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Literature review: Treadmill Exercise for Older Adults Improves The Quality of Life in Diabetes Melitus Disease and Potentially Enhances The Immune Response Post COVID 19

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ABSTRACT

The purpose of the literature review is to find out effect of treadmill exercises for older adults improves the quality of lifein diabetes mellitus disease and potentially immune response post COVID-19. The literature study also reveals the contribution of exercises in improving these factors. The results of the various studies included in this manuscript reveals that exercises improve quality of life (QOL) of patients suffering from diabetes mellitus is improving with exercise interventions but still extensive research needs to be done to further improve the QOL with respect to both physical and mental QOL. Lot of researches included in this manuscript state that when exercises are included in routine it helps in quality of life studies also reveal that exercises have proved to be beneficial in improving muscular strength, balance, gait, and fall related problems and immune response.

INTRODUCTION

Treadmill exercise provides a challenge to homeostasis throughout the body older adult diabetes mellitus patient with post COVID-19. The immune response, like many other physiological systems, displays substantial perturbations in response to a single bout of exercise. Many studies have documented a stereotypical immune response to vigorous treadmill exercise, consisting of a biphasic alteration in circulating immune cell numbers, reduced natural killer (NK) cell activity, reduced mitogen induced lymphocyte proliferation a reduced salivary immunoglobulin (Ig) secretion

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and elevated circulating cytokines. COVID-19 is an RNA virus with a crown-like appearance. Its diameter is approximately 60–140 nm. On one side, it has a concave surface with a ridge. It makes a larger binding interface, as well as more contacts with ACE2. It can make better contact with the N-terminal helix of ACE2 and have higher affinity. It is transmitted through respiratory droplets from coughing and sneezing and enters the nasal system by inhaling and starts replicating. ACE2 is the main receptor for the COVID-19 virus.

The spike protein (S protein) present on the surface of COVID-19 is pinched inside the host cell binding to the ACE2 receptor. Here, the enzyme furin is present in the host cell and plays a vital role for the virus to enter, which was absent in SARS-CoV. Next, the virus starts to propagate with limited innate immune response and can be detected by nasal swabs. The virus then propagates and reaches the respiratory tract, where it faces a more robust innate immune response. At this stage, the disease is clinically manifest and an innate response cytokine may be predictive of the subsequent clinical course. For beta and lambda infections, viral-infected epithelial cells are a major source. The disease will be mild for 80% of the infected patients and mostly restricted to the upper and conducting airways. With conservative symptomatic therapy, these individuals may be monitored and monitored at home.

Approximately 20% of the infected patients develop pulmonary infiltrates and some of these develop very severe disease. The mortality rate of severe patients with COVID-19 can be as high as 49%, based on a recent epidemiological by China CDC. In Wuhan, 292 patients with COVID-19 were studied. Age was the risk factor of patients with a severe condition, as shown by the Lasso algorithm. When the age of patients with a severe condition increased by 5 years, the risk increased by 15.15%. Most of the patients with COVD-19 were elderly patients in the severe group, with basic diseases.

Chronic obstructive pulmonary disease, hypertension, malignant tumor, coronary heart disease, and chronic kidney disease were more frequent in the severe group than in the mild group. Of 145 severe cases, 51 patients died (34.69%), and 90.2% of the patients who dies were over 60 years old. Forty patients had basic disease out of 51 deaths (78.43%).

Reports have demonstrated that patients aged older than 60 years who have comorbidities, especially diabetes mellitus and hypertension, are at risk for severe disease and death from SARS-CoV-2 infection. Diabetes mellitus is a growing epidemic in older adults, affecting 1 in 4 people aged 65 years and over. Diabetes mellitus (DM) is a chronic metabolic disorder characterized by elevated blood glucose levels due to relative

insulin deficiency or insulin resistance or both. Its sign is a growing public health problem and is considered one of the major threats to human health in the twenty-first century. Significant patient and community research is one of the main causes of disease complexity, increased risk of medical comorbidities such as fatigue, recent weight loss, severe limitation of mobility and strength and increased propensity to fall. According to the Centers for Disease Control, about 26 million children and adults live with diabetes. In addition, nearly 79 million people have "prediabetes". The overall magnitude of DM in adults older than 20 years was estimated at 171 million in 2000. The prevalence is likely to be double the current prevalence by 2030. Type 2 diabetes mellitus is the most common type of diabetes and accounts for 90-95% of all diabetes cases. The number of adults with DM in the world increased from 108 million to 422 million between 1980 and 2014.

