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Review Article

Review on the Effect of Regular Physical Exercise on the Diabetic Peripheral Neuropathy

Anees Alyafei*, Wadha Albaker, Hissa Almuraikhi

Wellness program, preventive medicine, Primary Health Care Corporation, Doha, Qatar

***Address for Correspondence:** Anees Alyafei, Wellness In charge, Primary Health Care Corporation, Doha, Qatar. Mobile: +97455080077; E mail: qat900@yahoo.com

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ABSTRACT

Diabetes mellitus is the leading etiology for Diabetic Peripheral Neuropathy (DPN). There is no definitive treatment for it. Evidence progressively indicates the decisive role of regular Physical Exercise (PE) on enhancing DPN from clinical perspectives. However, there is a literature agreement on the consequence of PE on diabetes. But the evidence is still scattered and in need of further appraisal about exercise and DPN.

This review aims to address the DPN burden comprehensively from an epidemiological angel, clinical presentation & diagnosis, and management. Further, it explores the effect of regular PE on DPN on attempts to answer the reasons behind PE induce an effect on diabetic peripheral neuropathy.

Keywords: Diabetic Peripheral Neuropathy, Diabetes Mellitus, Physical Exercis

Abbreviations

CCM Corneal Confocal Microscopy, CRP C-reactive protein, DM Diabetes Mellitus, DN4 Douleur Neuropathique en 4, DNS Diabetic Neuropathy Symptom, DPN Diabetic Peripheral Neuropathy, HDL High Density Lipoprotein, HDL High Density Lipoprotein, IENFs Intra-Epidermal Nerve Fibers, IL-6Interleukin, LANSS Leeds Assessment of Neuropathic Symptoms and Signs, MNSI Michigan Neuropathy screening Instrument, NDS Neuropathy Disability Score, NHS National Health Service, NPQ Neuropathic Pain Questionnaire, PE Physical Exercise, QST Quantitative Sensory Testing, TCNS Toronto Clinical Neuropathy Score, TG Triacylglycerol, TNF-a Tumor Necrosis Factor-a, UENS Utah Early Neuropathy Scale, WHO World Health Organization.

Introduction

The pandemic of Diabetes Mellitus (DM) is associated with more prevalent systematic complications in the long term, including Diabetic Peripheral Neuropathy (DPN), a life quality demanding influencer. The epidemiology and burden of DPN are entirely documented in the literature, where almost half of the diabetic patients will suffer one form of DPN during their lifetime. The spectrum of clinical presentation of DPN ranges from asymptomatic to very painful manifestation that affects the daily habits and may result in los of function [1, 2].

There is no agreed medical management for DPN globally, but there is an ignored evidence-based knowledge of the effect of regular Physical Exercise (PE) on DPN's progression. This review aims to address the epidemiology of DPN, its clinical manifestation, and discuss the latest available evidence of the effect of the PE on the DPN progression.

Epidemiology of Diabetic Peripheral Neuropathy

The World Health Organization (WHO) reported global increase in the prevalence of DM among adults from (4.7%) during (1980) to (8.5%) in (2014). This increase is more profound in low and middle-income countries. There is gradual international increase owing to

alarming rates of obesity, economic evolution, nutrition transition and more sedentary lifestyle. Nevertheless, it is the most leading cause of cardiac, eye, renal failure, and lower limp amputation due to DPN [3, 4].

Definition

The definition of DPN is "the presence of symptoms and signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes." [5] It is the most known micro vascular complications among people with diabetes, which can present with central & autonomic nervous system and peripheral manifestations.

Diabetic Peripheral Neuropathy can clinically present as asymmetrical polyneuropathy, leading to massive nerve damage in the extremities predominantly the feet, and radiculopathy, and mononeuropathy [6-8].

Generally, the diabetic neuropathy classified into symmetric and asymmetric neuropathy. Where, symmetrical type is basically polyneuropathy with many subtypes. While, asymmetric group is more confined to one specific nerve dysfunction. It is very vital to know that DPN is subgroup of diabetic poly neuropathy. Diabetic peripheral neuropathy is the commonest subtype which accounts for (75%) of all diabetic neuropathies [9] (**Table 1).** Summarizes the classification of diabetic neuropathy.

