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Review

Physical activity and autoimmune diseases: Get moving and manage the disease

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ABSTRACT

Physical activity, by definition, is any skeletal muscle body movement that results in energy expenditure. In the last few decades, a plethora of scientific evidences have accumulated and confirmed the beneficial role of physical activity as a modifiable risk factor for a wide variety of chronic diseases including cardiovascular diseases (CVDs), diabetes mellitus and cancer, among others. Autoimmune diseases are a heterogeneous group of chronic diseases, which occur secondary to loss of self-antigen tolerance. With the advent of biological therapies, better outcomes have recently been noted in the management of autoimmune diseases. Nonetheless, recent research highlights the salient role of modifiable behaviors such as physical inactivity on various aspects of the immune system and autoimmune diseases. Physical activity leads to a significant elevation in T-regulatory cells, decreased immunoglobulin secretion and produces a shift in the Th1/Th2 balance to a decreased Th1 cell production. Moreover, physical activity has been proven to promote the release of IL-6 from muscles. IL-6 released from muscles functions as a myokine and has been shown to induce an anti-inflammatory response through IL-10 secretion and IL-1β inhibition. Physical activity has been shown to be safe in most of autoimmune diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), inflammatory bowel diseases (IBD), as well as others. Additionally, the incidence of RA, MS, IBD and psoriasis has been found to be higher in patients less engaged in physical activity. As a general trend, patients with autoimmune diseases tend to be less physically active as compared to the general population. Physically active RA patients were found to have a milder disease course, better cardiovascular disease (CVD) profile, and improved joint mobility. Physical activity decreases fatigue, enhances mood, cognitive abilities and mobility in patients with MS. In SLE patients, enhanced quality of life and better CVD profile were documented in more physically active patients. Physically active patients with type 1 diabetes mellitus have a decreased risk of autonomic neuropathy and CVD. Both fibromyalgia and systemic sclerosis patients report decreased disease severity, pain, as well as better quality of life with more physical activity. Further, SSc patients improve their grip strength, finger stretching and mouth opening with increased level of exercise. The purpose of this paper is to review the clinical evidence regarding the safety, barriers to engagement, and impact of physical activity on autoimmune diseases.

Contents

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1. Introduction

Physical activity is defined as any body movement that is produced by skeletal muscular action that leads to energy consumption. "Physical activity" is often a term used interchangeably with the term "exercise", yet there are important differences. Exercise can be defined as a planned, structured, and repetitive physical activity [1]. Physical inactivity is one of the most prevalent modifiable risk factors for acquiring disease worldwide [2]. It is the fourth leading risk factor for global mortality and is responsible for an estimated 13.4 million disability-adjusted life-years worldwide [2]. Physical activity levels have been shown to correlate with many chronic diseases including type 2 diabetes mellitus, cardiovascular disease, and metabolic syndrome [3].

An autoimmune disease develops when the immune system fails to recognize self from non-self and mounts an immunologic response damaging its own tissues [4,5]. The etiopathogenesis of autoimmune diseases is not completely understood, but complex interactions between genetic and environmental factors including lifestyle behaviors have been postulated to play a role in disease etiology [6–9]. Pharmacological therapies have been shown to be valuable in enhancing outcome and prognosis [10]. Research suggests that modifiable behaviors such as physical inactivity may be targeted to reduce the incidence as well as improve the outcome of these diseases [11,12].

Despite the widely known favorable effects of physical activity on our health, we still lack a thorough understanding of the immunologic effects and influence on autoimmune diseases. The goal of this review is (a) to summarize the impact of physical activity on the immune system, (b) to investigate the role of physical activity in reducing the incidence of autoimmune diseases (Table 1) (c) to discuss the perceived barriers against engagement in physical activity (d) to examine the impact of physical activity on the many manifestations of autoimmune diseases (Table 2).

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Table 1
Physical activity and autoimmune diseases incidence.

Reference	Design	Case no	Main finding
Di Giuseppe et al. [69]	Cohort	30,112	A statistically significant reduction of RA risk in women with highest leisure time PA. RR = 0.65, 95% CI [0.43–0.96]. The relationship remained significant after adjustment for age, smoking history, and BMI.
Dorans et al. [110].	Cohort	193,527	Women in the highest quartile for PA engagement had a 27% reduction of MS rates. RR = 0.73, 95% CI [0.55–0.98]. This relationship remained significant after adjustment for age, smoking, vitamin D, and BMI.
Khalili et al. [217]	Cohort	194,711	CD was inversely associated with physical activity (P for trend 0.02). RR = 0.64, 95% CI [0.44–0.94]. In contrast, higher PA was not significantly associated with UC. Age, smoking, BMI did not modify the significance of these studies.
Klein et al. [220]	Case-control	88 IBD patients (55 UC, 33 CD). 109 healthy controls.	IBD patients showed a significant reduction of PA engagement in the pre-illness period ($p < 0.001$).
Persson et al. [219]	Case-control	297 IBD. (152 CD, 145 UC). 305 healthy controls.	Weekly PA reduced the risk of IBD, RR = 0.6, 95% CI: [0.4–0.9], daily exercises showed an inverse relationship with disease risk RR = 0.5, 95% CI [0.3–0.9].
Frankel et al. [269]	Cohort	86,665	After adjustment for age, smoking, alcohol use, and BMI, increased PA is significantly and inversely associated with psoriasis, RR = 0.72, 95% CI [0.59–0.89].

Note: PA-physical activity; RA-rheumatoid arthritis; RR-relative risk; CI-confidence interval; BMI: body mass index; CD: Crohn's disease; UC: ulcerative colitis; IBD: inflammatory bowel disease.

2. Influence of physical activity on the immune system

In the past, research on physical activity primarily focused on various health determinants such as the all-cause mortality risk. Eventually, due to the growing evidence that physical activity is beneficial in such a diverse list of diseases, researcher explored its effect on immunomodulation (Fig. 1).

2.1. Physical activity effect on the adaptive immune system

The impact of physical activity on the immune system is multifaceted. During exercise, lymphocyte concentration tends to increase, with a consequent reduction down to below pre-exercise levels after strenuous physical activity [13]. The decrease in lymphocyte concentration following a period of exercise has been partially attributed to an increase in apoptosis [14]. The biological mechanism for this increase in apoptosis was shown to occur due to a decrease in the levels of glutathione concentrations in the lymphocytes, increased DNA fragmentation and increased caspase contents. Taken together, these factors induce a state of high oxidative stress.

T-cells are an integral part of adaptive immune system. The two major groups of T-cells are CD4 T-cells and CD8 T-cells. CD4 T-cells can further be divided into Th1 and Th2 cells respectively. Th1 cells produce interferon (IFN-γ) and interleukin (IL)-2, whereas Th2 cells secrete IL-4, IL-5, IL-6, and IL-10 [15].

Steensberg et al. [16] demonstrated that prolonged exercise leads to a significant decrease in Th1 cells, but not in Th2 cells [16]. This selectivity was attributed to the increase in hormonal levels, most notably cortisol, in response to exercise. Cortisol has been postulated to induce inhibition of the production of IL-12 from antigen presenting cells (APC), a well-known stimulator of Th1 cells [17]. Concomitantly, epinephrine, which is also elevated during exercise, works on Th1 cell suppression *via* two distinct mechanisms including APC inhibition and direct T-cell receptor blockage [18].

Strenuous exercise has been shown to potentially have an adverse effect on host immunity. Human and animal studies suggest that physical activity induces a shift in the Th1/Th2 balance to a Th2 cell predominance [19,20]. It has been theorized that this is due to the up-regulation of Th2 cell related genes. Moreover, evidence points towards the up-regulation of CD28 and CD86. CD28 is essential in the interaction with two ligands on APCs, namely CD80 and CD86. Binding of CD28 to CD80 preferentiality enhances Th1 activation while CD28 binding to CD86 increases Th2 cell population activation [21]. The Th1/Th2 ratio influences individual susceptibility to infections, allergy and autoimmunity. Th1 cells have been long implicated in the genesis of multiple autoimmune diseases including rheumatoid arthritis, multiple sclerosis and Hashimoto thyroiditis while Th2 cells have also been found in specific autoimmune diseases including systemic lupus erythematosus (SLE) [22]. Further research is needed to explain how these alterations in Th1 and Th2 cells could influence the course and progression of autoimmune diseases.

Regulatory T-cells (T-reg cells) are a subset of T helper cells that express both CD4 and CD25. FoxP3 is a key transcription factor that drives the maturation of T-reg cells [23]. Wilson et al. [24], investigated how a high intensity swimming exercise influences T-reg cells and proved that acute exercise was shown to cause a significant elevation in T-reg cells. The mechanism and the pathway involved in this process remain to be elucidated [25].. Weinhold et al. [26], also demonstrated, in addition to exercise-induced increase of T-reg cells, higher levels of TGF-β, which is a known anti-inflammatory cytokine that contributes to the immunosuppressive effects of T-reg cells.

Lymphocyte is known to have specific immunogenic specificity and the process of maturation is complex. In human studies, exercise curbed the proliferation process of T-cells post introduction of polyclonal mitogens for the purpose of lymphocyte induction [27]. Similar results were demonstrated in animal models [18].

In response to exercise, B-cells were not shown to be affected, however, suppression of immunoglobulin secretion has been reported in several studies [28,29]. The mechanism for immunoglobulin secretion inhibition is still not understood, yet it has been hypothesized that IL-2 released from the expanded population of monocytes during exercise sensitizes B-cells and renders them susceptible to inhibition by prostaglandins. This claim is supported by the reversal of this inhibition and elevated immunoglobulin release after exposure of IL-2 stimulated B cell cultures to indomethacin [30].

2.2. Physical activity effect on the innate immune system

Natural Killer (NK) cells are effector lymphocytes of the innate immune system with natural cyto-toxicity to viruses and tumor cells independent of Major histocompatibility complex (MHC) presentation. There are two main groups of NK cells: $CD56^{dim}CD16^{+}$ and $CD56^{bright}CD16^{-}$ [31]. The former group is active in the peripheral circulation and generally acts with cell-mediated cytotoxic activity *via* perforins, while the latter releases cytokines such as TNF-α, IFN-γ, and IL-10 to help mounting an immune response [31].

With respect to exercise, NK cells seem to have a certain sensitivity to the exercise-induced stress with the effect varying based on time spent and intensity of training. For example, research has shown that during and shortly afterwards brief intense exercise NK cells cytotoxic activity (NKCA) and NK cells levels increase [32]. In repetitive chronic exercise, only the regulatory $CD56^{bright}$CD16-cells activity increases, while in moderate exercise overall NK cell activity increases. Lastly, very intense exercise has been shown to suppress NK cells activity even after the exercise completion. It has been postulated that this reduced NK activity is caused by the prostaglandin E2 released from

Table 2
Selected study on the role of physical activity and exercise on autoimmune disease aspects.

