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Effects of moderate intensity treadmill exercise with gradual increase in speed and inclination on serum C-reactive protein in male with type 2 diabetes mellitus

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Abstract--The aim of this study is to look at the effect of moderate-intensity treadmill exercise for 30 minutes with an increase in speed and inclination of male with type 2 diabetes patients in reducing the chronic low-grade inflammation. A randomized two-group study was carried out between July 2019 and September 2019. Ten male patients with type 2 diabetes (30-55 years old) without complications, with blood sugar controlled from Endocrine Polyclinic Internal Medicine RSUD dr. Soetomo, was recruited and allocated randomly into two groups. In the treatment group, each patient received moderate intensity treadmill training with increased speed and inclination. The exercise is carried out for 30 minutes for 4 weeks, 2-3 times a week. In the control group, each patient received standard treatment along with physical activity education for 150 minutes a week. Measurement of serum CRP levels was done on the first and

last day. In the treatment group, serum CRP levels were measured 30 minutes after aerobic exercise. This study showed that aerobic exercise for 4 weeks did not reduce serum CRP levels in type 2 DM patients. However, there was a tendency to increase serum CRP levels in the exercise group in this study which was consistent with the increase in serum CRP levels after exercise in the acute phase.

Keywords---Treadmill exercise, Moderate intensity, Increased speed and inclination, DM type 2, C-Reactive Protein (CRP).

Introduction

Type 2 diabetes mellitus is a multifactorial disease characterized by increased blood glucose levels due to defects in insulin secretion from pancreatic beta cells and impaired insulin action on target cells (Taneera et al., 2014). Worldwide there are 326.5 million people of working age (20-64 years) with diabetes, and 122.8 million people aged 65-99 years with diabetes. The number of people with diabetes of working age is expected to increase to 438.2 million, and the number of people with diabetes aged 65-99 years will increase to 253.4 million by 2045. The prevalence of diabetes in women aged 20-79 years is estimated to be 8.4 %, slightly lower than men at 9.1%. The prevalence of diabetes in women is estimated to increase to 9.7% in women and 10.0% in men (Cho et al., 2018). Diabetes is a major cause of death, morbidity and health care spending, so tackling this chronic disease is one of the greatest health challenges in the world today.

In general, worldwide the incidence of type 2 diabetes occurs at a young age. In Japan, 80% of newly diagnosed diabetes cases in adolescents are type 2 diabetes. In Mexico City, 25% of the population of type 2 diabetes is classified as "early onset". In Bangladesh, the median age at diagnosis in 2005 was significantly lower than in 1995. This shift towards a younger age of onset is important as evidence suggests that early-onset type 2 diabetes may be more aggressive (Jaacks et al., 2016). Health behaviors contribute to the adverse clinical profile observed in young diabetes. Lower levels of physical induced early-onset type 2 DM compared with later-onset type 2 DM (Colberg et al., 2016).

C-reactive protein is generally recognized as a marker of systemic inflammation, the increase of which is associated with cardiovascular disease. These markers increase immediately after exercise, but long-term exercise is associated with lower CRP levels, suggesting one of the beneficial effects of exercise. Men with diabetes mellitus who are inactive in their leisure time have higher CRP levels than women in the United States than women. However, another study showed a statistically significant decrease in CRP values in women with type 2 Diabetes Mellitus with increased activity compared to men. The value of CRP decreased in the overweight elderly diabetes mellitus population with a sedentary lifestyle after undergoing 6 months of aerobic exercise (Colberg et al., 2016).

The main risk factor for morbidity and mortality in diabetes is measured by cardiorespiratory fitness. The cardiorespiratory fitness assessment refers to

maximal aerobic capacity. Treadmill exercise can improve cardiorespiratory fitness (Rueggger & Booth, 2018). Another study showed that treadmill exercise can mitigate oxidative damage caused by diabetes in the hippocampus of Zucker diabetic fatty rats (Quartuccio et al., 2018).

Research on CRP in men with Diabetes Mellitus who are given exercise using a treadmill is still limited. Therefore, the aim of this study was to compare CRP before and after being given moderate intensity treadmill exercise with a gradual increase in speed and with a gradual increase in inclination in young men with Diabetes Mellitus.

Methods

Study design

This research was performed from October to December 2019 with study design was an experimental method with a pre-test and post-test randomized control group. All recruitment, sampling of blood, and intervention during the study were conducted at Dr. Soetomo Hospital.

Sampling Method

Recruitment began in September 2019, the research subjects were DM Type 2 patients who treated regularly at the Endocrine Outpatient Clinic Dr. Soetomo Hospital. Subjects were selected with consecutive sampling to reach a minimum sample size of 22 subjects. Sample size was determined by hypothesis testing using formula for difference in means. Inclusion criterias were male diabetes mellitus type 2 patients, 35-55 years old, normal cognition, IMT were 18.5-29.9 kg/m², blood pressure 110-130 mmHg systole and 70-80 mmHg diastole and patients sign informed consent.