Table 1: Classification of Diabetic Neuropathy.

Diabetic Neuropathy	
Symmetrical	• Diabetic Polyneuropathy • Diabetic peripheral neuropathy • Painful autonomic neuropathy • Diabetic cachexia • Insulin neuritis • Inflammatory demyelinating polyneuropathy • Polyneuropathy related to ketoacidosis
Asymmetrical	• Radiculoplexoneropathy • Lumbosacral, Thoracic, Cervical • Mononeuropathy • Nerve Specific • Median, Ulnar, Peroneal, Cranial

Burden

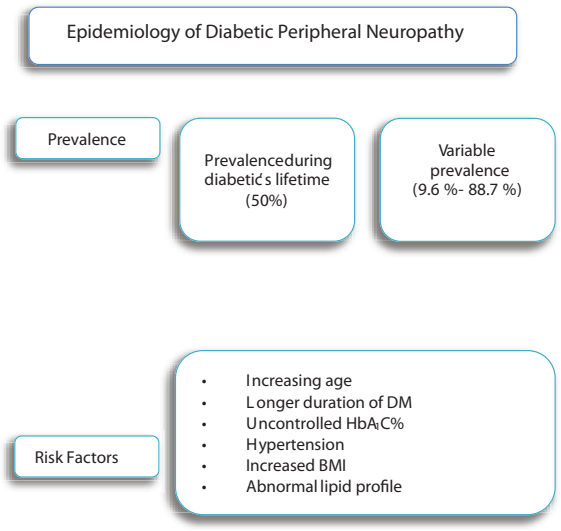
The prevalence of DPN significantly varies between (9.6% to 88.7%) worldwide. This is explained by global variability of the DM prevalence, duration of occurrence, associated risk factors, and glycemic control [10-14].

The long-term complications of DPN are well recognized in the literature mainly foot ulcer with lifetime incidence of about (25%) and is implicated in (50–75%) of nontraumatic foot amputations [15-17].

Risk Factors

The accumulated data demonstrated the following risk factors are strongly associated with development of DPN: increasing age, the longer duration of DM since diagnosis, uncontrolled HbA_1C%, presence of hypertension, postprandial blood glucose, overweight & obesity, high lipid profile mainly Triacylglycerol (TG), and High Density Lipoprotein (HDL) **(Table 2)** highlights the important epidemiological aspects of DPN [18, 19].

Table 2: Epidemiological Features of Diabetic Peripheral Neuropathy.



DM: Diabetes Mellitus, BMI Body Mass Index

The DPN considered as late DM complication and is greatly positively correlated with longer duration since the diagnosis of DM. The DOLOR study, Multicenter cross-sectional and longitudinal cohorts, involves thousands of participants addressed the different risk factors related to the neurological pain associated with DPN. Where, age, DM, cardiovascular disease, glycemic control plays significant role as risk factors to develop DPN. Further the study proposed the great interaction between genetic susceptibility and psychological factors & physio metabolic imbalance in the progression of DPN [20].

Direct Diabetic Peripheral Neuropathy Cost

It was not thoroughly reported the total direct cost of DPN from management and its related complications perspectives. In U.S., the direct cost was calculated to be ($4.6 and $13.7) billion during 2003 [21]. While, it was estimated to be (£252) million as reported by National Health Service (NHS) during (2003) in UK [22].

Clinical Presentation

Clinically detectable sensorimotor signs of DPN develop during about (10-15) years from the onset of diagnosis of DM in almost half of the patients [23].

There is well known inconsistency in the clinical presentation of DPN, arrays from non-painful asymptomatic to tingling sensation, numbness, burning, stabbing sensations, pain with wide severity, toes & foot infection with variable depth ulcers and non-traumatic amputations that subsequently lead to disability. The huge clinical manifestation capriciousness is related to the complexity of anatomical, metabolic, vascular and hemostasis mechanisms.

It is well reported that many metabolic and vascular factors involve in the pathogenesis of DPN. The most common form of DPN is distal symmetric polyneuropathy. It is obviously the above-mentioned symptomatology is not valid indicator for occurrence of DPN as half of the diabetic patients are found asymptomatic with clinical signs during routine diabetic clinic visits [24, 25].