Reference	Design	Case no	Main finding	Intervention
Rheumatoid arthritis (RA)				
Sandberg et al. [76]	Cross sectional	617	Higher level of PA before disease diagnosis decreased the likelihood of having a severe disease as measured by DAS-28 (above the median) OR = 0.58, 95% CI [0.42–0.81]. Significant even after adjustment to smoke, BMI, sex, and period of diagnosis.	Leisure time physical activity 5 years before the diagnosis was assessed by questionnaire.
Metsios GS et al. [80]	Cross sectional	65	PA in RA pts. Led to a significantly CVD risk profile as compared to inactive RA patients. Active RA patients had significantly lower systolic blood pressure, cholesterol levels, low density lipoprotein, homocysteine, Apo lipoprotein B, von Willebrand Factor, and Type-I plasminogen activator inhibitor antigen.	International Physical Activity Questionnaire, patients were used to divide patients to active, moderately active and inactive.
Metsios GS et al. [81]	Case-control	20 cases, 20 controls.	EG showed a significant increased aerobic capacity, and improvement of DAS-28 score. ($p < 0.001$, $p = 0.008$, respectively). PA led to significant improvement of microvascular function as reflected by acetylcholine and sodium nitroprusside mediated vasodilation ($p = 0.016$, $p = 0.045$ respectively)	A 6 months individualized resistance and aerobic exercise intervention.
Lemmey et al. [87]	RCT	28	PRT increased LBM and improved muscle strength including chair stands by 30%, knee extensor strength by 25%, and arm curls by 23%, p values ranged from 0.001–0.027. Following RPT, previously inhibited IGF-1 increased. ($p < 0.05$)	24 weeks of twice-weekly persistent resistance program.
van den Ende et al. [100]	Cross sectional	64	Physical functioning was significantly improved in RA patients involved in PA. RA pts undergoing physical activity had significantly better dynamic muscle, decreased pain, and disease activity.	The exercise program included knee and shoulder dynamic and isometric muscle strengthening exercises against resistance five times a week and conditioning bicycle training three times a week for 1 month.
Multiple sclerosis (MS)				
Pilutti et al. [130]	Meta-analysis (17 RCT)	568	Exercise training is associated with a significant reduction of fatigue in MS pts. Weighted mean ES was 0.45, 95% CI [0.22–0.68], $p \leq 0.001$.	Different interventions: including aerobic, endurance and resistance exercise regimens. 3–26 weeks, 30–60 min, on average 3 time per week.
Ensari et al. [137]	Meta-analysis	477	Exercise was associated with a significant decrease of depression in MS pts. Mean ES = 0.36, 95% Ci [0.18–0.54], $p < 0.001$.	Different interventions: including aerobic, endurance forms for 4–26 weeks, 3 times per week for a 30–70 min per session.
Beier et al. [141]	Post-hoc correlational study	88	Executive function and cognitive functioning showed a significant improvement after engagement in physical activity, this results remained significant after age, sex, MS type and disease activity adjustment.	MS pts. chose a health promotion activity (exercise in the present analysis) for a 12 week duration.
Briken et al. [144]	RCT	42	Aerobic exercise led to improved capacity, walking ability, depressive symptoms, fatigue, and cognitive function.	MS pts. were randomized to one of three exercise interventions (arm ergometry, rowing, bicycle ergometry) for 8–10 weeks.
Dalgan et al. [149]	RCT	38	Improvement of functional capacity and isometric lower extremity muscle strength was noted in the EG that underwent PRT ($p < 0.05$ for both).	EG underwent biweekly 12-week lower extremity PRT program.
Snook et al. [153]	Meta-analysis	600	Exercise training in MS pts. led to improvement of walking mobility with a mean ES of 0.19, 95% CI [0.09–0.28].	Different exercise programs including aerobic; non aerobic; resistance; and a combination of aerobic and resistance programs
Tarakci et al. [155]	RCT	99	Exercise training is proven to be safe in MS pts. Berg Balance Scale showed a significant improvement in MS pts ($p < 0.001$). Additionally, spasticity, fatigue and Qol was significantly improved in the EG.	EG underwent flexibility, range of motion, strengthening exercises for lower extremity, core stabilization, balance and coordination exercises and functional activities. The program consisted of 60-minute sessions thrice weekly for 12 weeks.
Systemic lupus erythematosus (SLE)				
Wu et al. [166]	Meta-analysis	164	Aerobic exercise decreases fatigue in SLE patients (MD = −0.52, 95% CI [−0.91, −0.13], $p = 0.009$) and increase vitality (MD = 14.98, 95% CI [7.45, 22.52], $p < 0.001$).	Aerobic exercise three times a week was employed. Two studies lasted for 8 weeks and one study lasted for 12 weeks.
Avaux et al. [169]	RCT	45	Endurance exercise led to statistically significant improvement of fatigue.	Endurance exercise (walking or bicycle) and strengthening exercises (with elastic band or weights for both upper and lower limbs) 3 h per week during 12 weeks.
Miossi et al. [278]	RCT	24	Exercise training was shown to be safe in SLE patients and led to a reduction of chronotropic incompetence and improved the heart rate recovery ($p < 0.05$).	12 weeks of exercise training performed twice a week. Training included a 35–40 min of resistance training, followed by a 30 min of treadmill aerobic training.
Dos Reis-Neto et al. [185]	RCT	38	Physical exercise was shown to be safe in SLE patients, and was proven to improve both aerobic capacity ($p = 0.027$), and endothelial function ($p = 0.006$).	One-hour walking session three times per week for 16 weeks
Type 1 diabetes mellitus (T1DM)				
Kennedy et al. [204]	Meta-analysis	452	HbA1c reduction post exercise was not shown to be statistically significant. Reasons for this finding could include increased calorie intake, insulin dose reductions around the time of exercise.	High intensity aerobic and resistance exercise including endurance exercises, 6–20 weeks, 30–240 min weekly.

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Table 2 (*continued*)

Reference	Design	Case no	Main finding	Intervention
Tonoli et al. [205]	Meta-analysis	185	Aerobic exercise, resistance exercise, mixed exercise (aerobic combined with resistance training) acutely decreased blood glucose levels. Aerobic exercise led to a decrease of HbA1c, whereas resistance and mixed training did not show similar studies.	Various exercise forms were employed, most studied lasted from 6 to 20 weeks, with 2–3 sessions per week, 30–60 min per session.
Seeger et al. [212]	Cohort	9	Aerobic capacity and physical fitness improved after physical training, $p = 0.039$. Endothelial function measured by brachial artery flow mediated dilation was also improved ($p = 0.038$).	18 weeks running exercise training at a frequency of two times a week, for 60 min (30 minutes' interval running, and 30 minutes' group activity).
Wadén et al. [209]	Cross sectional	1945	Low intensity leisure time PA was associated with diabetic nephropathy (OR = 1.90, 95% CI [1.39–2.60]), proliferative retinopathy (OR = 1.49, 95% CI [1.15–1.93]), and CVD (OR = 2.58, 95% CI [1.79–3.74])	Self-reported leisure-time PA by a questionnaire
Fibromyalgia				
Bidonde et al. [243]	Meta-analysis	839	Aerobic exercise has been proven to moderately enhance Qol, decrease pain intensity, fatigue and stiffness	Various aerobic exercises. The frequency of exercises employed varied but generally lasted 25 min per session, twice or thrice weekly, over a duration of six to 24 weeks
Bidonde et al. [244]	Meta-analysis	881	Aquatic exercises were shown to significantly improve physical function, pain stiffness, lower extremity muscular strength and cardiovascular submaximal function. Aquatic exercises were not shown to be more effective than land based exercises. Improvement of strength favored land based exercises.	Aquatic exercise was defined as exercise conducted in vertical position while submerged to the waist, chest or the shoulder in vertical position. No restriction on the type of aquatic exercise equipment including flutter boards, tubing, dumbbells was done.
Busch et al. [245]	Meta-analysis	219	Resistance training is shown to significantly improve pain, tenderness, muscle strength and multi-dimensional function in fibromyalgia. Aerobic exercise was not shown to be superior than resistance training. Nevertheless, pain alleviation favored resistance training.	8–21 weeks of moderate- to high-intensity resistance training using free weights or body weights.
Inflammatory bowel disease (IBD)				
Hoffman-Goetz et al. [227]	Experimental	96 colitis model mice (C57BL/6) (48 cases, 48 controls)	EG mice had lower TNF-α and caspase 7, and higher IL-10 and IL-6 in intestinal lymphocytes. Exercise has been shown to foster an anti-inflammatory process.	16 weeks of freewheel running
Cook et al. [225]	Experimental	C57Bl/6J mice including 132 undergoing FTR and 26 undergoing VWR. 20 healthy control mice.	VWR significantly decreased colitis symptoms and decreased inflammatory gene expression ($p < 0.05$). FTR led to a significant exacerbation of diarrhea and IL-6, IL-1β, IL-17 colon gene expression. The reason for which is to be elucidated.	VWR involved 30 days' access to wheels. FTR involved 8–12 m/min, 40 min, 6 weeks, 5 times per week.
Sjögren syndrome (SS)				
Strombeck et al. [277]	Case-control	11 cases, 10 controls	Aerobic capacity, fatigue, and depression was significantly improved in the EG *vs.* the CG ($p = 0.03$, 0.03, 0.02, respectively). No differences in anxiety or Qol.	Nordic walking for 45 min three times a week for 12 weeks.
Systemic sclerosis (SSc)				
Schouffoer et al. [266]	Prospective cohort	53	At the end of intervention EG had significant improvement of grip strength $p = 0.001$, and HAQ score $p = 0.025$.	12-week, once weekly individual treatments, group exercises, and group education
Antonioli et al. [264]	Cohort	33	EG had a statistically significant improvement of hand mobility, additionally they had improvement in QoL.	30 minute daily sessions for 2 weeks. Each session consisted of motor functions training, and respiratory exercises (diaphragmatic breathing and controlled coughing). Motor exercise training consisted of treadmill and free-walking, as well as upper limbs finger-stretching exercises and occupational therapy.
Oliveira et al. [263]	Case-control	7 SSc patients with pulmonary impairment, 7 healthy controls	Exercise led to increased aerobic capacity and exercise tolerance The improvement between baseline and post-intervention assessment was statistically significant $p = 0.006$. Difference between the two was not statistically significant ($p = 0.149$), These results highlight the efficacy and safety of exercise in SSc.	8-week program consisting of moderate intensity aerobic exercise.