The prevalence of diabetes mellitus in Indonesia tends to increase every year. As many as 13% of the population were diagnosed with diabetes mellitus in 2013. Most individuals with diabetes mellitus will visit a physiotherapy in the multidisciplinary clinic where they receive are for their DM related problems. Physiotherapy is professionally allowed to exercise in several treatment settings including acute care, inpatient and outpatient rehabilitation settings. Physiotherapy also worked in conjunction with the rehabilitation team to design components of community based rehabilitation strategy so as to enhance physiological, anatomical and psychosocial outcome. Physiotherapy is a thus corner stone of prevention and treatment of diabetes mellitus. Physiotherapy directed movement and exercise programs are clinically effective in helping diabetic patients to produce the desired quality of life (QOL) outcomes.

METHOD

Searches for relevant studies were conducted of the following databases: Medline, Pubmed, Scielo, and PEDro. Search terms included words relating to treadmill exercise, quality of life and physiotherapy. In addition, we contacted authors about trials that we knew were in progress from trial registration. Titles and abstracts were displayed and screened by one reviewer to identify relevant studies. Only peer-reviewed papers were included. Full paper copies of relevant studies were retrieved and hand searching of reference lists was carried out to identify further relevant studies. The methods and abstracts of the retrieved papers were extracted so that reviewers were blinded to authors, journal, and outcomes. The papers for inclusion flowchart and selection of articles criteria (Figure 1).

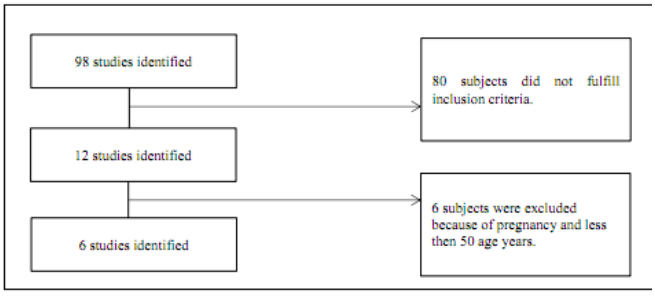

Figure 1. Flowchart of the search and selection of articles during the literature review process.

RESULT AND DISCUSSION

A total of 6 relevant articles was properly selected and critically evaluated for their potential support (or comparative lack of active support) for study hypothesis (The treadmill exercise could represent an effective factor for covid-19 patients) (Table.1). Included articles directly or indirectly indicated that treadmill exercise deficiency may be typically associated with covid-19 mechanism pathophysiology. However, no published study was typically found on treadmill exercise measurement in older adult with diabetes mellitus in response COVID-19.

We found the maximal walking distance on the treadmill exercise to be lower in patients with diabetes than those without diabetes, although the self-reported maximal walking distances were comparable between groups. This suggests that objectively measured exercise tolerance is lower in patients with diabetes than patients without diabetes with claudication, as previously observed. This finding appears not to be solely explained by group differences in BMI, as previously suggested, because statistical significance persisted after adjustment for this variable. The fact that self-reported walking capacity did not differ between the two groups does not exclude the possibility that patients with diabetes have slightly more severe symptoms in everyday life compared with patients without diabetes. Another hypothesis is that symptoms could be masked by a slower walking velocity in patients with diabetes than in patients without diabetes. This is an interesting question for future studies.

Results of this study show that patients with and without DM have a similar increase in walking distance after 6 months of community-based SET. This indicates that SET as primary treatment for intermittent claudication is equally effective in improving walking distance in patients with and without diabetes. However, we found that absolute walking distance was significantly lower in the DM group at baseline as well as at every follow-up moment.

