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Effects of Submaximal Endurance Training and Vitamin D_3 Supplementation on Pain Threshold in Diabetic Rats

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Abstract

Background: According to beneficial effects of endurance training and vitamin D_3 in diabetes mellitus, purpose of this study is effects submaximal endurance training and vitamin D_3 supplementation on pain threshold in streptozotocin induced diabetic rats.
Materials and Methods: Male Wistar rats (250±20 g, N=40) were made diabetic by streptozotocin (60 mg/kg, subcutaneously). 72 h after injection diabetes induction was confirmed by tail vein blood glucose concentration (>300 mg/dl). Then animals were divided to five groups: diabetic control (DC), diabetic trained (DT), diabetic -vitamin D (DD), diabetic trained and vitamin D (DTD), and control (C). Animals were submitted to endurance training by treadmill and vitamin D_3 treatment (twice aweek, intrapretonally) for 4 weeks. 48 h after at the end of exercise and treatment protocol, we used tail-flick to assess the effects of training and vitamin D_3 on thermal pain threshold. We used one way ANOVA statistical analysis to compare differences between groups, significance level of $p<0.05$ was considered.
Results: Diabetic induced hyperalgesia were decreased significantly by vitamin D but not 4 weeks endurance exercise training. Concurrent effects of training and vitamin D on thermal pain threshold were not significantly higher than vitamin D effects alone.
Conclusion: It is concluded that vitamin D administration given at the time of diabetes induction may be able to restore thermal hyperalgesia. But effects of endurance exercise training needs to more investigation in diabetic rats.

Introduction

Increasing nerve damage is associated in chronic diseases such as diabetes. Diabetes leads hyperexcitability in central neurons (central sensitization) and generate spontaneous impulses in pain receptors. Excitability is associated respectively in the pain threshold by reducing and increased in the activation threshold and response to transient activity [1, 2]. High blood sugar (hyperglycemia) has a key role in the development of diabetic neuropathy. The roles of hyperglycemia in diabetic neuropathy have been reported recently, Smith et al. showed that individuals with impaired glucose tolerance (IGT-Impaired glucose tolerance) are neuropathic [3].

Furthermore, several studies have shown that endurance exercise includes physical activity involved with large muscles (such as running, cycling and swimming) for 20 to 60 minutes per session, 3 to 5 times a week with an intensity of 50 to 85% of maximal oxygen consumption (VO_2 max) [4] have a useful potential effects on metabolism, cardiac function, blood lipid levels and glycemic control [5]. Increase insulin sensitivity and improve vascular structures are other effects of endurance exercise [6, 7]. Endurance training can stimulate muscle glucose uptake by transport mechanism and regulates blood sugar in diabetics diseases [8]. Endurance training may be important factor in the prevention and treatment of neuropathic pain. It is well known that moderate intensity regular exercise through increasing antioxidant defense subsides oxidative stress and diabetic complications such as neuropathy [9]. Moreover, it has been found that exercise augments opioid system and growth and corticotrophin hormones are known pain relief following it [10].

Many years ago relationship between vitamin D_3 deficiency and diabetes mellitus are known. Since 1980, it has been shown that vitamin D_3 is essential for the function of pancreatic gland and insulin secretion. Vitamin D_3 associated with the normal function of pancreatic beta cells and immune cells have been identified [11].

Skalli et al. found that diabetic patients with vitamin D_3 deficiency were all suffering from neuropathy [12]. Vitamin D_3 may be due to potential effects on nerve function, which is involved in its pathology. Moreover, it seems vitamin D_3 needs increased in diabets patients undergoing endurance exercise training. On the other hand, recent studies have shown that vitamin D_3 also has antioxidant effects [12]. Thus, the beneficial and protection effects of vitamin D_3 and submaximal endurance exercise on nervous system and body metabolism, especially in diabetics, the purpose of this study is effects of endurance exercise and vitamin D_3 on pain threshold in diabetic rats.

Materials and Methods

In this experimental study all experiments were carried out on adult male wistar rats (8-10 weeks aged) weighting 200-250 g (Razi Institute, Karaj, Iran). Animals were housed four per cage under a 12-h light/dark cycle in a room with controlled temperature (20-25°C). Food and water were available ad libitum. The animals were divided into five equal groups (N=6); diabetic control (DC), diabetes and exercise (DT), diabetes supplement vitamin D_3 (DD_3), diabetic group combined exercise and vitamin D_3 (DD_3T) and healthy controls (C). Diabetes was induced by a single S.C injection of STZ (60 mg/kg). Three days later, fasting blood glucose levels were determined. Animals were considered diabetic if plasma glucose levels exceeded 300 mg/dl. Animals were submitted to endurance training by treadmill and vitamin D_3 treatment for 4 weeks.