Note: PA-physical activity; DAS-28-disease activity score-28; OR-odds ratio; CI-confidence interval; CVD-cardiovascular disease; RA-rheumatoid arthritis; RR-relative risk; EG-exercise group; PRT-persistent resistance training; IGF-insulin growth factor; RCT-randomized controlled trials; QE: quasi-experimental; MS-multiple sclerosis; ES-effect size; Qol-quality of life; MD-mean difference; EG-exercise group; CG-control group; SLE-systemic lupus erythematosus; VWR-voluntary wheel running; FTR-forced treadmill; SS-Sjogren disease. SSc-systemic sclerosis; HAQ-health assessment questionnaire; pts-patients.

monocytes, which has global suppressive effect on the immune system [32]. Besides, following periods of exercise induced-differential mobilization of lymphocytes, higher ratios of $CD56^{bright}CD16^{-}$: $CD56^{dim}CD16^{+}$ are noted. $CD56^{bright}CD16^{-}$ are known to have an immunoregulatory role especially in autoimmune diseases [33]. Suzui et al. [34], showed that heavy exercise training leads to a decrease in NKCA and lytic units per NK cell. Other studies, on the contrary, did not show any correlation between exercise and NKCA. These contradictory results have been attributed to the variability in the exercise regimens employed, and therefore more standardized research is needed to better delineate this relationship.

Neutrophils are the most abundant white blood cell in the body and an essential component of the innate immune system. They are the first cell type recruited to a site of inflammation and are a hallmark of acute inflammation [35]. Neutrophils have a large arsenal of capabilities to carry out their function to defend its host, including phagocytosis,

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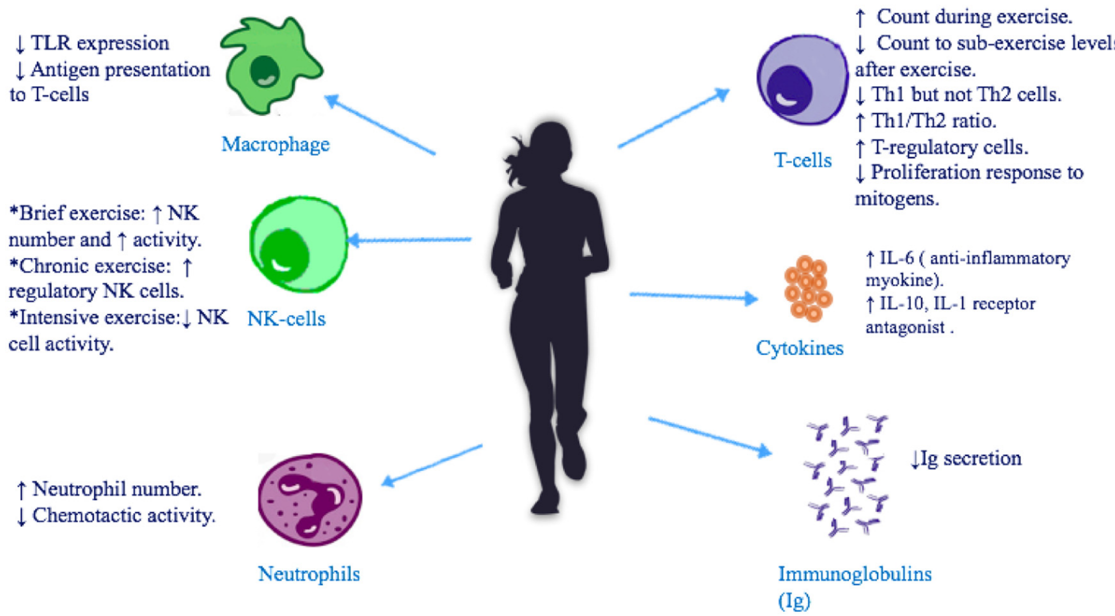

Fig. 1. The impact of physical activity on the immune system.

degranulation and reactive oxidative burst [35]. Exercise increases the number of circulating neutrophils due to the surge in catecholamine and cortisol produced during exercise which secondarily causes neutrophils to emarginated from blood vessels and the bone marrow [36]. Wolach et al. [37], demonstrated a decrease in the chemotactic activity of neutrophils 24 h after aerobic exercise with no influence on their bactericidal activity or their superoxide anion release. In other reports, exercise severity has been shown to influence neutrophil function; moderate exercise was shown to increase the process of chemotaxis, phagocytosis and oxidative burst, whereas extreme, strenuous exercise was shown to reduce phagocytosis and oxidative burst, yet chemotaxis and degranulation remained unaffected [38,39].

Macrophages are a major component of the mononuclear phagocyte systems and play an integral role in antigen presentation and therefore in adaptive immune system activation. Macrophages play an important role in the initiation, maintenance and resolution of inflammation [40]. Aerobic exercise leads to attenuation of TLR expression in macrophages and thus compromises the presentation of antigens to T lymphocytes, especially Th1 cells [41]. Other reports revealed that aerobic exercise results in an increase in the microbicide capacity of macrophages and therefore increases the pro-inflammatory cytokine profile released including for example IFN-γ and TNF-α [42].

2.3. Physical activity and cytokine levels

Research suggests that, due to physical activity, IL-6, a pro-inflammatory cytokine and anti-inflammatory myokine, increases to as much as 100-fold in blood sera when compared to baseline [43–45]. Acting as a pro-inflammatory cytokine, IL-6 promotes the proliferation and activation of T-cells and the differentiation of B-cells into antibody-producing plasma cells. Following physical activity, IL-6 mRNA transcription activity in skeletal muscle has been shown to surge [46]. It is important to note that this elevation occurs without signs of muscle damage and is not preceded by TNF-α production as commonly occurs in inflammatory conditions [47]. Acting as a myokine, IL-6 induces the consequent release of IL-1 receptor antagonist (IL-1RA), and IL-10. IL-1RA is a natural inhibitor of IL-1β, which is a pro-inflammatory cytokine that has an integral role in multiple immune diseases including rheumatoid arthritis [48]. IL-10 is a known potent anti-inflammatory immunomodulator, which can result in T-cell inhibition and inflammation attenuation [49].

2.4. Physical activity and hormonal levels

Exercise stimulates the release of both epinephrine and norepinephrine from both the adrenal medulla and sympathetic nerve terminals, respectively. The plasma concentrations of these catechol amines increase linearly with the duration of exercise and exponentially with disease intensity [50]. β adrenoceptors are expressed on various cells of the adaptive immune cells including T-cells and B-cells [51]. When activated, β receptors initiate and potentiate an intracellular cascade that results in cyclic adenosine monophosphate (c-AMP) production and subsequently adenyl cyclase activation [52]. This signal transduction through the c-AMP pathway triggers IL-10 production from T-cells [53]. While these results have been proved by means of *in vitro* studies, there is a dearth of studies in the literature replicating these effects *in vivo* and in human subjects.

Plasma concentration levels of cortisol have been shown to vary in relation to exercise duration. Long-term exercise was associated with increased cortisol levels, whereas short term exercise did not influence cortisol levels [54]. Corticosteroid levels can cause lymphocytopenia secondary to its exercise-associated induction of apoptosis, which reaches its maximal levels 4 h after its release [55].

Exercise and physical stress have also been shown to cause a 3–10-fold elevation in the levels of endorphins [56]. β-Endorphin was shown to inhibit T-cell and B-cell activity resulting in a decrease of antibody secretion. In contrast, when β-endorphins were incubated with NK cells, β-endorphins increased their activity [57–59].

Finally, sex steroid levels where shown to be positively associated with exercise. Testosterone for example was shown to influence both cellular and humoral arms of the adaptive immune system. Testosterone causes a reduction in IL-4, IL-5, IFN-γ, Ig-M and Ig-G antibodies [60,61].

When the body is challenged as in physical stress, this neuroendocrine pathway has been shown to be important in driving many of the aforementioned effects. The results in adaptive immune system are stereotyped, however, research examining the effect of physical activity on the innate immune system is conflicting. Furthermore, most of the research studies assessed the effect of acute exercise on the immune system. More studies are needed to clarify the relationship between other forms of exercise on the immune system.

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3. Physical activity and rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory joint disease that ultimately leads to pain, swelling and stiffness of the joints [62]. RA commonly affects small joints, including the joints of the hands and the feet. Less commonly affected are the larger joints, including the knee, elbow and shoulder. Over time this joint damage results in joint deformities and limited mobility [63,64]. RA manifestations are not exclusive to the joints. In some people the heart, lungs, or eyes are affected. The progression of RA is variable [65,66]. Although the advent of biologic therapy has improved patients prognosis substantially, patient management remains a multidisciplinary approach with lifestyle modifications playing a major role [67,68].

3.1. Physical activity and RA risk of occurrence

Growing evidence supports the notion that physical activity curbs inflammation. Di Giuseppe et al. [69], conducted a prospective cohort study on 30,112 women aged between 54 and 89 years and collected data on the physical activity habits of the participants including leisure time activities such as walking, cycling and other forms of exercise including for instance aerobic, endurance or resistance exercise. Their results showed a statistically significant inverse association between leisure time physical activity and RA (relative risk (RR) 0.65, 95% CI [0.43–0.96]). In addition, physical activity that involved only household work and walking and standing at work was correlated with a decreased risk of RA, albeit non-statistically significant. The main conclusion of this prospective cohort study was that women who incorporated leisure-time activities in their lifestyle had a reduced risk of developing RA. This finding was more pronounced in women who cycled or walked >20 min per day and exercised more than 1 h per week [69].

3.2. Perceived barriers to engagement in physical activity

There is ample evidence in the literature highlighting the positive role that physical activity has on various aspects of RA including improvement in functional capacity as well as amelioration of psychological status [70–72]. Unfortunately, recent research showed that physical activity levels among patients with RA are lower in comparison to healthy control subjects. One study found that as much as 71% of RA patients do not participate in regular physical activity [73,74]. These finding indicate that certain barriers reduce the engagement of RA patients in physical activity. Van Zanten et al. [75] performed an extensive review of 26 qualitative and quantitative articles that dealt with perceived barriers to physical activity in RA patients. The most frequently identified barriers to engaging in physical activity were pain level and fatigue. Moreover, reduced mobility, stiffness, and deformity were additional arthritis-related barriers that were reported, but to a lesser extent. Other non-physical barriers were also noted and included for instance lack of knowledge about appropriate exercise activities that do not cause further damage to the joints [75].

3.3. Impact of physical activity on disease activity

Sandberg et al. [76] investigated the association between RA and disease activity and showed that RA patients that were physically active during the 5 year period before their formal diagnosis developed a milder disease. Physical activity significantly reduced the odds of having a disease activity score (DAS)-28 above the median (OR = 0.58, 95% CI [0.42–0.81]). A similar effect was seen using the Visual Analog Scale for Pain (VAS-Pain) (OR = 0.62, 95% CI [0.45–0.86]).

3.4. Impact of physical activity on cardiovascular risk

Patients with RA have a 1.5–2.0-fold increased risk of developing coronary artery disease when compared with general population. Cardiovascular disease (CVD) is considered a leading cause of mortality in patients with RA [77,78]. The increased susceptibility has been postulated to result from the continuous inflammatory process [77]. Endothelial dysfunction is one of the earliest signs of CVD and remains a superior early marker of atherosclerosis [79].