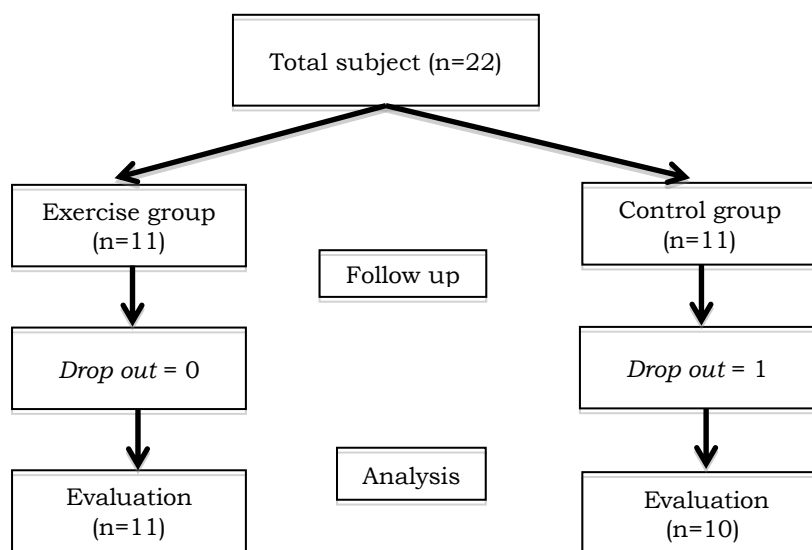


Figure 1. Subject recruitment

The exclusion criterias were patients had routinely exercise twice a week, erythema, peripheral neuropathy, range of motions abnormal on both ankle, cardiac disease, pulmonary disease, neuromusculoskeletal disease, balance disturbance and vision disturbance. Drop out criterias of the subject were unwillingness to follow the study protocol, a development of unstable clinical condition during study period, a development of hypoglycemia, fatigue and dizziness.

Intervention

Subjects drew a lottery to conclude whether the subject entered the control or intervention group. Initial Serum CRP evaluation was done before starting the treatment. Subjects in the control group underwent conventional therapy for 4 weeks, while the intervention group underwent a conventional therapy and exercise three times per week for 4 weeks. Treadmill exercise using BTL Treadmill. Another serum CRP evaluation was done after the treatment period was over. The experimental group also checked serum CRP 30 minutes after exercise at the first day and last day of exercise program and followed by data analysis. All study subject had signed the informed consent form and this study had ethical clearance from the ethical committee of Dr. Soetomo General Hospital.

Data analysis

The statistical distribution of the data was analyzed using SPSS version 20. One-sample Kolmogorov-Smirnov test to determine the homogeneity of the data in each group. Paired t-test to compare CRP before and after a 4-week exercise program in the intervention and control groups. Independent sample t-2 test (independent t-test) to compare the increase in CRP before and after a 4-week exercise program in the intervention group versus the control group.

Results

Total subject was 22 patients who met the inclusion criteria and did not include the exclusion criteria. Subjects were divided into 2 groups, consisting of 11 subjects in each group. Of the 22 patients, there were 1 patient who dropped out due to illness requiring treatment and withdrew from the study for personal reasons, so there were 21 patients were able to continue the study.

Table 1. Baseline Characteristic of the subject

	Intervention (n=11)	Control (n=10)	<i>p</i>
Age (years old)	50,36±4,43	46,00±3,68	0,045 ^a
BMI (kg/m ²)	23,31±3,87	26,25±5,02	0,181 ^a
Heart Rate Reserved	92,09±6,23	85,20±8,43	0,027 ^a
Random Blood Glucose (mg/dl)	164(140-300)	174(118-228)	0,805 ^b
Diabetic Onset (years)	7,09±6,09	7,00±5,39	0,672 ^a
Smoking	4 (36,4%)	3 (30%)	1,000 ^c
Hypertension	2 (18,2%)	2 (20%)	1,000 ^c
Dyslipidemia	1 (9,1%)	1 (10%)	1,000 ^c

Sample size (N); average (mean), standard deviation (SD); significant *p* if *p*<0,05

^a=Independent *t*-test; ^b=Mann-Whitney Test; ^c=Chi-Square Test;

Table 2. Control and intervention group comparison of initial serum CRP

Group	N	Median (Min-Max) (mg/dL)	p
Intervention	11	0,1(0,1-0,4)	0,125
Control	10	0,2(0,1-0,8)	

Mann-Whitney test; sample size (N); significant p if $p < 0.05$

Table 3. Intervention group comparison of serum CRP before and after exercise program

Serum CRP	N	Median (Min-Max) (mg/dL)	p
Before	11	0,1(0,1-0,4)	0,121
After	11	0,1(0,1-0,3)	

Wilcoxon test: sample size (N); significant p if < 0.05

Table 4. Control group comparison of serum CRP before and after 4 weeks

Serum CRP	N	Median (Min-Max) before(mg/dL)	p
Before	10	0,2(0,1-0,8)	0,085
After	10	0,25(0,1-1,2)	

Wilcoxon test: sample size (N); significant p if < 0.05 .