They initially trained 10 m/min for 10 min in the first week, 10 m/min for 20 min in the second week, 14-15 m/min for 20 min in the third week, and finally 14-15 m/min for 30 min in the 4th week. Injection of vitamin D_3 (1 mg/1 ml propylene glycol per twice a week) was injected intraperitoneally (three day after diabetes induction) and continued for 4 weeks. The tail-flick test was used to assess the antinociceptive effect of all groups. Radiant heat was applied to the tail from 5-8 cm of the tip using a tail flick apparatus (Iran). Tail flick latency time was measured as the time from the onset of the heat exposure to the time of withdrawal of the tail. The intensity of radiant heat was adjusted to establish the baseline latencies for 3-5 seconds. The heat stimulus was discontinued after 12 seconds to avoid tissue damages. (Cut off point=12 s). All research and animal care procedures were performed according to international guidelines on the use of laboratory animals and were approved by Bu Ali Sina University ethical committee for animal research. All data are expressed as mean S.E.M. Differences. Among groups were statistically tested by one-way analysis of variance (ANOVA) with LSD as post hoc test. Probability values less than 0.05 were considered significant.

Results

Our data showed that all diabetic rats have low pain threshold in compared to healthy controls rats before starting the exercise protocol and vitamin D_3 therapy, In the other word, the diabetes has been cause hyperalgesia (increased sensitivity to painful stimuli) and decreased TF latency in diabetic rats (p<0.01) (Fig. 1). Four-week endurance exercise increases pain threshold in diabetic rats in compared to diabetic control but this increase is not statistically significant. It has been observed that vitamin D_3 increases pain threshold in diabetic rats in compared to diabetic control. Endurance exercise with vitamin D_3 increases significantly the pain threshold in compared to the control group (p<0.01). Figure 2 demonstrated that administration of vitamin D_3 can be realized more effectively influence on pain threshold in DD_3 rats group in compared to endurance exercise in DT rats group at the end of 4 weeks. No difference was observed between DD_3 and DD_3T rats group (Fig. 2).

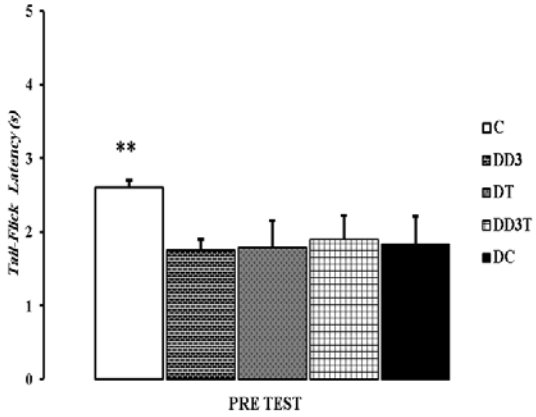

Figure 1. Tail-flick latencies in diabetic control (DC), diabetes and exercise (DT), diabetes supplement vitamin D3 (DD3), diabetic group combined exercise and vitamin D3 (DD3T) and healthy controls (C) (N=6) Onset of experiment. Data expressed as Mean±SD
**: Significantly different from C group (p<0.01).

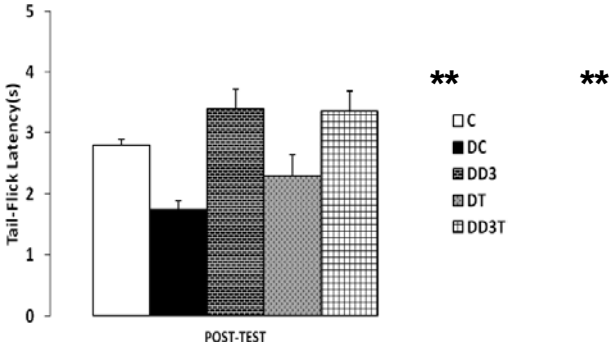

Figure 2. Tail-flick latencies in diabetic control (DC), diabetes and exercise (DT), diabetes supplement vitamin D_3 (DD_3), diabetic group combined exercise and vitamin D_3 (DD_3T) and healthy controls (C) (N=6) at the end of experiment. Data expressed as Mean±SD.
**: significantly different from DC group (p<0.01).