In a cross-sectional study, patients were subsequently divided into active, moderately active and inactive groups using the International Physical Activity Questionnaire. Among the investigated groups, inactive RA patients had a significantly worse CVD risk profile when compared to active RA patients. Active RA patients had significantly lower systolic blood pressure, cholesterol levels, low density lipoprotein, homocysteine, Apolipoprotein B, von Willebrand Factor, and Type-I plasminogen activator inhibitor antigen. The results remained significant even after adjusting for age, sex, smoking status as well as RA disease severity and activity [80].

Metsios et al. [81], investigated the influence of both aerobic and resistance exercise on microvascular and macrovascular function in RA patients. Forty RA patients, matched according to age, gender and BMI, were divided into an experimental and control group. The experimental group received six months of individualized training programs. Cardiovascular parameters, endothelial function and disease activity were monitored. In the experimental group, a significant increase in maximal oxygen consumption, a valid proxy of aerobic capacity, was documented ($p < 0.001$). Additionally, significant improvement in the patients' DAS-28 score was observed ($p = 0.008$). Finally, engagement in exercise led to significant improvement in microvascular function, as reflected by an increase in acetylcholine and sodium nitroprusside mediated vasodilation ($p = 0.016$, $p = 0.045$). This study highlights the beneficial physiological adaptations of exercise in patients with RA that results in improved cardiovascular outcomes [81].

Exercise has been shown to exert its beneficial effect on endothelial cellular function through three major mechanisms; reversal in endothelial dysfunction, anti-atherogenic effects and anti-inflammatory effects [82]. Exercise has been shown to increase the blood flow to muscles, and induce vasodilation *via* nitric oxide [83]. Moreover, shear stress due to increased blood flow increases the expression of prostaglandin I2 (PGI2), a vasodilator and inhibitor of platelet aggregation [84,85]. Exercise is proven to reduce adipose tissue, which has a role in pro-inflammatory cytokine release [86].

Despite the clinical relevance of this association between cardiovascular risk and RA, there is a dearth of studies that investigated the role of exercise intervention in relation to CVD in RA. Based on the modest results available, physical activity should be advised in RA patients due to its anti-inflammatory and anti-atherogenic effects.

3.5. The impact of physical activity on rheumatoid cachexia

Rheumatoid cachexia affects two thirds of RA patients and is defined as a predominant loss of skeletal muscle [87]. In contrast with other conditions associated with cachexia such as cancer and AIDS, patients with rheumatoid cachexia maintain a stable bodyweight due to a replacement of muscle mass with adipose tissue [88]. The biological mechanism of rheumatoid cachexia remains unclear, but a complex interplay of various factors including pro-inflammatory cytokines, low physical activity, and steroid use are believed to play a role [89,90].

Lemmey et al. [87], investigated the effect that long-term high intensity progressive resistance training (PRT) has on muscle growth in patients with RA. RA subjects were divided into a control and experimental group. The experimental group (N = 13) completed biweekly high intensity progressive resistance training (PRT) for 24 weeks, while the matched control group engaged in range of movement home exercises. PRT was shown to significantly increase lean

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body mass and reduce fat mass. The PRT group had significantly improved training strength, chair standing, knee extensor strength, arm curls and walk time when compared to control. Serum analysis showed a significant elevation in previously inhibited IGF-1 and IGF binding protein 3 in patients in the PRT group suggesting that IGF-1 and IGF binding protein 3 may be involved in rheumatoid cachexia [87]. IGF is known to regulate skeletal muscle mass maintenance and hypertrophic adaptation when stressed [91]. Progressive resistance training was consistently shown to be effective in stimulating muscle growth in patients with RA as compared to controls [92,93].

3.6. The impact of physical activity on bone mineral density

Several factors may contribute to the decreased bone mineral density seen in RA patients, including sedentary lifestyle, systematic inflammatory process characterizing the disease, and the use of high dose steroids [94]. The effect of high intensity weight bearing exercises on RA patients' disease course is complex. Two studies incorporated high intensity weight bearing exercises intended to strengthen subjects' quadriceps, biceps brachial and abdominal muscles. When compared to controls, no significant changes in bone mass density in the femoral neck or spine was noted in the RA group [95,96]. In a randomized control study, de Jong et al. [79], found that two years of high intensity weight bearing exercises led to decreased levels of radiologic joint damage as assessed by Larsen score in the feet and the hands as compared to usual care physical therapy group. The damage noted on radiographs was independently associated with disease activity, frequency of glucocorticoid use, and aerobic fitness [97]. These results substantiate the protective effect of weight bearing exercises on small joints as compared to larger joints, the reason for which remains unknown.

3.7. The impact of physical activity on joint mobility

RA is characterized by joint damage, stiffness and deformity. Due to the nature of RA it was initially believed that exercise could possibly cause an exacerbation of joint damage, and thus RA patients were advised to refrain from engaging in physical activity [98]. A considerable amount of contradictory evidence to the once believed assumption was accumulated in recent years highlighting the benefit of exercise in inhibiting the progression of RA and in increasing a patient's functional ability [99]. The underlying mechanism is believed to occur through enhanced muscle coordination and muscle hypertrophy. Van den Ende et al. [100], investigated the influence that an intensive exercise regimen has on physical function in RA patients. During the observation period, joint motility, strength and functional ability was significantly improved in all RA patients that performed exercise program consisting of range of motion, isometric, and isokinetic exercises involving the various feet, hand, and knee joints.

3.8. The impact of physical activity on fatigue

Another common, debilitating symptom of RA is fatigue, which is experienced in close to 40% of patients [101]. Fatigue, a highly subjective construct, is known to influence quality of life measures in patients with chronic illnesses. Currently, randomized controlled studies on the influence of exercise on fatigue symptoms are lacking. However, two quasi-experimental reports showed that RA patients who engage in low intensity aerobic exercise or PRT had significantly decreased self-reported fatigue [102–104]. Additionally, a cross-sectional study found in RA patients who are moderately to severely physical inactive a negative association between fatigue and physical activity levels [105].

In conclusion, physical activity and engagement in various forms of exercise has been shown to improve various aspects of RA. Therefore, physicians should encourage patients to engage in physical activity.

4. Physical activity and multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system [106]. Immune cells attack the myelin that surround the axons and ultimately interfere with the salutatory movements of nerve signals resulting in conduction problems [107,108]. The course and severity of MS is highly variable. Based on progression and disease course, MS is divided into different forms including relapsing remitting, primary progressive, secondary progressive, and progressive relapsing MS. MS can present with mobility problems, spasticity, ataxia, visual impairment, fatigue as well as other manifestations [106]. These symptoms affect the quality of life, and therefore multimodality management approaches should be employed including lifestyle modifications to maintain central nervous system reserve function [109].

4.1. Physical activity and MS risk of occurrence

Most of the research presented in the literature investigated the influence of physical activity on the disease course. Nevertheless, few studies shed light on the association between physical activity and the incidence of MS. Dorans et al. [110], studied the association between MS and physical activity in two prospective cohort studies, termed the Nurses' Health Study. Of the subjects who developed MS after the baseline physical activity assessment, there was significantly higher proportion of MS cases in the group of women reporting lower physical activity (RR = 0.73, 95% CI [0.55–0.98], $p = 0.08$).

It has been suggested that exercise reduces MS occurrence by increasing the release of neuroprotective molecules including for example IGF-1, as well as other molecules which are important in maintaining neuroplasticity [111]. Not all studies on the topic have supported these finding. Two case control studies found physical activity unrelated to the MS risk of occurrence. However, these studies were plagued with biases including recall, selection, and exposure measurement error [112,113].

4.2. Perceived barriers to engagement in physical activity

In a large meta-analysis, researchers found that MS patients tended to engage in less physical activity compared to healthy people. Additionally, physical activity in patients with primary progressive MS (PPMS) was shown to be significantly lower than in relapsing remitting MS (RRMS) [114]. A possible explanation for this event is the more advanced progressive course of the disease, and therefore the higher likelihood for disability [114].

In addition to the common deterrents to engage in exercise, MS patients have many disease-specific perceived barriers. One such limitation they possess is impaired mobility, occurring in roughly 90% of patients [115]. This limitation necessitates MS patients to use assistive devices such as canes or wheelchairs, both of which can limit the exercises in which patients could participate [116]. Fatigue is another frequently reported symptom, especially early in the disease course. Fatigue influences many domains of MS patients' life including work and social life and likelihood to engage in physical activity [117]. The most severe symptom reported by MS patients is pain, seen in >50% of patients. Pain, as a solitary symptom or when combined with other symptoms such as fatigue, limits engagement in physical activity [118,119]. Another unique symptom in patients with MS is heat sensitivity [120]. Patients suffering from heat sensitivity suffer worse symptoms when either their temperature or the temperature of the environment is elevated [120]. Although the mechanism is poorly understood, it has been postulated that an elevation in temperature impairs conduction along demyelinated nerves and therefore results in an aggravation of MS patients' symptoms [121].

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4.3. Impact of exercise interventions in MS mouse models

The impact of physical exercise on multiple sclerosis has been extensively studied in animal studies. In MS mouse models, the pathogenesis of MS may involve the auto-activation of T-cells resulting in Th1 and Th17 cell selective differentiation and proliferation [122]. Once activated, these cells cross the blood brain barrier (BBB) and induce inflammation [122]. The BBB is maintained by intricate coordination of endothelial cells, astrocytes as well as other cells. If damaged, central nervous system pathologies may develop, including MS [123].

In mouse models, researchers discovered that exercise reduces oxidative stress, a potential cause of endothelial injury, ultimately leading to tight junction dysfunction and loss of the BBB integrity [124,125]. Moreover, post-exercise levels of pro-inflammatory cytokines released by Th1 and Th17 such as IFN-γ, IL-17, and IL-1β were significantly decreased in the spinal cord of mice models. Exercise was also shown to increase T-reg cells causing an increase of IL-10 release [126]. This altered cytokine profile is associated with a decreased expression of adhesion molecules, as well as increased expression of tight junctions such as occludins which decreases BBB permeability and inflammatory immune cells diapedesis [127].

Exercise was shown to be protective against memory loss which has been generally attributed to hippocampal demyelination. In MS mouse models, experimental autoimmune encephalomyelitis (EAE) mice that were treadmill exercised, five times weekly for a month demonstrated better performance on step-down avoidance tasks which are employed to assess memory ability [128]. Furthermore, a decline in demyelination with a concomitant increase in brain derived neurotropic factors was noted in the exercise group [128]. Brain neurotropic factors play a pivotal role in neuronal cell proliferation and survival. Additionally, the levels of apoptosis in the hippocampus of the exercised mice were shown to be decreased. This was reflected by the decrease in the apoptotic signal (bax) and increase of anti-apoptotic proteins (bcl-2) the exercised EAE group as compared to the EAE group [128].