Our results are in contradiction with research by Ubels et al.,33 who reported that SET has a greater relative gain in patients with DM. A possible explanation for the different results is the small number of diabetic patients (n ¼ 33) included in that study. Second, Ubels et al. used a 6-km/hr corridor test to measure walking distance, which is more difficult to standardize.

Our study is the frst to present the characteristics of cardiac performance parameters in large group of HF patients with vs. without diabetes undergoing cardiac rehabilitation emplying innovative HCTR vs. UC. We have to emphasize that the randomization in the TELEREH-HF trial was done to compare HFrEF patients undergoing HCTR vs. UC and analyses of DM vs. nonDM groups is a secondary post-hoc analysis. Te patients with and without DM were initially diferent in their clinical characteristics (Additional fle 1: Table S4) and the CPET dissimilarities (Additional fle 1: Table S5) were therefore consequences of its metabolic disparities. Till now, there were no large available data on the CPET in patients with HFrEF and DM. Terefore, it seems that our study is the frst to present the characteristics of cardiac performance parameters in this specifc but numerous group of patients.

In this substudy of the TELEREH-HF clinical trial, we analyzed efects of 9-week HCTR in comparison to usual care on parameters of cardiopulmonary exercise capacity in HF patients according to history of DM. Patients with DM accounted for about one-third of studied patients. Among DM patients, diferences in cardiopulmonary parameters from baseline to 9 weeks remained similar among HCTR and UC patients. In contrast, among patients without DM, HCTR was associated with greater 9-week changes than UC in exercise time, in ventilation at rest and in VE/VCO2 slope. The benefts of HCTR versus UC on the improvement of physical performance, ventilatory profle and gas exchange parameters were found to be more pronounced in patients with HFrEF without DM as compared to patients with DM.

We conducted a randomized, controlled, single-blind trial within university-affiliated clinics in our local community. We randomized 145 participants (45 women) with diabetes and PAD to our interventionda 6-month behavioral intervention targeting levels of readiness to engage in routine walking for exercisedversus attention control. Our primary outcome was 6-month change in maximal treadmill walking distance. Secondary outcomes included 3-month change in maximal walking distance, lower limb function (i.e., walking impairment scores), quality of life (Medical Outcomes Short Form Survey), exercise behaviors, depressive symptoms, and self-efficacy at 3 and 6 months.

Other studies did not concern SET but limited their research to the influence of diabetes on exercise tolerance in patients with intermittent claudication. Evidence in the literature is conflicting. Carter et al.34 and Katzel et al.35 did not report any difference in exercise tolerance between diabetic and nondiabetic patients. However, results of these studies might have been

biased by the fact that patients with severe comorbidities were excluded, including patients with poorly controlled diabetes. More recent studies, which did not exclude patients with poorly regulated DM, did report lower exercise performance in patients with DM.

We hypothesized that an already suboptimal metabolic environment can contribute to a lower exercise performance in patients with intermittent claudication and DM. Skeletal muscle metabolism might be less efficient in DM patients, which can result in a more rapid appearance of ischemic pain and thus decreasing FCD and ACD. Results of our study support this hypothesis only partially. Despite the fact that absolute walking distance in diabetic patients was lower than in nondiabetic patients, we found that increase in walking distance was similar in both groups. The latter suggests that the beneficial effect of SET is not negatively influenced by presence of diabetes.

Measured VO2 during a maximal symptom-limited CPET is the most objective method to assess functional capacity and consists of the following components such as maximal heart rhythm, stroke volume, the net oxygen extraction of the peripheral tissues. Peak oxygen consumption is an important predictor of prognosis in HF patients In patients with HF, the important prognostic value of a reduced peak VO2 has been studied in detail to identify patients at higher risk.