Pathophysiology of diabetic peripheral neuropathy

Diabetic peripheral neuropathy is an outcome of multiple synergistic factors associated with DM nerve damage more rapidly progressive among poorly controlled patients. These factors are:

- Metabolic:
  - Including hyperglycemia and poor glycemic control beside another known metabolic imbalance in DM.
  - Mitochondrial dysfunction.
  - Increase in the Oxidative effect.
  - Activation of polyol pathway.
  - Increase advance glycated end products.
- Cardiovascular and pulmonary factors:
  - Ischemic factors include micro infarctions of the nerve and thickening and hyalinization of the walls of small blood vessels.
  - Associated hypertension
  - Poor peripheral circulation
  - Reduced pulmonary capacity
  - Endothelial dysfunction.
- Inflammatory factors:
  - Reduction in endoneurial oxygen tension in the sural nerves.
  - Oxidative stress.
  - Reduction of neurotrophic factors.
  - Increase in all inflammatory biomarkers and other molecular chronic inflammatory changes [26, 27].

Diagnosis

There are different schools of diagnosis of DPN with many readily available tools ranging from simplified clinical examination to more complicated and invasive ones which require equipment or specific settings. Such way for diagnosis varies in validity in term of sensitivity & specificity, cost, and time consumption. Among most common ways for diagnosis of DPN are the followings:

- Screening at the clinic

There are many documented tools used to screen patients with DM, usually during annual checkup, in form of interview or self-administered questionnaires that investigate the presence of the common symptoms of DPN and examine occurrence of any related sensory, motor, and autonomic deficits. All the known tools have moderate sensitivity and already validated in the literature.

The below listed tools are among the commonest tools:

- Douleur Neuropathique en 4 (DN4) [28].
- Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) [29].
- Diabetic Neuropathy Symptom (DNS) [30].
- Neuropathic Pain Questionnaire (NPQ) [31].

- Diagnosis and assessment of the severity

More diagnostic tools are existing, that combine both interview questionnaire and clinical assessment. Clinical assessment includes sensory, skin, motor, and other neurological examination to diagnosis and to help clinicians in classification of DPN severity.

- Toronto Clinical Neuropathy Score (TCNS)

Is a known reliable tool for the diagnosis and staging of PDN, particularly if there is profound sensorimotor dysfunction. It is used widely to detect early DPN as well as in many clinical and intervention studies. There are two versions original one that measures the response for symptoms, sensory tests and reflex scores out of 19 points. While the modified version measures both the symptoms and sensory test scores with a maximum 33 score [32].

- Michigan Neuropathy Screening Instrument (MNSI) is a validated tool that evaluates distal symmetrical DPN. It is made up of two major elements for evaluation: a 15-item self-administered questionnaire and a lower limps clinical examination. Abnormal responses in the tool summed up and total of 7 points and more indicates abnormal results [33, 34].
- Utah Early Neuropathy Scale (UENS) is another validated tool for assessing small nerve fibers damage, which is sensory in origin.
- It has five components to assess motor examination, pin sensation, hyperesthesia, large fibers sensation, and deep tendon reflexes. The total maximum score is (42), where tool scores points between (0-2) in each component [35].

- Neurophysiology and namely the nerve conduction study is classically used to assess objectively the DPN. Although, it is widely practiced as a gold standard test, but it requires especial equipment. It measures the large fibers conduction and unable to detect the smaller fibers dysfunction which usually occurs in the early disease course [36].
- Skin biopsy is also a gold standard diagnostic test for DPN. It permits quantification of Intra-Epidermal Nerve Fibers (IENFs). It has very decent and valid reproducibility. Nonetheless, it is invasive procedure, costly and requires expert staff to perform it [37].
- Quantitative Sensory Testing (QST) is objective assessment of DPN that quantifying the functions of both small and large nerve fibers. It is usually done through many user-friendly commercial devices. However, it is non-invasive, rapid and requires not much training, but it has variable sensitivity [38, 39].
- Corneal Confocal Microscopy (CCM) is another painless procedure to assess the DPN through reiterative ophthalmic imaging technique. It was reported a gradual loss of corneal sub-basal nerve fibers in DM patients with severe DPN. Currently, CCM is used to study DPN more largely as easy and rapid reliable test but it is very costly, and it necessitates skilled technical staff [40-42].