4.4. Impact of physical activity on fatigue

Fatigue remains a common symptom in MS patients that can debilitate and limit their daily activities. Fatigue has been associated with higher disability scores including depression, cognitive impairment and pain [129]. The influence of exercise on fatigue was assessed in a large meta-analysis that included 17 randomized control trials (RCT) [130]. The effect size (ES) of the individual studies was measured as the difference between exercise groups to control groups divided by the pool of baseline standard deviation. A positive result reflects improvement of fatigue scores after exercise. The weighted mean ES was 0.45 (95% CI [0.22–0.68], $p < 0.001$). The meta-analysis found that engagement in exercise training led to a moderate reduction in fatigue levels (correlation coefficient $r = 0.22$). The estimated reduction in the mean fatigue severity scale (FSS) was calculated to be 0.9 and the average FFS score of RCT included was close to 4.9, generally a reduction of 0.7 signifies a notable difference in fatigue assessed [7]. Therefore, summed evidence highlights the influence of exercise in reducing fatigue in MS patients [130,131]. A major limitation of the meta-analysis is generalizability as well as heterogeneity. Most of the studies included in the analysis were specifically conducted recruiting RRMS patients. Additionally, the exercises employed varied in form, severity and length.

In the literature, the influence of physical activity on fatigue is conflicting. Smaller sized studies failed to demonstrate a positive influence of exercise on fatigue. The limitation in these studies was a lack of consistency in study design [132,133].

4.5. Impact of physical activity on mood

Roughly 50% of people affected by MS will develop a clinically diagnosed depression over the course of the disease [134]. Depression in MS patients affects cognition, decision making, compliance to medication, and increases the ideation of suicide [135,136].

Ensari et al. [137], compared the effect of exercise *versus* control on depression in patients with MS by conducting a meta-analysis that included 13 RCT. Expanded disability status scale (EDSS) of MS patients ranged from 2.2–6.0, excluding one study that enrolled patients with EDSS score of 6.6–8.0. In this meta-analysis a total of 477 patients were pooled. Effect sizes (ES) were calculated with positive result indicating an improvement in depression score after physical activity. Depression was measured by various scoring systems in individual studies including the Beck Depression Inventory and the Major Depression Inventory. Further, mode of exercise included both aerobic exercises and endurance exercises which varied depending on the study. The overall mean ES was 0.36 (95% CI – 0.18–0.54, $p < 0.001$). The result of this study supports the beneficial effect of exercise on depression, albeit small. The correlation coefficient was calculated to be $r = 0.18$. One limitation in the literature and used in the aforementioned meta-analysis is that depression was not the primary outcome of the studies. Additionally, fatigue, commonly seen in MS patients, was associated with depression, and may have been a confounding variable [138]. The RCTs included in this meta-analysis had recruited MS patients with mild to moderate disability and generally of relapsing-remitting subclass. Further research is required and should focus on depression as a primary outcome, and involve MS patients from different subgroups [137].

4.6. Impact of physical activity on cognitive function

Attention deficit, processing dysfunction, memory and executive function have been shown to affect roughly 40–60% of patients affected by MS [139]. These cognitive impairments impact on daily living and quality of life. Promisingly, in other neurologic degenerative disease (*i.e.* Alzheimers) exercise has been shown to ameliorate cognitive dysfunction [140].The studies investigating cognition and MS are scarce. In a *post-hoc* correlational pilot study, 88 MS patients with an EDSS of <5.5 were studied. In this study, processing speed, calculation ability, attention, psychomotor speed, and visual scanning were investigated. Of the patients enrolled, 70% had RRMS though all subgroups of MS were represented. After controlling for covariates including disease activity and MS type, patients who exercised had a significant improvement in executive functioning. This study was limited by the fact that neuropsychological evaluation employed in the study covered only limited domains of cognitive function. The findings from this study highlight the need for further trials to better describe the relationship between physical activity and cognitive function [141].

In another randomized controlled pilot study, forty-two secondary progressive MS patients with EDSS of 4–6 who did not have physical disability were randomized into three exercise interventions (arm ergometry, rowing and bicycle ergometry) *versus* controls for 8–10 weeks. Neuropsychological function was one of the outcomes investigated using different test including symbol digit modalities test [142], verbal learning and ergometry test [143], and a battery of attention tests. Exercise was shown to significantly improve 4 out of the 10 measures including for instance verbal learning, delayed memory, alertness and shift of attention. These findings were significant only in patients that performed bicycle and arm ergometry exercises. This study was considered a pilot study due to its small sample size, and multiple end points investigated. Further studies are, therefore, required to examine these effects on larger samples, recruiting patients with higher disability scores. Additionally, it remains unclear whether these effects can be seen when MS patients engage in exercise for longer periods. Evidence on the best exercise activity that causes improved outcomes remains to be elucidated [144].

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4.7. Impact of physical activity on mobility

MS has a substantial impact on quality and activity of daily life. Impairment of mobility is one of the most visible signs of MS. The prevalence of impaired mobility varies depending on the definitions used and population studied from 50% to as high as 90% [145,146]. It has been estimated that 50% of MS patients will reach an EDSS score of 6.0 after 15–25 years from diagnosis, a score that necessitates the use of a walking aid [147]. The prevalence of impaired mobility has changed dramatically due to the advent of disease modifying agents.

Evaluating 13 different bodily functions in patients with relatively new disease diagnosis (<5 years) *versus* patients with >15 years diagnosis, Henseen et al. [129] found that regardless of the disease status, the current level of disability or EPSS score, lower limb dysfunction or weakness was the primary concern to these patients' independence [148].

Assessing 38 RRMS patients with an average EDSS score of 3.9, Dalgas et al. [149] investigated the impact of a 12 week, biweekly resistance training program on muscle strength and functional capacity compared to controls. At baseline and after the 12 weeks of interventions, MS patients from both groups were assessed for their muscle strength (isometric knee extension) and functional capacity using a combined score of four tests. MS patients in the resistance training program showed a significant increase in muscle strength and functional capacity ($p < 0.05$). The beneficial effect of exercise on muscular strength was replicated with different exercise interventions including aquatic fitness [150], aerobic activity [151], and treadmill training [152]. Of note, most of these studies were conducted in patients with moderate disability, and in patients with RRMS. Further studies are needed to include MS patients with different subtypes, and variable levels of disability.

Snook et al. [153], meta-analyzed 22 studies that pooled 600 MS patients investigating the influence of various types of exercises on physical strength in patients with MS. Of the 22 studies, 20 of them enrolled patients with an EDSS score lower than 4.5. Recruited MS patients were not exclusive to RRMS and instead included the various forms of the disease. Calculated size effect was significant with a SE = 0.19 (95% CI [0.09–0.28]). This converging evidence highlights the importance of engagement in physical activity as a potential modifiable factor. The effect of exercise was also more significant in a supervised setting when compared to home, a result that can be explained by a lack of guidance, oversight, or motivation.

Mobility is not only influenced by muscular strength. Additional integral components to mobility might be compromised in MS patients including for instance, balance and spasticity. These effects were assessed in a randomized 12-week exercise program *versus* controls study on 110 MS patients with a mean EDSS of 4.2. Sixty-six percent of the patients had RRMS, while the rest were diagnosed with either the primary or secondary progressive subtypes. Modified Ashworth scale was employed to measure specificity, while the Berg Balance Scale was used to asses balance which has been shown to be highly reliable and valid in MS [154]. The results revealed that patients undergoing supervised exercise program had significant improvement of balance, spasticity, fatigue and quality of life as compared to the control group [155]. The significant decrease of spasticity was demonstrated in the tone of hip flexors, hamstrings, and Achilles muscles. Exercise interventions were devised and conducted by physical therapists that focused on lower extremity, core stability and coordination exercises [155]. Improvement of spasticity score were also found in leg cycling exercises and locomotor exercises [156,157].

Collected emerging evidence support the positive role of physical activity on the various aspects of MS. Although some studies reported heterogeneous results, no study showed worsening of clinical disease secondary to physical activity, and therefore physical activity should be recommended in patients with MS.

5. Physical activity and systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is characterized by multiple organ involvement such as the joints, skin, lungs, kidneys and the nervous system. With the advent of advanced management modalities, the survival rates of SLE patients 20 years post-diagnosis has been estimated to be close to 80% [158].

Physical activity has been shown to be an important component in the management of chronic diseases. Traditionally, physical activity was infrequently incorporated as a behavioral modality in the care for patients with SLE. Despite the lack of support in the literature, the European League Against Rheumatism (EUALR) highlighted the proposed benefit of weight control, physical exercise and smoking cessation as adjuvant therapy in patients with SLE in general, and in SLE patients with increased risk of CVD in particular [159]. Physical activity has been shown to be effective in influencing multiple aspects of the disease process, for instance: cardiovascular risk, psychological symptoms, physical fitness, quality of life and fatigue.

5.1. Perceived barriers to engagement in physical activity

Patients with chronic disease including SLE patients are entrapped in a vicious cycle. Fatigue, depressed mode, and arising disability secondary to disease process can negatively impact on general quality of life and drive patients to stay at home, thus fostering a sedentary state which, in its turn, leads to higher degrees of fatigue and depressed mood [160]. Tench et al. [161], compared the effect of aerobic exercise on 93 SLE patients with 41 healthy sedentary controls. SLE patients were shown to be less fit and had reduced muscle strength. Moreover, SLE patients had lower oxygen uptake, reduced exercise capacity, and a decreased resting lung function as measured by means of the forced expiratory volume (FEV). Regression model showed that SLE was associated with fatigue, higher body mass index and depression.

Accumulated evidence corroborated these findings, SLE patients were shown to have significantly lower oxygen consumption at baseline. After adjusting for sex and age, it was revealed that SLE patients have a 46% decrease in performance as reflected by their maximal oxygen consumption [162].

These findings highlight the role of decreased aerobic capacity at baseline in limiting the engagement of SLE patients in recreational activities including physical exercise, and preventing normal daily functioning. Nevertheless, aerobic exercise has been shown to increase exercise tolerance and improve baseline oxygen consumption. Other barriers to physical activity in SLE patients exist. Manscuso et al. [163] investigated the physical barriers in 50 SLE patients and showed that 54% of the patients reported joint symptoms to be the most frequent SLE induced barriers. Second in frequency, SLE sufferers stated that fatigue played a negative impact on incorporating physical activity as part of their everyday routing. Other barriers included lupus related neuropathy, osteoporosis, pleurisy, skin sensitivity, and serositis. All of these barriers encouraged sedentary lifestyle, a physical state that is not usually addressed by physicians during routine follow up.

