INTRODUCTION

In this globalization era coincidence with urbanization of lifestyle, the prevalence of type 2 diabetes mellitus (T2DM) has a gradually increasing trend, not only in developing countries but also in developed countries, which approximately 425 million people in 2017 (8.3% of the world’s population) suffered T2DM and is predicted to increase by 48% by 2045. Furthermore, the national prevalence of DM in Indonesia as a developing country is doubled from 1.1% in 2007 to 2.0% in 2018 with an age over 15 years old. In the United States, in comparison, has reached 9.3% of the population in 2015. This, consequently, makes healthcare providers evaluate the most effective intervention, particularly in physical activity as a non-pharmacological therapeutic strategy.

Exercise is considered as an attempt to improve insulin sensitivity, muscle mass, and glycemic control of those with DM. However, the benefits of exercise and the potential of exercise prescription still are lack of success to encourage those with T2DM to participate because of impediments, both real and perceived. Having exercise might be a challenge for people with T2DM since they have biological impairments that are going to be analyzed in this review. Moreover, exercise prescription also becomes a challenge for providers to educate persons with DM regarding the essential role of exercise prescription and its delivery and to contemplate the safety, attaining, and effective activity. This can be seen in Portugal that only 60% of T2DM people reported not practicing any kind of exercise. A reason that might influence little participants who conduct exercise is insufficiency of knowledge related to the crucial of the exercise for them. There are some modalities of exercise can be undertaken by those with T2DM, such as aerobic training, resistance training, combination of aerobic-resistance training, and high-intensity interval training (HIIT) which all of them will be summarized and updated in this review.

IMPORTANCE OF EXERCISE

Exercise exerts definitely an improvement in quality of life, although the scale of measurement of quality of life is still inconsistent, in general, and metabolic control specifically for patients with T2DM. Thus, it is important to those caring for patient T2DM to understand the mechanism of

Modalities of Exercise Intervention for Type 2 Diabetes Mellitus: Narrative Review
Luthfia Dewi

Department of Nutrition, Universitas Muhammadiyah Semarang, Semarang, Indonesia

ABSTRACT

Background: Exercise is one of the crucial factors in the management of type 2 diabetes mellitus (T2DM). Many papers have highlighted the role of exercise for people with T2DM; nevertheless, the latest information is needed to be summarized. Furthermore, there is still a lack of manuscripts revealing the types of exercise for T2DM comprehensively with the mechanism involved which results in the advantageous outcomes from the exercise. The aim of this manuscript is to summarize the modalities of exercise for T2DM with a brief metabolic mechanism.

Key words: Exercise, outcomes, type 2 diabetes mellitus

Address for correspondence:
Luthfia Dewi, Department of Nutrition, Universitas Muhammadiyah Semarang, Jl. Kedung Mundu Raya No 18, Semarang 50273, Central Java, Indonesia. Tel.: +6823 2535 8329. E-mail: luthfia@unimus.ac.id

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Exercise prescription including type, intensity, duration, frequency, and intervention period which issues the heterogeneity.

Related to weight loss and muscle mass and muscle tone improvement, exercise affects the self-image on their performance and body composition. Exercise, in general, in patients with T2DM is hypothesized to restore the availability of cAMP-response element-binding protein, which regulates the differentiation of neurons, β-cells, adipocytes, and smooth muscle cell.

Regular exercise, either aerobic or resistance training, is proven improving insulin sensitivity in T2DM. The possible reason for recommendation exercise no less than every 48 h by The American College of Sports Medicine and American Diabetes Association (ADA) is the effect of exercise in insulin-sensitizing improvement may be lost after 48–72 h. Another meta-analysis reported that performing exercise training in 13 weeks, which similar to the lifetime of red blood cells, will improve glycated hemoglobin (HbA1C%), it is, therefore, stimulating the change of HbA1C% through exercise training is possible in such a short timeframe.

In addition, chronic exercise training effect on those with T2DM is an adaptation in glucose/insulin metabolism. The surprising finding is that there is heightening blood pressure reduction (−6.17 mmHg; 95% confidence interval [CI] −8.83–−3.51) in individuals with T2DM conducting exercise more than 150 min/week compared to the exercise performed <150 min/week (−2.80 mmHg; 95% CI−3.86–−1.74). Accordingly, exercise training also alleviates both vascular structure and function by alleviating endothelium-dependent dilation and vascular rarefaction in skeletal muscle microcirculation which is reversing the effect of T2DM. Even though an exercise program seems promising to whom with T2DM, that is still becomes a challenge to encourage people with T2DM to participate in exercise program due to a lack of comprehension of their disease and lack of confidence in the ability to get involved in exercise program. In addition, they may have some physical barriers that limit their movement.

### AEROBIC TRAINING

Aerobic training is characterized by continuous and large muscle group movement rhythmically, such as walking, jogging, and cycling, for most T2DM patients, brisk walking and jogging are considered as a moderate-intensity and vigorous-intensity aerobic exercise, respectively. ADA stated that at least 150 min/week or more of moderate to vigorous-intensity activity (for instance, at 50–70% maximal heart rate) and once in 3 days of daily exercise is recommended to enhance insulin action. It is recommended to conduct a weekly minimum of 90 min of vigorous-intensity aerobic exercise for T2DM patients with no cardiovascular or musculoskeletal contradictions.