Management

Very restrict glycemic control is a well-recognized effective intervention of DPN, which needs a more comprehensive approach [43-45].

Multiple treatments are available for the management of neuropathic pain, slowing the ulceration, and significantly improving tissue healing [46]. There is some evidence about the effectiveness of regular PE on the progression of the DPN.

Physical Exercise and Diabetic Peripheral Neuropathy

Physical Exercise Recommendations for Diabetics

Physical exercise is defined as a structured, repetitive movements of group of muscles to obtain health-related or/ and skill-related benefits. Health-related benefits mainly include cardiopulmonary fitness, body components improvement, muscular strength & endurance, and flexibility. While skilled related benefits are coordination, reaction time, balance, agility, power, and speed [47-48]. Generally, PE can be of two major types aerobic and resistance exercises. Aerobic exercises are those exercises that increase the heart rate and energy lost. While resistance exercise where a group of muscles moves against weight [49].

For patients with DM, it is recommended by the American College of Sports Medicine to exercise a total of 300 minutes of moderate-intensity aerobic exercise per week, which is equivalent to 60 minutes per session, five times a week.

Best examples of aerobic exercises are cycling, swimming, and running. Furthermore, two to three sessions in non-consecutive days of resistance exercise of (60) minutes each per week greatly impact the general health of people with diabetes. Best example of resistance exercises is dumbbells lifting. Most recommendations are with having mixed PE programs of both aerobic and resistance exercises [50].

For maximum health benefits from the PE, all patients with DM must get medical clearance from their treating physician before commencing any PE program. Before start PE, it is advisable to check random blood sugar, which must not be less than (90mg/dl) to start the exercise, ingestion of 15-30gm of sugar is a must. If it is between (90-250 mg/dl), it is safe to perform PE, unlike if it is more than (250 mg/dl) where ketone tests and not starting the PE are recommended.

Moreover, a gradual warming up and a slow cooling down are particularly essential to prevent muscle cramps and glucose hypoglycemia. After the exercise session drinking enough water, resume regular eating and DM management regimen as prescribed by the treating physician [51].

Evidence of the Role of Exercise on Diabetic Peripheral Neuropathy

There is no definitive treatment for DPN, gathered evidence starts to grow regarding the significant effect of regular PE on the natural history and progression of DPN. Many studies support the effectiveness of the long-term supervised aerobic physical exercises on suppression and delay the commencement of DPN [52].

Patricia M. *et al.* found significant improvement in pain, neuropathic symptoms, increased intraepidermal nerve fiber branching and density & branching in a lower extremity through a pre & post-test study done among adult with DPN during (2012). Patricia M. *et al.* used a 10-week aerobic and strengthening PE program.

She found a statistically significant reduction in the pain by pain visual analog scale, improvement of neuropathic symptomatology assessed by MNSI questionnaire, nerve function measures, an increase of nerve branching by IENF, vast improvement on the skin biopsies. The study proposed that vascular circulation and intraepidermal nerve fibers branching is the primary explanation for the improvement of DPN symptomatology [53].

Similar findings were reported by Snehil Dixit and his team in (2014). A single-blinded controlled trial was conducted to assess the distal peroneal nerve's conduction velocity, sensation, and MNSI mean score following moderate-intensity physical aerobic training. Snehil Dixit and his team thought that great improvement is due to vascular and glycemic control associated with PE on diabetics [54].

Furthermore, Singleton J. Robinson *et al.* observed significantly reduced IENFD on both metabolic syndrome and diabetic groups. That was after 30- days' intervention that includes both regular PE and lifestyle modifications [55].

Gordon Smith confirmed the improvement in the IENFD, neuropathic pain, MNSI, and sensation on the lower limbs among patients with DPN. They underwent individualized PE and lifestyle modification program for one year. Smith and his team anticipated similar factors that improved the DPN as more metabolic control and enhancement in cardiovascular function. Nevertheless, increased cutaneous regenerative capacity was also explaining the enhancement of sensation of the lower limbs [56].