5.2. Impact of physical activity on fatigue

Fatigue is considered to be one of the most common symptoms in patients with SLE, affecting roughly 80% of patients [164]. The etiology of fatigue in SLE patients still needs to be elucidated, but it has been partially explained by sleep problems and depression that are affiliated with the disease process [165]. Wu et al. [166] performed a meta-analysis that focused on the effectiveness of physical activity in ameliorating fatigue in patients with SLE. In their meta-analysis, they included two randomized control studies [161,167] and one quasi experimental study [168]. 163 adults were pooled with a mean SLE-disease activity index (SLEDAI) score of 2–5.6, and a median duration of SLE ranging from 2.5–14.4. Aerobic exercise was shown to significantly decrease

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fatigue severity as assessed by the Fatigue Severity Scale (FSS) (MD = −0.52, 95% CI [−0.92 to −0.13], $p < 0.009$). Additionally, longer term exercise programs had a greater influence when compared to shorter exercise programs. (12-weeks - MD = −0.68, 95% CI [from −1.2 to −1.7], p = 0.009) *vs*. (8-weeks - MD = −0.31, CI [−0.91–0.29], p = 0.31). Exercise activity was also proven to have a significant positive effect on short form-36 (SF-36) vitality. Higher SF-36 vitality score corresponds to less fatigue, MD = 14.98, 95% CI [7.45–22.52], $p < 0.001$.

Avaus et al. [169], studied the influence of home training and supervised training on reported fatigue score *versus* controls on 54 SLE patients with SLEDAI of 1.78 to 3.60. Both intervention groups underwent endurance exercises such as walking or cycling for 3 h per week for 12 weeks. Exercise, regardless if supervised, was shown to cause an improvement in FSS scores, and a decrease in reported fatigue when compared to control.

5.3. Impact of physical activity on lipid profile

Benatti et al. [170], investigated the influence of exercise on 33 physically inactive SLE patients, SLEDAI < 4, with no prior CVD and had not underwent treatment with statin or antihypertensive drugs. Twice weekly aerobic exercise for 12 weeks was employed and assessment of lipids including total cholesterol, HDL, LDL, VLDL was done at baseline and at the end the program. Strikingly, exercise did not lead to a significant improvement in the lipid profile of SLE patients. Only Apo-B protein trended downwards in response to exercise (p = 0.06). Apo-B is a known atherogenic material and has a role in cholesterol deposition in the artery and is therefore predisposing to higher cardiovascular risk [171]. The resistance to lipid profile modification post-exercise still needs to be elucidated. It is postulated that pro-inflammatory cytokines associated with the disease including for instance TNF-α and IFN-γ have been shown to down-regulate plasma lipoprotein lipase activity, which ultimately impairs HDL synthesis [172,173].

Exercise therapy has been shown to be beneficial on multiple aspects of SLE, yet the optimal exercise program that could modify SLE patients' lipid profile is yet to be determined.

5.4. Impact of physical activity on CVD

SLE patients are at a higher risk of developing CVD, due to higher body mass index (BMI), dyslipidemia, hypertension and diabetes. Additionally, medications employed such as glucocorticoids as well as the systemic inflammation increase this risk as well [174–177].

In response to exercise, SLE patients have been shown to possess an abnormal cardiovascular response characterized by chronotropic incompetence and a delayed post-exercise heart rate recovery. The dysautonomia associated with SLE consequently results in an elevated risk for cardiovascular events [178,179]. Miossi et al. [180], investigated the influence of physical activity in counteracting these effects. The impact of treadmill exercise for 12 weeks on SLE patients with mild disease (SLEDAI < 4), and without a history of diagnosed cardiovascular or conduction disturbances was compared to sedentary SLE patients and healthy controls. The exercise training program was shown to be effective in increasing the chronotropic reserve, and improving heart rate recovery in the exercise group. The results of this study highlight the safety of exercise training as well as its efficacy in reducing the dysautonomia that results from the disease itself. The mechanism that can explain the effect of physical activity on the autonomic nervous system is to be elucidated, but some studied postulated the possible exercise induced angiotensin II down regulation that can lead to increased vagal activity, as well as nitric oxide release which augments the parasympathetic response, and thus counterbalances the dysautonomia [181,182].

Other abnormalities of the cardiovascular system exist in patients with SLE, including coronary artery disease and ischemic heart disease, which is the leading cause of mortality in SLE patients [183]. Atherosclerosis occurs in SLE patients 20 years earlier than in the general population [183,184]. Dos Reis-Neto et al. [185], evaluated the impact of walking exercise three times per week for 16 weeks on SLE patients. Endothelial function measured by brachial artery flow mediated dilation showed a significant improvement in the exercise group *versus* control. Exercise tolerance, and threshold speed also demonstrated similar effects. These finding underlined the role of physical exercise in improving endothelial function and aerobic capacity, in patients with SLE without causing a deterioration in SLE disease clinical severity.

5.5. Impact of physical activity on other disease aspects

The beneficial role of exercise on SLE is believed to occur secondary to immunomodulation. Perandini et al. [186], demonstrated that leukocytes extracted from the sera of SLE patients undergoing aerobic exercise had a significant down-regulation of inflammatory gene expression including as TLR3, IFNG, GATA3, and STAT4. All of these factors have an integral role in immune cell selective differentiation from naïve cells to specialized effector and helper cells resulting in orchestrating pro-inflammatory cascade and cytokine release.

5.6. Impact of physical activity on other disease aspects

Obesity is common in SLE patients and this comorbidity leads to decreased functional capacity, increased fatigue, and a higher risk of metabolic syndrome. Therefore, SLE patients should be advised to lose weight and thus enhance their functional capacity and inflammatory state [187].

SLE patients are at a higher risk of developing osteopenia (25%–46% of patients), and osteoporosis (1–23% of patients) [188]. These effects occur secondary to inflammatory cytokines released that can cause bone remodeling, decreased physical activity, or as an adverse effect to corticosteroid therapy treatment [189]. Regular exercise has been proven to be protective of bone dissolution and decreased density and therefore, aerobic exercise as well as weight bearing exercise has been recommended for patients with decreased bone density [190].

Sleep disturbances are commonly reported in SLE patients. Patients complain of difficulties in falling asleep as well as longer and more frequent nocturnal awakenings [191]. Current evidence suggests that engagement in moderate intensity exercise program such as 30–50 minute training sessions of low impact aerobic exercise weekly can significantly improve sleep quality [192,193].

The accumulated evidence stresses the benefit of physical activity on different aspects of the SLE disease process and therefore, it can be concluded that SLE patients should be encouraged to engage in physical exercise.

6. Physical activity and type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease that is characterized by selective destruction of beta cells in the islet of Langerhans resulting in insufficient insulin release and therefore glucose level dysregulation and hyperglycemia [194]. Several factors have been implicated in disease etiopathogenesis including genetic and environmental factors. The goal in disease management revolves around maintaining glucose levels within normal range while minimizing hypoglycemic episodes [195].

6.1. Perceived barriers to engagement in physical activity

Although, physical activity has been shown to improve several health outcomes in the general population, >50% of patients with T1DM are sedentary [196]. This high number of inactive subjects can be partially explained by the presence of barriers against engagement of patients with T1DM in physical activity. The Barriers to Physical Activity in Type 1 Diabetes (BAPAD-1) is a reliable and a valid structured questionnaire that is used to evaluate the perceived barriers to physical activity in T1DM [197]. Among patients with T1DM assessed by BAPAD-1, hypoglycemia has been shown to be the most common adverse event and barrier to engagement that could occur during or after physical activity. Indeed, hypoglycemia can have serious and fatal consequences including the loss of consciousness and sudden death [198]. Other preponderant barriers included the fear of loss of control over diabetes and the lower basal level of fitness. Non-disease specific barriers also demonstrated a salient effect including busywork schedule [199]..

Some T1DM patients develop serious health issues over time primarily caused by T1DM that make it potentially dangerous to exercise. For example, patients with proliferative retinopathy are advised against severe physical activity and Valsalva like maneuvers due to the possibility of a vitreous hemorrhage [200]. Additionally, autonomic neuropathy can negatively influence heart rate and blood pressure adaptation during exercise [201]. Furthermore peripheral neuropathy and foot ulcers can debilitate patients and decrease their ability to exercise [202]. Finally, diabetic patients can be limited by morbidity associated with myocardial ischemia, systolic or diastolic dysfunction or limb ischemia which occurs at a higher rate in patients with T1DM as compared to the general population [203].

6.2. Impact of physical activity on glycemic indices

The effect of exercise on glycemic control was investigated in a large meta-analysis that pooled 452 T1DM patients from 12 studies, eight of which were RCTs. The duration of interventions in each study varied between three and six months and the exercises employed differed between studies and included both aerobic exercise of various intensities and resistance exercises. Glycemic control was reflected by glycosylated hemoglobin (HbA1c). This meta-analysis demonstrated that the engagement in physical activity did not lead to a significant reduction in HbA1c (standardized mean difference (SMD) −0.25, 95% CI [−0.59–0.09]).

The limitations of this meta-analysis were multiple. Firstly, there was a variation in the duration of intervention and type of exercise. Secondly, it is not known whether the duration of the intervention was sufficient enough to result in a reduction of HbA1c, which reflects the long-term blood glucose level. Thirdly and most importantly, dietary intake was not reported strictly, a factor that significantly influences glycemic markers in diabetes [204].

Tonoli et al. [205], carried out another meta-analysis that investigated the effect of different exercise interventions (single bout of aerobic training, aerobic training, strength training, and combined aerobic and strength training) on two types of glycemic indices: acute (capillary, intestinal or venous plasma glucose levels), and chronic (HbA1c). All exercise forms had a significant large effect on acute indices, whereas their effect on chronic glycemic control were smaller but significant (ES = −0.23, 95% CI [from −0.44 to −0.02]). Regular aerobic exercise has been shown to significantly decrease HbA1c (ES −1.03, 95% CI [−1.56 to −0.49]) whereas other forms of exercise did not show a similar effect on HbA1c levels in the blood. This meta-analysis highlights the beneficial impact of physical activity on T1DM, yet this study was limited by the variability of insulin dosages used by T1DM patients, and dietary intake.

6.3. Impact of physical activity and T1DM chronic complications

The engagement in physical activity in type 1 diabetes mellitus has been shown to improve spontaneous baroreflex, and heart rate variability, both of which are good measures for autonomic function and can be involved in patients with long standing uncontrolled diabetes mellitus [206,207].

T1DM patients engaging in physical activity demonstrate decreased requirement for insulin dosages. Increased insulin sensitivity can positively influence disease course leading to decreased chronic complications. Increased insulin sensitivity improves glucose clearance from the blood; this has been postulated to occur secondary to elevated uptake by myocytes [208].

In the cross-sectional Finnish diabetic nephropathy study (FinnDianne), increased leisure time physical activity was associated with a lower risk of chronic diabetic complications including renal function, proteinuria, retinopathy and cerebrovascular disease [209].