In one recent trial, among many CPET variables assessed in patients with HF, VO2 peak, percent predicted VO2, and exercise duration had the strongest ability to predict mortality in HFrEF In line with that, improvements of cardiopulmonary capacity determined by VO2 peak, percent predicted VO2 and distance, was observed in our study in majority of patients after HCTR. An aerobic exercise training has been recommended as non-pharmacological treatment for patients with HFrEF. As we described in the previous article of TELEREH-HF trial, the HCTR intervention was efective at 9 weeks, signifcantly improving VO2 peak (0.95 [95% CI 0.65–1.26] ml/kg/min vs. 0.00 [95% CI −0.31 to 0.30] ml/kg/min; $p<0.001$) EMPA-TROPISM Trial with 84 HFrEF patients demonstrated that empaglifozin was associated with signifcant improvements in peak VO2 (1.1±2.6 ml/min/kg vs. −0.5±1.9 ml/min/kg for empaglifozin vs. placebo; $p=0.017$).

We telephone-screened 1,756 people and excluded 1,294 (Fig. 1). Of the 462 eligible for an in-person visit, we excluded 371 for lack of objective evidence of PAD or inability to complete treadmill testing. We enrolled 145 participants; 19 (13.1%) provided no treadmill outcome measures at the 6-month followup visit.

Table 1 gives baseline characteristics of randomized subjects. Mean age was 66.5 (SD 10.1) years. Atherosclerotic risk factors were common: 106 (73%) mental health. The intervention group's average walking speed improved by 5.7 (2.2) percentage points, whereas the control group's average score decreased by 1.9 (2.8) percentage points (P = 0.034); and the intervention group's mentalhealth average score improved by 3.2 (1.5) units, compared with a decrease of 2.4 (1.5) units for the control group (P = 0.01). There was a nonsignificant trend toward greater improvement in quality of life (i.e., physical functioning and role-emotional) for the intervention group compared with the control group.

Regular practice of treadmill exercise should be positive to health; however, parameters such as volume and intensity need to be considered for the prescribed programs to obtain the best results. Generally speaking, exercise of moderate intensity promotes protection against infections caused by intracellular microorganisms, since it guides the immune response to a predominance of Th1 cells. Conversely, high-intensity activities cause increases the concentrations of anti-inflammatory cytokines (Th2 pattern), presumably to decrease damage in muscular tissue resulting from inflammation, although it may result in an increase of susceptibility to infections. The table 1 summarizes the main effects of treadmill exercise in the immunological system. Recent improvements in treadmill exercise support have improved quality of life the complex interactions between exercise stress and immune function within diabetes mellitus the enhance response immune COVID-19. Metabolomics, proteomics, and lipidomics have revealed that metabolism and immunity are inextricably interwoven and has led to a new area of research endeavor termed immunometabolism. In a typical study with human athletes exercising intensely for more than 2 h, significant increases in at least 300 identified metabolites can be measured as body glycogen stores are depleted and an extensive increase occurs in numerous and varied lipid super-pathway metabolites, including oxidized derivatives called oxylipins. Treadmill exercise-induced muscle tissue injury and inflammation elicit a strong innate immune response involving granulocytes, monocytes, and macrophages. Immune-specific proteins are produced to regulate the innate immune response, with oxylipins involved in initiating, mediating, and resolving this process.

Most of the expressed immune-related proteins including lysozyme C, neutrophil elastase and defensin 1, proteins S100-A8/A12, cathelicidin antimicrobial peptide, α-actinin-1, and profilin-1 are involved with pathogen defense and immune cell chemotaxis and locomotion. Other proteins including serum amyloid A-4, myeloperoxidase,

complements C4B and C7, plasma protease C1 inhibitor, α-2-HS-glycoprotein, and α-1-acid glycoprotein 2 increase chronically during recovery and are involved in the inflammatory acute phase response. This profound, treadmill exercise-induced perturbation in metabolites, lipid mediators, and proteins more than likely has a direct influence on immune function, decreasing the capacity of immune cells to increase oxygen consumption rates after activation. In response to an acute immunologic challenge such as exercise stress, cells of the immune system must be able to engage in growth and proliferation to generate effector cells that produce specific molecules such as cytokines and the proteins listed in the previous paragraph. Immune activation is associated with oxygen and biosynthetic demands, and immune cells must engage in metabolic reprogramming to generate sufficient energy to fuel these demands.