Aerobic training enhances mitochondrial density, insulin sensitivity, oxidative enzyme, conformity of blood vessel, lung function, and cardiac output. It uses oxygen utilization from free fatty acid, muscle/liver stored, and circulating glucose. The recommendation of aerobic training – comprises continuous, rhythmic movement of large muscle group which can be found in walking, jogging, and cycling – for T2DM should be engaged moderate to vigorous (65%–90% of maximum heart rate) training at least 2–3 days/week or 150 min/week with no more than 2 consecutive days. Supervised aerobic training at least 8 weeks has an impact significantly and clinically to improve VO_{2max} and HbA1c whereas the protocol performed in the studies varies between 8 and 52 weeks. It is reported that aerobic training within 12 weeks is successful to improve β-cell function to those who have less severe conditions of diabetic.

Individuals with T2DM are well-described with decreasing of cardiorespiratory fitness leading to impair cardiac, vascular, and skeletal muscle parameters. Diabetes per se is an obvious contributor to those damages in which insulin resistance (IR) is the culprit for decreasing maximal oxygen consumption and or submaximal exercise capacity. Furthermore, individuals with T2DM have slower oxygen uptake kinetics implying declined capacity in an acute change in oxygenation requirement at the beginning of the exercise. The previous narrative review gives a further explanation regarding mitochondrial dysfunction in T2DM, particularly in cardiac tissue, skeletal muscle, and the vasculature which can decrease vasomotion and generate excessive reactive oxygen species (ROS) in the vascular. Decreasing of peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) expression, one of the transcriptional activators of mitochondrial biogenesis, occurs in T2DM conditions leading to mitochondrial adenosine triphosphate (ATP) deterioration and excessive ROS production. Relating to mitochondrial biogenesis, exercise in people with T2DM is might warrant to increase PGC-1α expression as a key mitochondrial regulator. Nevertheless, it is needed further to study the effect of different training modalities in those with T2DM toward PGC-1α expression since there is still no sufficient data explaining both aerobic and resistance training impacting mitochondrial biogenesis. The data by Barres et al. accounted for stationary cycling at 40% and 80% of maximal aerobic capacity leading to decrease PGC-1α, peroxisome proliferator-activated receptors, and pyruvate dehydrogenase kinase 4 methylation in humans. Another supporting detail that potentially increases glucose uptake after training in individuals with T2DM is increasing of glucose transporter 4 (GLUT4) through transcription factor myocyte enhancing factor (MEF2A) and increases phosphorylation of AS-160 (still in postulate).

### RESISTANCE TRAINING

Another type of exercise prescription in individuals with T2DM is resistance exercise, which benefits to improve...
Exercise for type 2 diabetes mellitus

Resistance training is proven to improve HbA1c values. HbA1c, a product formed by glucose and the free amino acid of the hemoglobin β chain-N-terminal proline, is a unanimously acceptable parameter to monitor long-term blood glucose levels. A meta-analysis concluded that resistance training is capable of lowering HbA1c values on average 0.48–0.67%. The explanation regarding the roles of resistance training to improve glycemic control mainly enhances the strength and the size of muscle. Some reviews by Codella et al. and Pesta et al. demonstrate further details that those results from three ways [Figure 1]. First, phosphatidylinositol 3-kinase-Akt-mammalian target of rapamycin pathway which induces activation of phosphorylated adenosine monophosphate-activated protein kinase (AMPK) activity. This increases ATP production through target protein phosphorylation. The phosphorylation of target proteins also intensifies GLUT 4 translocation and lipid oxidation which eventually increases glucose uptake. Second, resistance training is able to activate a crucial sensor for intracellular calcium signaling and muscle remodeling called calmodulin-dependent protein kinase II leading to activation of transcription factors such as MEF and its target genes such as PGC-1α and glucose GLUT4. Third, oxidant production during resistance training might benefit on muscle differentiation and lead to initiate mitochondrial biogenesis. This is considered as transient ROS which is essential to handle the pro-oxidant environment. Another explanation states glucose utilization during resistance training promotes insulin action in skeletal muscle through enhancement of GLUT-4, insulin receptor, protein kinase B-α/β, glycogen synthase, glycogen synthase total activity, insulin-stimulated-glucose disposal, glycogen synthesis, and probably muscle modification into fast-type to slow-type fibers.

Two major types of resistance training, namely, lactic-acid free and lactic-acid related. Lactic acid-free covering jumps, launches, weight lifting, and 100-m dashes are really short duration and low energy consumption. While lactic-acid related including 400–800 m runs, hurdle and anaerobic phases of team sport matches are featured by short (from 1 to 5 min) and partial combustion of glycogenolysis-dependent glucose.