In the “Pittsburgh Insulin Dependent Diabetes Mellitus Morbidity and Mortality Study”, it was demonstrated that T1DM male patients who engaged in sport activities during their teen years showed a significantly decreased risk in cardiovascular disease and all year mortality 25 years after disease diagnosis. Also, engagement in physical exercise during teen years was found to be protective against the development of diabetic nephropathy and neuropathy in subjects tested. In the same study, women were found to be half as active as males, a result that could explain the lack of sufficient power to detect the benefit of exercise on diabetes endpoints in the female population. This study is limited by being a retrospective cohort design [210].

T1DM increases the risk of CVD in a pattern and impact that is similar to Type 2 diabetes mellitus [211]. Seeger et al. investigated the impact of 18 weeks twice weekly running intervention *versus* control on cardiovascular measure in two BMI matched, and waist circumference-matched T1DM groups. Maximal oxygen consumption, a measure of physical fitness, was significantly improved post exercise ($p = 0.039$). In addition, brachial artery flow mediated dilation was shown to be significantly elevated post exercise. These results support the positive role of exercise in T1DM patients in reversing endothelial dysfunction, the initiating step in CVD onset [212].

The body of evidence that discusses the impact of exercise on T1DM is limited as compared to type 2 diabetes mellitus. Further research is required and should include RCT, large sample sizes, homogenous exercise interventions for sufficient periods, and attention to the subjects' dietary intake and insulin doses administered.

7. Physical activity and inflammatory bowel diseases

The main two types of inflammatory bowel disease (IBD) are Crohn's disease (CD) and Ulcerative colitis (UC). Both are chronic autoimmune diseases of the gastrointestinal tract and are characterized by clinical bouts of relapses and remissions [213]. While CD presents with transmural inflammation, UC is characterized by an inflammation that is limited to the mucosa and superficial submucosa [213]. IBD generally results in malnutrition and altered body composition [214]. Extra-articular manifestation also exists including skin lesions, arthritis, osteoporosis among others [214]. IBD patients are predisposed to the development of colon cancer development and therefore follow up is advised [215,216].

7.1. Physical activity and IBD risk of occurrence

Khalili et al. [217], examined the association between physical activity and the risk of developing IBD by examining two prospective cohort studies (Nurses' Health Study I&II) that included a total of 194,711 women. On follow up, the risk of developing CD was shown to be inversely associated with increased physical activity ($p < 0.02$), even after adjusting for age, sex, BMI and smoking history. Interestingly, Khalili et al. [216] found no association between physical activity and the risk of developing UC [217]. The finding of this study was consistent with the results of previous studies that highlighted the inverse relationship between higher physical activity and risk of IBD development [218–221]. This relationship has been more pronounced in CD as compared to UC [222].

7.2. Perceived barriers to engagement in physical activity

The perceived physical barriers against the engagement of patients with IBD were minimally studied. However, Brevinge et al. [223],

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studied the impact of small bowel resection on physical activity in CD patients. When compared to healthy adults and after accounting for body composition and metabolic parameters, maximum loading on ergometer exercises was shown to be inversely related to the extent of small bowel resection. More specifically, a 9% reduction in maximal load was associated with mild resection (<10 cm), and a 40% reduction of maximal load was demonstrated in resections of >50% of the intestine. Thus it is not advisable for patients with higher intestinal resections to engage in high energy consuming activities [223].

Muscle strength and endurance was also noted to be reduced in CD patients as compared to healthy controls. Weakness and decreased endurance was more pronounced in the muscles of the lower limbs ($p < 0.001$). This result was independent of disease duration, severity, accumulative dose of glucocorticoids ingested, and global habitual physical activity [224]. Similar studies in UC patients are lacking.

7.3. Impact of physical activity on disease activity in mouse models

The effectiveness of physical activity and exercise on IBD progression has not been studied in humans and is poorly understood. However, the influence of physical activity on IBD was observed in colitis mouse models. Cook et al. [225], revealed that voluntary running in colitis mouse models decreased colitis symptoms by significantly reducing diarrhea episodes, as well as reducing inflammatory gene expression of pro-inflammatory markers including IL-17 and IL-1β. In contrast, forced treadmill running for six weeks, four days/week, 480 m per session led to exacerbation of disease symptoms which manifested as increased diarrhea and pro-inflammatory cytokines [225]. This result contradicted the results of other studies that showed treadmill running at various speeds significantly led to a decrease in pro-inflammatory markers in experimental colitis [226]. The induction of colitis in mouse models results in the elevated secretion of TNF-α. Hoffman-Goetz et al. [227], showed that 16 weeks of wheel running led to a significant decrease of TNF-α secretion, and enhanced the section of IL-10; a well-known anti-inflammatory cytokine [227]. Several other studies supported the positive role of exercise in reducing pro-inflammatory process and decreasing the intestinal barrier dysfunction [228,229].

7.4. Physical activity and extra intestinal manifestations

Extra intestinal manifestations commonly occur in patients with CD. In approximately 20% of CD patients, peripheral arthritis ensue along disease course [230]. Ankylosing spondylitis (AS), which is a special form of peripheral arthritis develops in 0.9%–8% of patients with CD [230]. Noteworthy, the treatment of AS is mainly focused on a combination of exercise and drug interventions. It therefore stands to reason that engagement in physical activity leads to the improvement in disease symptoms, as proven by randomized control trials [231–233].

An additional common feature among patients with CD is decreased bone mass. Fifty percent of patients with CD develop osteopenia, and one third of those patients progress to osteoporosis [234]. The increased risk in the CD population has been attributed to the medications prescribed in disease management, as well as an increase in inherent bone resorption. A randomized control study investigated the influence of exercise on bone density in CD patients and demonstrated that low impact exercise for 12-month led to a significant increase in bone mineral density in the hip and spine as compared with the control group. Also, bone marrow density was shown to increase proportionately with the increased number of sessions [235].

Other symptoms of IBD include fatigue, pain, sleep disturbances and stress. There is a dearth of studies on the influence of physical activity on these parameters. Physical activity has been shown to ameliorate fatigue, pain, stress in other autoimmune diseases, thus a similar possible impact is expected among patients with IBD, yet further research is need to validate such assumptions.

8. Physical activity and fibromyalgia

Fibromyalgia is the second most common rheumatologic disease affecting 2–8% of the general population [236]. Fibromyalgia is diagnosed by the presence of chronic widespread pain and tender points. Newer diagnostic criteria, which is not based on tender point examination exists but is not fully adopted [237]. Non-restorative sleep, fatigue, memory disturbance and morning stiffness are part of the myriad symptoms of fibromyalgia [237]. The etiopathogenesis of fibromyalgia is fraught with ambiguity. Fibromyalgia can be either primary, or secondary to other chronic conditions such as osteoarthritis, rheumatoid arthritis and SLE [238].

Fibromyalgia is treated by the combination of pharmacological and non-pharmacological approaches. The best non-pharmacological approaches include health education, cognitive behavioral therapy, and exercise. To achieve long terms desired effects, adherence to exercise and physical activity should be encouraged.

8.1. Perceived barriers to engagement in physical activity

Adherence and maintenance of an exercise regimen in the fibromyalgia disease population is influenced by various factors. Dobkin et al. [239], investigated the predictors of maintaining an exercise regimen in patients with fibromyalgia and illustrated that high stress was one of the best predictors of poor exercise maintenance. Additional factors included older age, and higher physical disability as measured by the Fibromyalgia Impact Questionnaire (FIQ). In a different study, disease severity was associated with lower levels of engagement in aerobic activity. They also found that patients with a relatively new diagnosis had a higher stress level and were therefore less likely to engage in physical activity [240,241]. As seen generally in chronic pain syndromes, lower physical activity levels and a depressed mood at baseline, lower sense of self control, poor social support, and fatigue act as barriers to engagement in physical exercise [242].

8.2. Impact of exercise interventions on fibromyalgia

Accumulated evidence supports the integral role of physical exercise in the management of fibromyalgia. A relationship that has been substantiated across a variety of exercise interventions.

Bidonde et al. [243], conducted a meta-analysis that involved 839 patients with fibromyalgia examining the effect of aerobic exercise on major fibromyalgia outcomes. The aerobic interventions varied and included walking, cycling, and running. In the studies examined, the time each exercise session lasted was homogenous and was roughly 25 min. The frequency varied between two and three times a week, while the duration ranged from six to 24 weeks. Aerobic exercise was shown to be well tolerated among fibromyalgia patients with a similar withdrawal rate in the exercise group as compared to the control group. Three outcomes exhibited a significant improvement after aerobic exercise engagement including quality of life, physical function and pain. The influence of aerobic activity on fatigue and stiffness was shown to be positive, albeit not reaching significant levels.

In another report Bidone et al. [244], explored the influence of aquatic exercise on fibromyalgia outcomes. Aquatic exercises were defined as any exercise conducted in vertical standing position with the participant submerged to waist, chest or shoulder depth without limitation to equipment used including flutter boards, tubing, dumbbells, or calisthenics exercises. Fibromyalgia patients engaging in aquatic events reported a significant improvement on multidimensional function as assessed by the FIQ. Furthermore, significant improvements were found using self-reported physical function, pain, stiffness, strength, and cardiovascular sub-maximal function. Withdrawal and adverse effects from aquatic events in both aquatic exercise group *versus* control was poorly reported, thus concluding remarks on the tolerability of aquatic exercises are lacking. When compared to land-based exercising

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activities, aquatic interventions were not shown to confer a statistically significant advantage. Noteworthy, improvement of strength favored land-based training.

Based on another meta-analysis, moderate to high intensity resistance exercise with the intention of improving muscle strength, endurance and power over 16–21 weeks was shown to significantly improve multi-dimensional functioning, self-reported physical function, pain, tenderness, and muscles strength. Similar to previous comparisons, engagement in resistance training was not proven to confer statistical significance over aerobic exercises in all reported measures. However, pain sensation was significantly reduced favoring aerobic exercises. Withdrawal rates between the resistance and aerobic interventions were shown to be similar [245].

The improvement of fibromyalgia parameters subsequent to various exercise regimens highlights the importance of engagement in physical activity as adjuvant to standard disease management.