Although more research is needed, preliminary data support that immune cell metabolic capacity is decreased during recovery from physiologically demanding bouts of intensive exercise, resulting in transient immune dysfunction. Immunonutrition support, especially increased intake of carbohydrate and polyphenols, has been shown to counter these exercise-induced decrements in immune cell metabolic capacity.

CONCLUSION

Among the 1228 patients fulfilling the inclusion criteria, 16 (1.3%) could not be classified as having diabetes or not having diabetes because they were unable to give their treatment and medical history; these patients were excluded from the analysis. These 16 patients had an age, stature and body mass of 64 more or less 14 years, 168 more or less 8 cm and 71 more or less 14 kg, respectively, and 13 (81%) of them were male. Their self-reported maximal walking distance and maximal walking distance on treadmill test were 284 more or less 255 and 296 more or less 162 m, respectively.

In conclusion, SET for patients with intermittent claudication is equally effective in improving walking distance for both patients with and without DM, although ACD remains lower in patients with DM. SET as primary treatment for PAD seems equally effective in improving walking distance for patients with and without diabetes. However, in absolute terms, patients with diabetes perform on a lower level. The benefts of hybrid comprehensive telerehabilitation versus usual care on the improvement of physical performance, ventilatory profle and gas exchange parameters were more pronounced in patients with HFrEF without DM as compared to patients with DM.

A home-based walking intervention did not improve walking distance but did improve

walking speed and quality of life in people with diabetes and PAD. Clinicians should consider recommending home-based walking therapy for such patients. We have presented results from the first large-scale trial of a home-based walking intervention for people with DM and PAD. A 6-month home-based walking program did not improve the primary outcome of 6-month change in maximal treadmill walking distance compared with control. However, the 6-month home-based walking program did improve some secondary outcomes, specifically walking speed and 6-month physical functioning and mental health (i.e., role-emotional). These results suggest that home-based walking holds promise for improving walking speed and quality of life in people with DM and PAD. An additional benefit of our intervention was improvement in mental health per the SF-36 quality of life measure. Prior trials showed improved quality of life for people with PAD who completed a supervised treadmill walking program. We add to these prior studies by showing improved quality of life for people with PAD randomized to a 6-month homebased walking interventio. Our study is the first large-scale walking intervention trial in PAD to use homebased walking versus an attention control. We demonstrated that a home-based walking program can be used in patients with DM and PAD. Such a program may improve walking speed and quality of life in this high-risk population.

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Table 1. Studies summary treadmill exercise in COVID-19

First author/ year	Type of study	Sample	Assessment and intervention	Clinical outcome	Significance
G. Mahe et. al (2010)	A retrospective study	230 patients with diabetes and 982 patients without diabetes.	Assessment : TcpO2 Intervention : treadmill test	No significant difference two group.	P > 0.005
Kim M. van Pul. et. al (2012)	Experimental design	318 patients	Assessment : treadmill test Intervention : treadmill exercise	Significantly exercise for diabetes melitus	P < 0,001
Renata Główczyńska. et. al (2021)	TELEREH-HF trial	68 patients	Assessment :VAS Intervention : Treadmill exercise	Significant proportion of HF patients presents with DM there is interest in assessing efects of cardiac rehabilitation in DM vs. non-DM.	P = 0.044
TRACIE C. COLLINS, MD, MPH. et. al (2011)	the study exercise instructor	64 patients	Assessment : Intervention : Treadmill exercise	Significant differences between two study group. Group diabetes melitus and control.	P = 0,034
G. Mahe. et. al (2010)	A retrospective study	230 patients with diabetes and 982 patients without diabetes.	Assessment : TcpO2 Intervention : treadmill exercise	Significantly treadmill test for diabetes melitus complication with ischemia.	P > 0.005
Kim M. van Pul. et. al (2012)	Experimental design	318 patients	Assessment : treadmill test Intervention : treadmill exercise	Significantly treadmill test for diabetes melitus patients.	P < 0,001