AEROBIC-RESISTANCE TRAINING

Nevertheless, the effectiveness of the type of exercise is still unclear since another meta-analysis declared no difference between resistance and aerobic training. The previous meta-analysis concluded that resistance training (i.e., free weights, weight machines, body weight, and elastic resistance bands) would be considerably expected to lower HbA1c values and lipid profiles than aerobic exercise (i.e., walking, cycling, jogging, and swimming). A combination of resistance exercise and endurance training show more benefit compared to both groups per se and it affects greater improvement in variables related to glycemic control and inhibits cytokines inflammatory. Moreover, the previous meta-analysis by Sukala et al. stated that the biggest reduction of HbA1c value (−1.1−−2.2%) occurred to those with T2DM performing aerobic and resistance training at least 16 weeks. Furthermore, combination of aerobic and resistance training has demonstrated in numerous well-sized trials such as Health Benefits of Aerobic and Resistance Training in individuals with type 2 diabetes trial, Diabetes Aerobic and Resistance Exercise trial, and Italian Diabetes and Exercise Study study.

HIGH-INTENSITY INTERVAL TRAINING

HIIT is considered as time-saving exercise intervention that might benefit similarly with moderate-intensity aerobic training. HIIT comprises 15 s–4 min; ≥90% maximal oxygen uptake followed by a recovery period (40–50% maximal oxygen uptake) of equal or longer duration than the
work interval. In terms of HbA1C, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein, and low-density lipoprotein cholesterol, triglycerides, body mass index (BMI), and waist-to-hip ratio, there is no difference between those two modalities. HIIT could be performed on a stationary bike consisting 4–6 repeated in 30–60 s bouts and a single session lasts approximately 10 min. Compared to moderate-intensity continuous training, HIIT provides the higher functional capacity (VO$_{2\text{max}}$ increased 3.02 mL/kg/min) and it, in general, has been published that it is able to improve the cardiometabolic risks in individuals with T2DM, including reducing body weight and A1C levels, increasing aerobic fitness, controlling blood pressure, and alleviating lipidemia parameters. Nevertheless, there is still an extensive range of baseline age, duration of T2DM, glucose level, insulin utility, variation intervention, supervision, dietary management, and dietary management. A single bout of HIIT is able to activate PGC-1α through its nuclear translocation improvement and eventually induces AMPK activation.

The size effect of exercise in glycemic control varies between individuals with T2DM. It is still unclear the exercise prescription toward those with T2DM since numerous factors might be contributing to the effect.

1. **BMI**
   Individuals with T2DM with a high baseline BMI are contemplated to have lower glycemic control compared to those T2DM with non-obese status due to attenuating insulin signaling; which in turn, lower glucose uptake.

2. **Medication**
   Blood glucose levels should be ultimately controlled before addressing exercise to subject with T2DM. This means that the time of medications and meals needs to be monitored intended to make safe and effective exercise. One of the customarily prescribed oral antihyperglycemic medications is metformin which is the most recommended by ADA and has a role to increase insulin-stimulated glucose uptake through AMPK activation. Although it is well-known that metformin and resistance training has capability to independently activate AMPK, the synergistic effect of the combination of metformin and resistance exercise is still unclear since both of them might have a distinct adaptation in β-cell pancreas or in the liver. Insulin sensitizers such as thiazolidinedione and metformin have a crucial role in impacting the exercise outcome. Genes and signaling pathways which differ among individuals might lead to variation in the physiological response to medication. However, some medications are generally proven to improve VO$_{2\text{max}}$. Rosiglitazone, for example, with dose 4 g/day for 4 months is able to augment VO$_{2\text{max}}$ by 7%; as a result, there is improving insulin responsiveness on the participants with T2DM. Furthermore, subjects with T2DM who rely only on insulin injection for their medication have to know exactly the level of blood insulin after specific time of insulin injection since they experience two conditions, namely, blunt insulin production and “stress hormone” increment (including catecholamines, glucagon, and cortisol) which eventually lead to insulin deficiency.

3. **Complication**
   The exercise prescription for individuals with T2DM and with the complication existence needs to be personally tailored. The customarily exacerbating complications are cardiovascular disease, peripheral neuropathy, retinopathy, and nephropathy which each condition has different considerations. The previous review data explained that those with cardiovascular disease require an evaluation from the cardiologist, those with peripheral neuropathy are insisted to wear appropriate footwear and to examine their foot periodically, those with retinopathy have to be deliberated on the stage of retinopathy. Individuals with T2DM and moderate retinopathy non-proliferative are prohibited to have exercise causing sudden blood pressure spikes; those categorized in severe non-proliferative are not allowed to jump, sudden head shakes, and very intensive efforts; while those classified in intravitreal bleeding need to stop their exercise. In terms of nephropathy complication, subjects T2DM with nephropathy stage more than 3 are suggested to do their training started at low intensity and volume.

**CONCLUSION**

All modalities of exercise represent an effective interventional strategy to improve a diabetic condition. This narrative review provides updated information in the exercise as a part of the management of T2DM. There are numerous proved beneficial resulting from the exercise for T2DM, but it still becomes a challenge to encourage those with T2DM to perform the exercise accordant with the recommendations.

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The author is responsible for the substantial contributions to the conception or design of the work; or the acquisition,
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