8.3. Physical activity and its impact on disease pathology

The etiopathogenesis of fibromyalgia remains elusive, and while an inflammatory process is not universally accepted, the current prevailing theories support the claim that chronic inflammation in involved in the disease process [246]. Fibromyalgia has been associated with higher IL-8 levels, and an elevated pro-inflammatory cytokines profile. The modulatory action of exercise was investigated in patients with fibromyalgia. After a single bout of aerobic exercise, there was significant decrease in IL-8, and heat shock proteins. IL-8 is a known pro-inflammatory cytokine which is released by various immune cells and has an integral role mediating pain sensation and neutrophil chemotaxis [247]. Decreased neutrophil chemotaxis results in a subsequent decrease of reactive oxygen species production and therefore reducing oxidative stress. Heat shock proteins, including eHsp72, have been shown to induce a higher release of pro-inflammatory markers including IL-1β and TNF-α, which mediate local inflammation [248]. Combined, these effects reflect the possible mechanism of how physical exercise could modify the inflammatory response and mediate an anti-inflammatory state leading to the alleviation of fibromyalgia symptoms [249]. Physical activity might influence fibromyalgia outcomes by other mechanisms through its impact on the central nervous system by influencing neuro-chemical balances, counteracting central sensitization, and increasing descending inhibition. Further studies are required to delineate the possible interactions between physical activity and nervous system functioning in patients with fibromyalgia [250].

9. Physical activity and systemic sclerosis

Systemic sclerosis (SSc) is a chronic autoimmune disease of the connective tissue. Although, the etiology of the disease remains to be elucidated, the pathogenesis of SSC is characterized by the fibrosis of the skin and internal organs [251,252]. Classically, it is divided into two subgroups: diffuse cutaneous form and the more common limited cutaneous form. Although diffuse cutaneous form is less common, it has a worse prognosis. Diffuse SSc involves skin tautness of proximal extremities, interstitial lung disease, and cardiac fibrosis among other manifestations. Limited form present with less distal extremity fibrosis and therefore have better prognosis albeit a higher risk of developing pulmonary arterial hypertension [251,253,254].

In addition to dermatologic manifestations, pulmonary involvement including lung fibrosis or pulmonary artery hypertension (PAH) is common among patients with SSc (35%–50%, 20% respectively) [255]. Moreover, SSc are at a higher risk of premature CVD, independent of traditional cardiovascular risk factors [256]. In SSc patients, health-related quality of life has been shown to be reduced secondary to dyspnea, fatigue, depression, skin deformities and deformation [257].

9.1. Impact of physical activity on disease outcomes

Physical activity has been shown to be generally well tolerated among patients with SSc [258–260]. Nevertheless, in the subset of patients with interstitial lung disease, exercise can result in desaturation. Furthermore, SSc patients are at a higher risk of developing exercise induced PAH which occurs subsequent to increased ventricular filling pressure, and increased pulmonary vascular resistance associated with exercise [261,262].

The body of evidence regarding the impact of exercise in SSc remains limited, yet there exists a modest number of studies discussing the influence of aerobic and resistance exercise in SSc patients with and without pulmonary hypertension.

Oliveria et al. [263] demonstrated that SSc patients engaging in bi-weekly, 30 minute treadmill aerobic exercises for eight weeks had a significant improvement in their exercise tolerance and aerobic capacity, as reflected by a higher peak oxygen saturation level without exacerbating the disease.

Antonelli et al. [264], investigated the influence of 30 minute therapy including training of motor functions, respiratory exercise, walking, finger stretching and occupational therapy in 16 patients with SSc (half of which had concomitant interstitial lung disease) as compared to 17 SSc patients who underwent standard care. Four months into the intervention, the experimental group had improved hand motility as determined by the hand motility in scleroderma (HAMIS) test, better quality of life as assessed by SF-36, better exercise tolerance as assessed by a reduction in heart rate and improved dyspnea as assessed by VAS.

Pinto et al. [265] presented results that supported the positive effects of resistance and aerobic training program on patients with SSc. Involvement in exercise training programs was shown to significantly enhance muscle strength, exercise tolerance, and aerobic capacity without adversely affecting disease course.

Schouffoer et al. [266] compared the effectiveness of a 12 week training program involving individually tailored therapy that consisted of a standardized group of sessions (general exercise and hand/mouth exercises) on a mixed sample of patients of diffuse and limited SSc. Assessment conducted at the end of the intervention period revealed a significant improvement in the grip strength, mouth opening, and 6-minute walking distance. An improvement of peak oxygen consumption was not reported.

Another randomized controlled study compared the effect of physical therapy *versus* usual care. The SSc patients selected either had a disability ratio > 0.5 on the Health Assessment Questionnaire Disability Index (HAD-QI), decreased mouth opening or a limited range of motion of more than one joint. The intervention administered was personalized to disability which was assessed based on a standardized criterion. Additionally, all patients in the intervention group regardless of their disability received muscle strengthening exercises, respiratory exercises and functional rehabilitation. For the first month, the intervention was supervised, followed by 11 month of home based exercises. At 1 month, there was a significant reduction in disability score and pain, and an improvement in hand motility. Microstomia was found to be significantly improved in the intervention group *versus* the control group at both one month and 12 months [260].

In summary, exercise is proven to be safe and tolerable in patients with SSc and therefore patients should be encouraged to engage in exercise interventions. Similarly, in patients with pulmonary involvement accumulated evidence corroborates the benefit of exercise with no additional significant adverse effects.

10. Physical activity and psoriasis

Psoriasis is a chronic skin disease that is characterized by erythematous plaques that are covered by silvery white scales majorly dispersed on the extensor surfaces of the joints [267]. Generally, psoriasis affects 0.5%–5.0% of the general population [268]. Psoriasis has been associated

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with increased cardiovascular mortality as a result of higher prevalence of cardiometabolic risk factors including hypertension, hyperlipidemia, tobacco smoking, diabetes and obesity.

10.1. Physical activity and the risk of psoriasis occurrence

The association between physical activity and psoriasis was assessed in the Nurses' Health Study II, a large cohort study involving 86,655 women. In this study, Frankel et al. [269], showed that after adjustment to various confounding factors such as age, smoking and alcohol consumption, women who engaged in higher levels of physical activity had a lower relative risk of developing psoriasis as compared to women in the least active quintile (RR = 0.72, 95% CI [0.59–0.89], $p < 0.001$). Vigorous physical activity, defined as >6 metabolic equivalents, was also shown to be significantly inversely associated with the risk of psoriasis development, even after adjusting for BMI (RR = 0.66, 95% CI [0.48–0.86], $p < 0.001$). The mechanism explaining these findings require further analysis, but such effects has been postulated to be mediated by the immunomodulatory effect of physical activity and exercise on pro-inflammatory cytokine release including for instance TNF-α, IFN-γ, and CRP. These cytokines have been shown to mediate the disease's inflammatory process as well as influence cardiovascular risk factors [270].

10.2. Perceived barriers to engagement in physical activity

In a cross-sectional study conducted by Torees et al. [271], patients with psoriasis without psoriatic arthritis exhibited a reduced level of engagement in physical activity. The odds ratio for decreased physical activity for psoriasis patients was 3.42 (95% CI [1.47–7.91]). The reason for the decreased engagement in physical activities could be explained by psychological barriers including social avoidance and exercise avoidance [272]. From a physiological point a view, psoriatic skin is less efficient at heat dissipation thus interfering with sweating. Therefore psoriatic patients may not be able to put up with similar exercise efforts [273].

The research on the relationship between physical activity and psoriasis is still in its infancy. Further research is required to elucidate what the perceived barriers to engagement are and to define the governing relationship between physical activity and disease severity and progression, if existent.

11. Physical activity and Sjögren syndrome

Sjögren syndrome (SS) is a chronic autoimmune disease that is characterized by lymphocytic infiltration and ultimately fibrosis and destruction of apocrine glands [274,275]. SS manifests with salivary hypofunction and keratoconjunctivitis sicca [274].

Wan-Fai et al. [276] disclosed that SS patients are less active than their healthy counterparts, and engagement in physical activity was negatively correlated with fatigue, depressive symptoms, and decreased quality of life. In a comparative study between exercises *versus* standard care among patients with SS, the impact of low to moderate intensity aerobic activity was revealed to enhance aerobic capacity, ameliorate reported fatigue, increase orthostatic tolerance, and alleviate depression [277]. In the same study, exercise was not shown to be associated with health-related quality of life. In this study, SS patients engaged in Nordic walking for 45 min, three times a week for 12 weeks [277].

Taken together, these results encourage the integration of physical activity in the daily life of SS patients. The research on SS is still in its early stages and further research employing large scale interventional based studies will be required to verify these promising results.

12. Physical activity and other autoimmune diseases

Physical activity and exercise has been shown to influence certain aspects of different autoimmune disease evidenced by studies presented earlier. This interrelationship has been studied extensively in diseases including SLE, RA, MS and T1DM among others. Although clinically relevant, there is a scarcity in research investigating the impact of engagement in physical activity and thyroid autoimmune disease, temporal arteritis, giant cell arteritis, and pemphigus.

13. Future directions

Physical activity has been shown to induce immunomodulatory actions on the immune system, yet its global effect in autoimmune diseases remains to be further elucidated. The research involving physical activity and autoimmune diseases, especially disease onset and outcomes is still in its infancy. Moreover, more randomized clinical trials with larger sample sizes will need to be conducted to improve the likelihood that the results will be generalizable. Additionally, future research should have more consistent definitions of specific forms of exercise and physical activities, to make the conclusions more remarkable and allow for comparability. Finally, more studies should be conducted in patients with the various subsets of the same disease entity, and on patients with varied clinical severity presentation (*i.e.* EDSS score in MS and SLEDAI in SLE).

14. Conclusion

Patients with autoimmune diseases are much more sedentary and less active than the healthy population. Accumulated evidence supports the integral role of physical activity and exercise in the management regimens for various autoimmune diseases. Physical activity has been consistently shown to be safe, and a strong body of evidence supports its essential role in ameliorating various measured parameters including quality of life. Given the interrelation between physical activity and mental health, improving psychological parameters through physical activity, could be reflected with higher compliance and eagerness to be more physically active. Thus, it stands to reason that clinical physicians should encourage patients to include exercise regimens as part of their daily life routines.

15. Recommendations

1- Patients with autoimmune diseases are more physically inactive as compared to the general population, and therefore physicians should encourage their patients to engage in physical activity.

2- Generally, even healthy adults should consider implementing PA in their daily routines, subsequent to its role in decreasing the risk of developing rheumatoid arthritis (RA), multiple sclerosis (MS), inflammatory bowel disease (IBD), and psoriasis disease incidence.

3- RA patients should consider engagement in PA due to its amelioration of cardiovascular (CVD) risk profile, decreasing disease severity, preventing rheumatoid cachexia, enhancing joint motility and decreasing stiffness.

4- MS patients could benefit from PA due to the improvement in fatigue, mood, cognition, locomotion and balance.

5- SLE patients show a decreased CVD risk profile and improved fatigue parameters secondary to engagement in PA.

6- PA decreased type 1 diabetes mellitus chronic complications including retinopathy, nephropathy and CVD, and have been shown to mildly influence acute and chronic (HbA1c) glucose measures.

7- Fibromyalgia patients should be encouraged to include PA as part of their daily routines due to its beneficial effects on pain, stiffness, fatigue, and quality of life.

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Conflict of interest

None.

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