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Exercise Intensity and Wound Healing in Diabetic Mice

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HONORS PROJECT

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# Exercise Intensity and Wound Healing in Diabetic Mice

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## ABSTRACT

Along with the increase in the incidence of type 2 diabetes (T2D) in the United States comes an increase in the health consequences of elevated blood glucose levels, including delayed wound healing. Exercise has been demonstrated to advance wound healing; however in terms of wounds in diabetics, it is not known what intensity of exercise will have the most positive effects.

**PURPOSE:** The purpose of this study is to examine the effects of low- and high-intensity exercise on patterns of wound healing in diabetic mice.

**METHODS:** Twenty-one 10-week-old female diabetic mice (db/db or B6.BKS(D)-Lepr<sup>db</sup>/J) were randomly assigned to a sedentary control group (CON), low-intensity treadmill exercise (LEX), or high-intensity treadmill exercise (HEX). Mice were exercised for 30 minutes, five days a week, for three weeks on a 5% incline at 12 m/min (LEX) or 18 m/min (HEX). Three days after exercise began mice were wounded in the upper back with a 3.5mm punch biopsy instrument and wounds photographed at the same time every day until wounds were fully healed (<10% original size). Wounds were quantified by ImageJ (v1.48b; NIH, USA) and the pattern of wound healing was analyzed by repeated measure ANOVA (SPSS v.20, IBM Inc.).

**RESULTS:** CON mice healed in an average of 14.4 +/- 2.4 days, and HEX mice in 14.0 +/- 3.0 days. However, LEX mice healed in an average of 10.1 +/- 2.3 days. The patterns of healing in terms of the size of the wounds were also different by RMOVA ( $F_{1,18} = 4.7$ ;  $P = 0.023$ ).

**CONCLUSIONS:** In these diabetic mice, LEX mice healed faster than CON mice, but HEX did not. Based on these results, low-intensity exercise should be recommended to improve the healing of wounds in those with T2D, but not high-intensity exercise. Further research is necessary to clarify the mechanisms of these findings, as well as to confirm the effect in humans with T2D.

**KEYWORDS:** type 2 diabetes, wound healing, exercise intensity, diabetic mice

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## Introduction

Type 2 diabetes is becoming more and more prevalent throughout our country and one of the major health

concerns associated with this disease is poor wound healing. Poor wound healing leads to many

disadvantages including a decreased quality of life which results from increased pain, immobility, and insufficient productivity (Keylock & Young, 2010). This is an area of study that requires attention in order to improve the quality of life of individuals in this population, as well as to benefit people of the community by relieving them of the burden of the enormous health costs.

Millions of people across the globe are living with type 2 diabetes and poor wound healing, and it is estimated that there are 25.8 million diabetics in the United States alone (American Diabetes Association, 2011). Diabetes is associated with many serious health problems including increased risk of heart disease, blindness, and delayed wound healing which in some cases is so severe that amputation is necessary. Unfortunately, a large number of people are unaware of these negative health risks. In the United States alone, annual health care costs related to chronic wounds are twenty five billion dollars (Keylock & Young, 2010). Exercise is a cost effective way of improving this, which is something greatly needed, especially in today's economy where there is uncertainty and rising health care costs. In addition, participating in exercise allows individuals to avoid the side effects that result from many medications, as well as redeem other positive health benefits.

Evidence from previous research suggests that exercise may improve wound healing. Research

has found that physical activity is associated with decreased levels of inflammation, which supports the notion that there will be a decreased presence of proinflammatory cytokines after exercise. Inflammation is a critical part of the wound healing process, and many studies have demonstrated that faster and better wound healing results when there is less inflammation. A few investigations have indicated an inverse relationship between physical activity and inflammation.

Previous studies have shown that moderate intensity exercise can improve wound healing in diabetic mice. The purpose of the present experiment was to explore other exercise intensities and their impact on the wound healing process. Low exercise intensity may have a very different effect on wound healing than high exercise intensity, which is extremely valuable knowledge to obtain in order to enhance our society. Based on former evidence, a hypothesis was constructed that high-intensity level exercise would be the most productive in decreasing levels of inflammation, resulting in more efficient wound healing.