Table 5. Intervention group comparison serum CRP at first day and last day after exercise program

Serum CRP	N	Median (Min-Max) before(mg/dL)	Median (Min-Max) after (mg/dL)	p
First Day	11	0,1(0,1-0,4)	0,1(0,1-1,1)	0,564 ^a
Last Day	11	0,1(0,1-0,3)	0,2(0,1-1,1)	0,317 ^a

^a=wilcoxon test; sample size (N); significant p if < 0.05

There were 21 men in this study. The average age of study subjects and HRR in the treatment group was relatively younger than the control group. The average BMI and GDS in the treatment group were smaller than the control group. The average duration of diabetes in the treatment group and the control group was relatively the same. In the treatment group there was a history of smoking 4 people (36.4%) while in the control group there were 3 people (30%). In general, in the treatment and control groups, the majority of study subjects did not smoke, had no history of hypertension, and did not have a history of dyslipidemia.

There was no significant difference between the two groups in the variables of age ($p=0.045$), BMI ($p=0.181$), blood sugar ($p=0.805$) and duration of diabetes ($p=0.672$). Based on the Chi-Square homogeneity test, there was no significant

difference between the two groups in the variables of smoking history ($p=1,000$), history of hypertension ($p=1,000$), history of dyslipidemia ($p=1,000$).

Pre-treatment CRP values in the treatment and control groups before the exercise program shown in table 2. The mean basal CRP value in the treatment group was 0.1(0.1-0.4) mg/dL and the control group was 0.2(0.1-0.8) mg/dL. There was no significant difference ($p=0.125$) between the mean values of each variable. Characteristics of both groups before treatment were homogeneous.

In table 3, the mean value of serum CRP levels in the treatment group and after treatment showed the same results. In the control group (table 4), the mean of basal CRP values increased after 4 weeks. Based on Wilcoxon test, there was no significant difference between changes in basal CRP values after 4 weeks in the treatment and control groups.

Comparison of acute serum CRP levels before and after exercise on the first and last days shown that in the treatment group, there was no increase in basal and acute CRP levels after 30 minutes of the first exercise (table 5). At the end of 4 weeks of exercise, there was an increase in the mean value of CRP 30 minutes after exercise. Based on statistical tests, there was no significant difference between changes in acute CRP values in the first exercise ($p = 0.564$) and the last after 4 weeks ($p = 0.317$).

Discussion

Elevated CRP is associated with an increased risk of insulin resistance by impaired glucose delivery to skeletal muscle. In type 2 diabetes mellitus, an inflammatory atherothrombosis occurs which shows a higher prevalence of cardiovascular disorders. Type 2 diabetics who exhibit mild inflammatory symptoms show an increase in plasma CRP. A slight increase in CRP levels predicts the likelihood of developing cardiovascular disease in diabetic and non-diabetic individuals (Kim et al., 2015). Inflammatory and metabolic factors such as elevated blood glucose, adipokines, such as cytokines synthesized and released from adipocytes, modified lipoproteins, and plasma FFAs or free fatty acids associated with diabetes, have also been reported to trigger endothelial cells, smooth muscle cells and monocytes, and macrophage immune cells to synthesize and release circulating CRP. Local CRP production accelerates the occurrence of vascular disorders in type 2 diabetic individuals. Elevated CRP levels have been reported to predict early diabetes (Mugabo et al., 2010).

In this study, the average basal CRP was 0.1 mg/dL in the treatment group and 0.2 mg/dL in the control group. The plasma concentration of CRP in healthy subjects is 0,2 mg/dL or lower. In contrast, plasma CRP values can be up to 3000-fold in infection and tissue damage. Inflammation is observed in the pathogenesis of atherosclerosis and diabetes. Patients with type 2 diabetes who exhibit the inflammatory condition of atherothrombosis have a higher prevalence of cardiovascular disorders. Elevated CRP is associated with increased insulin resistance due to impaired glucose delivery to skeletal muscle. Patients with type 2 diabetes who show symptoms of low-grade inflammation show an increase in CRP (Ansar & Gosh, 2016).

