 people with 7,944 cases of gastric cancer, noted a protective association between physical activity and gastric cancer risk. The association was influenced in smokers, however the association was not influenced by alcohol, total energy intake, consumption of vegetables and fruits and infection with *Helicobacter pylori* [114].

Furthermore, exercise has also been shown to improve a number of cancer related factors in patients with cancer. Exercise improves quality of life, reduces side effects from peripheral neuropathy, improves balance control and physical performance in a study comprising 61 lymphoma patients [115]. Likewise, in breast and prostate cancer patients, daily walking or an exercise program reduces fatigue, improves symptoms and quality of life during adjuvant chemotherapy [116, 117]. In addition, engaging in physical activity reduces the risk of breast cancer recurrence [118]. The effect of exercise on immune function in patients with cancer however, is limited and additional research is required to understand the mechanism involved in exercise and immune function and its link to clinical outcome. Understanding the changes to neutrophils, natural killer cells, T cells, monocytes and cytokines during exercise in cancer patients, will result in an exercise immunotherapeutic approach for treating the disease. Indeed, the ProImmun study is the first trial investigating the effects of 6 months of endurance exercise training in prostate cancer patients, and determining the effects to immune parameters, IL-6, MIF, IGF-1, testosterone, immune cell ratios, oxidative stress, as well as VO_2 peak, fatigue and quality of life [119]. Interestingly, elderly subjects (70-77 years old) subjected to an exercise program for 12 weeks, demonstrated significant decrease in carcinoembryonic antigen, an antigen over expressed on adenocarcinoma cells, which may contribute to preventing cancer in the elderly.

h. Alzheimer's disease

Vascular disease is associated with increased risk of Alzheimer disease, and habitual aerobic exercises has been shown to improve disease outcomes [120]. Acute aerobic exercise in adults with Alzheimer disease is associated with increase brain-derived neurotrophic factor levels which may contribute to decreased cognitive impairment in Alzheimer disease [121]. Likewise, long term treadmill exercise inhibits the progression of Alzheimer disease, by reduction of beta-amyloid deposition and tau phosphorylation in the hippocampus and inhibition of GSK3 [122]. In a randomised controlled trial of 210 Alzheimer disease patients, those that were involved in an exercise program resulted in longer physical functioning without causing any adverse effects [123].

i. Conclusion

It is clear that short term and long term exercise alters the number and function of immune cells. However, the exact role of these changes and their role in susceptibility to disease and outcome, is not clear [26]. Whether the increase in immune cells is a good thing or a bad thing, is still not well understood. In addition, studies have reported that TLR-4 expression on antigen presenting cells is temporarily reduced following exercise which leaves an 'open window' for upper respiratory tract infections and post-exercise immune-suppression. Further research is required to understand the role exercise plays on immune cells and their relationship to altering disease outcomes. It is also not clear, how exercise duration, frequency and intensity might influence immune parameters. Furthermore, high-intensity interval training (HIT) has sparked interest in people who cannot exercise for long. Hence, lack of time has been one of the main reasons people do not engage in regular physical activity. Benefits of HIT have been shown in weight loss, improving athletic performance and physical fitness, and improving numerous diseases (including type-2 diabetes and cardiometabolic disorders) [124-126]. More needs to be known about the effects of immune functioning on HIT training, strength training and other exercises.

Expert Opinion and Five year view

A plethora of evidence is available indicating that low levels of physical activity, low levels of cardiorespiratory fitness and high levels of sedentary behaviors are linked with higher risk of CHD and CVD, type-2 diabetes, psychological factors, allergies, cancer, autoimmunity and metabolic syndrome. It is important however, to consider other factors that may counteract or enhance the effects of regular exercise to disease outcome. Such factors, include, the use of herbs, probiotics, supplements (vitamins and minerals), diet (high in fruits, vegetables, whole grains, anti-inflammatory foods), keeping a healthy weight, smoking, alcohol consumption, adequate sleep and radiation exposure (eg. hours of mobile phone and computer use). Understanding the changes and functionality of all immune cells at the cellular and molecular level, could lead to novel exercise-immune-based therapies for the treatment of disease progression or prevention. In the next 5-years, much research is required to understand the immunological reactions during short and long term exercise, including aerobic, strength and HIT exercise, and how this information could be used to manipulate the immune system through exercise as a novel immunotherapeutic regime to treat disease.

Key issues

- Physical activity keeps the metabolic balance, improves cardiovascular health, and influences autoimmune disease outcomes.
- Physical activity improves physiological and psychological outcomes of most patients
- Exercise aids in preventing cancer, and, improves recurrence rates and quality of life in cancer patients.
- Exercise decreases inflammation such as, CRP, TNF-alpha, L-6, IL-1beta, TLR2, TLR4, CD36, MHC-class II, although in some exercise regimes IL-6 is upregulated in the circulation and by muscle cells.

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