## Methods

To examine the effects of different exercise intensities on wound healing, a total of twenty-one ten-week-old female diabetic mice (dbdb or B6.BKS(D)-Leprdb/J) were randomly divided into three groups of seven mice each. These groups consisted of low-intensity exercise (LEX), high-intensity exercise (HEX),

and a sedentary control (CON) group that performed no exercise. Three days after the mice were randomized into groups and had begun exercising, two wounds were created in the upper back with a 3.5mm sterile, disposable punch biopsy instrument. The mice were anesthetized and the area surrounding the wound site was shaved and swabbed with seventy percent alcohol and Betadine solution prior to wounding. The wounding procedure lasted approximately one minute and photographs were taken immediately following the procedure. Once the wounding process was finished, the mice were placed in a clean cage and individually housed in order to prevent the mice from reopening each other's wounds. For one hour after the procedure, each mouse was monitored and their recovery was documented. The mice were assessed for recovery from anesthesia, as well as changes in behavior such as decreased grooming, decreased movement, etc. Body weights and food intake were also recorded daily. Since the goal of the study was to determine the impact of certain exercise intensities on the rate of wound healing, antibiotic ointment was not administered because of the effects it has on the wound healing process. The exercise training entailed running on a motorized treadmill adapted with individual lanes for the mice. The exercised mice ran at a low or high intensity, about sixty to eighty percent of their  $\text{VO}_2$  max.

Exercise took place in the morning for thirty minutes, five days a week, for three weeks on a 5% incline at 12 m/min (LEX) or 18 m/min (HEX). The mice were supervised at all times during exercise, and the control mice did not perform any exercise. To capture the changes in wound size, photographs were taken at the same time every day until the wounds were considered fully healed (less than 10% original size). Before taking the photographs, the mice were briefly anesthetized with isoflurane. Photographing took place in the morning and these images were used to analyze the wound sizes. Data was analyzed by comparing the changes in wound size of the low-intensity exercised mice and the high-intensity exercised mice. The wounds were quantified by using ImageJ (v1.48b; NIH, USA). This software allowed the pictures of the daily wounds to be traced and a measurement of the total wound area was generated. Once these measurements were obtained, the pattern of wound healing was statistically analyzed by repeated measure ANOVA (SPSS v.20, IBM Inc.).

## Results

While high-intensity exercise increased the healing rate slightly as compared with controls (0.4 days), this difference was not statistically significant. On the other hand, low-intensity exercise significantly increased the healing rate by 4.3 days (Fig. 1). The overall patterns of healing in terms of the size of the

wounds were also different by RMOVA ( $F_{1,18} = 4.7$ ;  $P = 0.023$ ).

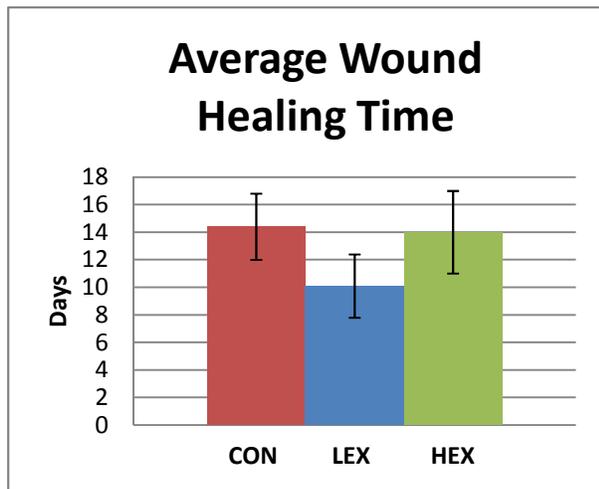


Fig. 1. Comparison of wound healing in high-intensity exercised mice, low-intensity exercised mice, and control mice.

## Conclusion

The hypothesis that high-intensity exercise would lead to better wound

healing was rejected. The research findings conclude that low-intensity exercise allows for quicker wound healing in diabetic mice than does high-intensity exercise or no exercise. The low-intensity exercised mice healed faster than the control mice, unlike the high-intensity exercised mice. Based on these results, the recommended exercise intensity to improve wound healing in those with type 2 diabetes should be low-intensity, approximately 60% of  $VO_2$  max. However, additional research should be done to further these results. The finding that low-intensity exercise improves wound healing in diabetic mice suggests it may be true in humans, but the effect needs to be confirmed.

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