Regular physical activity has the potential to improve chronic inflammation. Studies in a number of countries show that regular exercise with moderate intensity has been shown to play a role in the anti-inflammatory process in chronic inflammation. Exercise intervention with a sufficiently long duration (>3 months) and appropriate intensity can reduce inflammatory biomarkers. In addition, a decrease in the value of exercise-induced inflammation markers also occurred in studies with participants with high basal inflammatory markers such as obesity, old age and diabetes. In this study, there was no significant change in basal Serum CRP before and after the exercise program (Bouchard et al., 2015). In the control group, there was an increase in initial CRP of 0.2 mg/dL and at an interval of 4 weeks there was an increase in CRP of 0.25 mg/dL. This increase was not statistically significant.

The study also examined basal CRP, 30 minutes after moderate-intensity exercise for 30 minutes. An increase in serum CRP levels occurs at 30 minutes of an exercise program (Cerqueira et al., 2020). In the first exercise there was no improvement. However, in the last exercise there was an increase from 0.1 mg/dL to 0.2 mg/dL. In patients who rarely do exercise, exercise will increase CRP levels for a certain period of time, before eventually decreasing again. This is possible because of the body's adaptation to the changes that occur (Kasapis & Thompson, 2005).

The response of CRP to concentric and eccentric muscle contractions is associated with existing muscle damage. In concentric exercise, the increase in CRP is related to the duration of the exercise, not the intensity. CRP concentrations increase 30 minutes after exercise and persist for up to 2 days (Ostrowski et al., 1998; Hellsten et al., 1997). Muscle fiber contraction is a source of circulating CRP as found in studies of the vastus lateralis muscle. When practicing this CRP value can increase 5-100 times the value in the body's circulation, besides being found in muscle fibers, it is also found in interstitial tissue. This is in line with conducting simultaneous assessments of exercise-induced blood flow (Fischer et al., 2006; Langberg et al., 2002).

In general, the insignificant results in this study may be due to several factors that affect the serum CRP value, namely age, BMI, drugs consumption, comorbidities, and the study subject's physical activity was not assessed. CRP binds its receptors FcγRII to activate directly or interact with a number of signaling pathways in the process of ageing through inflammation and fibrosis process (Tang et al., 2017). Men with obesity have a 2.13 times greater probability of having an increase in serum CRP levels compared to men with normal weight. Each 1-SD increase in BMI in males is 1.38 times more likely to have an increase in serum CRP (Visser et al., 1999).

The use of β -blockers for the treatment of hypertension is associated with a decrease in serum CRP levels. The use of ACE inhibitors and ARBs is associated with lower serum CRP levels (Palmas et al., 2007). Insulin causes the most rapid decrease in serum CRP levels, ie a 40% reduction within 24 hours. Among the oral antidiabetic agents, Metformin and Thiazolidinediones decrease serum CRP levels with improved glycemic control. Sulfonylureas drugs have a small effect on reducing serum CRP levels (Dandona, 2008). A study also showed that Sitagliptin

has a strong anti-inflammatory effect characterized by a decrease in CRP levels compared to glimepiride in overweight type-2 diabetic patients (Hussain et al., 2019).

Elevated levels of C-reactive protein (CRP) are associated with coronary heart disease, stroke, and mortality. Physical activity prevents cardiovascular disorders, which can be partially mediated through reducing inflammation, including serum CRP levels. Physical exercise affects the immune system by reducing the number of mononuclear cells in peripheral blood which are a source of pro-inflammatory cytokines such as (IL1, IL-6, IL-8, CRP) (Echavez et al., 2016). The decrease in IL-6 also affects the decrease in CRP, IL-6 is a stimulator of hepatic CRP secretion. Continuous light exercise can reduce CRP and IL-6 levels in obesity cases (Vella et al., 2017).

Limitation

This study has several limitations, which is limitations of researchers to monitor other chronic disease conditions, such as kidney disease, liver and other metabolic diseases that may affect the results of the study. The use of CRP markers in which less sensitive when compared to HS-CRP. Limitations of researchers to monitor diet, drugs and daily physical activity of research subjects outside the exercise program provided.

Conclusion

Moderate-intensity treadmill exercise with a gradual increase in speed and inclination for 4 weeks was not decreasing serum CRP levels in the type 2 DM. However, there was a tendency to increase serum CRP levels in the exercise group. There was no increase in serum CRP levels in the control group receiving standard therapy. There was also no difference in serum CRP levels in the type 2 DM group who received moderate-intensity treadmill exercise at a gradual pace and inclination for 4 weeks compared to the control group.

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Conflict of Interest

The authors declared no conflict of interest.

Author Contribution

All authors equally contributed to preparing this article.

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