Discussion

Our results showed that 4 weeks of endurance training increased the pain threshold in diabetic rats, whereas this increase is not statistically significant. While vitamin D_3 significantly increased pain threshold in diabetic rats compared to diabetic control. Beneficial effects of regular exercise on glycemic control, insulin sensitivity, lipid metabolism and hypertension has been reported, however, little research has examined the benefits of exercise on diabetic neuropathy [13-15]. Studies have shown that regular exercise swimming prevent oxidative changes induced by streptozotocin and has neuroprotective effects and can prevent oxidative stress [16]. Other report indicated that oxidative stress as inducer of cellular damage decreased after treadmill exercise in patients with

diabetic neuropathy [17]. Long-term exercise may be effective in diabetic neuromuscular parameters. Several vascular and metabolic changes caused by exercise may be effective in improving diabetic neuropathy. Human and experimental studies suggest that short-term exercise stimulates endothelium-dependent vasodilatation. Higher vascular endothelial growth factor (VEGF) expression during short-term exercise has been proposed to play a role in endoneurial blood flow [18].

It is known that exercise training exposes the vessels to repeated episodes of hyperemia. The elevated shear stress from the increased blood flow of aerobic exercise augments vasodilatation over the long term by increasing the vascular expression of nitric oxide (NO) [19]. The increase of NO synthesis or bioavailability may be useful in preventing diabetes-induced changes in the polyol pathway [20]. In Chen et al. study [21] treadmill exercise decreased hyperalgesia in STZ diabetic rats. Nonetheless in this study exercise training don't decrease hyperalgesia in DT group rats. It may be for low training intensity. The speed of running was 30-60 m/min whereas in our study the final speed was 15 m/min. Bigdeli et al. [22] reported that 5 and 8 weeks swimming training could increase pain threshold in diabetic rats whereas in 3nd weeks swimming couldn't increase pain threshold significantly. In our study probably acclimatization to exercise needs long duration of training more than 4 weeks. Further investigations are needed to estimate the optimal intensity and duration of endurance training for neuropathy protection in diabetic persons.

We found that vitamin D_3 significantly increased pain threshold in diabetic rats compared to diabetic control. For many years, has been known that vitamin D_3 deficiency associated with skeleto-muscle and many other diseases such as cancer, microbial and metabolic [23, 24]. Some animal and human studies suggest vitamin D may be involved in peripheral and central nervous system development [25].

Vitamin D_3 may be involved in neuropathology due to potential effects on nerve function [26]. Several studies have reported an association between vitamin D deficiency and the prevalence of chronic pain [27]. Too much vitamin D receptors in sensory and motor areas of the brain and spinal cord shows different actions of the vitamin in the central nervous system. Recent studies show that constant use of vitamin D_3 in animals reduce age-related effects, such as reducing the number of damaged neurons in hypocampus and prevent stroke induced-neuron damaged [28].

Epidemiology of diabetic neuropathy suggests vitamin D_3 deficiency significantly higher in these patients, almost all patients with diabetic neuropathy faces with Vitamin D_3 deficiency [3]. Vitamin D_3 in the control of chronic pain, can increase the expression of growth factors such as NGF, GNDF, NT_3 (Neurotrophin 3) [29, 30].

Vitamin D_3 by reducing the autoimmune process, possibly by regulating the function of B lymphocytes and T, decreased production of inflammatory cytokines and increased production of inflammatory cytokines, resulting in the prevention and treatment of diabetes complications [9, 31].

We also observed in this study, there was not the synergistic effect between exercise and vitamin D_3 on pain threshold in diabetic rats. In other word there wasn't significant difference between effects of vitamin D_3 and vitamin D_3 combined endurance exercise on pain threshold in diabetic rats. But no convinced evidence exist that demonstrate exercise and physical activity increase need of vitamin D_3 [32]. Athletes training at altitude or in sports halls probably are failing to get enough sunlight are at risk of vitamin D_3 deficiency. Exercise can prevent oxidative stress [33] and vitamin D_3 with regulation of the immune, increase of nerve growth factors and inhibition expression of nitric oxide synthase and nitric oxide (NO and NOS) in the central nervous system [34] can prevent complications of diabetes, such as neuropathy. However, this synergistic effect wasn't observed in the pain threshold in DD_3T rats group probably due to the short duration of treatment protocols and long-term need of exercise to acclimatization. Vitamin D_3 may be a way to contain and treat pain in diabetic neuropathy. Effect of exercise on pain threshold in diabetic neuropathy may require further investigation.

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Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

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