Other authors established the improvement in vibration perception threshold, distal nerve latency, and nerve conduction study readings. Also, the proportion of diabetic patients that developed long term DPN was expressively less comparing those on control group [57-59].

Additionally, many researchers consistently reported the significant improvement beyond the DPN measurements to more patient`s clinically and quality of life aspects. Such improvement is crucially essential for people with diabetes to prevent them from falls, balance-related trauma, and foot ulcers. Regular PE mainly aerobics enhances DPN walking distance, cardiopulmonary fitness, body fat mass, coordination, reaction time, performance-oriented mobility, joint mobility, postural stability, muscular strengthening, and overall mental, physiological, and glycemic control [60-65].

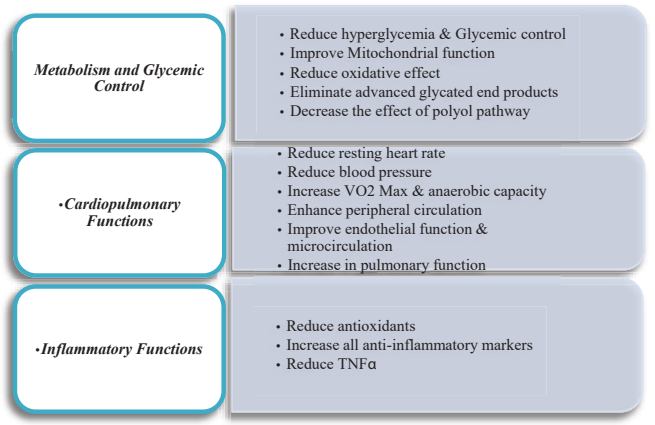
Mechanisms of Physical Exercise on Pathophysiology of Diabetic Peripheral Neuropathy

Regular PE reverses many of the factors mentioned earlier or slows down the progression due to the usual glycemic & metabolic control, cardiopulmonary function enhancement, and regular diabetic exercisers. Physical exercise on both aerobic and resistance exercise improves glycemic control & metabolism, cardiopulmonary function, and inflammatory biomarkers to an extent equivalent to some pharmacological intervention. The effect is comprehensive and simultaneous. (**Table 3)** Summarizes the possible mechanism by which PE improve DPN.

Effect of Physical Exercise on Metabolism and Glycemic Control

Physical exercise improves fasting glucose level and insulin sensitivity, regulates cellular glucose uptake, hepatic, and muscular glucose metabolism, resulting in more glycemic control on the DM patients. A regular PE is an attractive option for patients who prefer not to use any pharmacological interventions or wish to obtain additional glycemic control health benefits [66-68].

Table 3: Mechanisms of Physical Exercise on Pathophysiology of Diabetic Peripheral Neuropathy.



Physical exercise effect on glycemic control is due to overall reduction in the insulin sensitivity, such effect is divided into an acute effect the following changes are observed:

- Acceleration in the uptake of glucose into the active skeletal muscles by non-insulin-dependent mechanism.
- Stimulation of the hepatic gluconeogenesis to meet the need of energy by body systems.
- Regular PE can improve the instant actions of insulin that could be post-exercise till 2-3 days post-exercise session.
- The risk of getting hypoglycemic effect during or after the PE is minimal unless therapeutic insulin is used.
- Vigorous exercise may lead to transient hyperglycemia on some diabetic post-exercise.

While for those with daily habit of regular PE the following changes are observed on the long run:

- Reduction in the probability or deaccelerate occurrence of known long term DM complications. This is related to stabilization of metabolic, glycemic control, improvement of vascular, neurological, and cardiovascular functions.
- Reduction in all cause of mortality including the CVD.
- Increasing in overall skeletal muscle mass, with reduce in total body fat mass.
- Overall great improvement in mental, musculoskeletal, and quality of life.
- Reduction in the overall DM related inflammatory markers.

Some researchers added the evidence suggesting improvement of mitochondrial functions with a considerable increase in the mitochondrial capacity,

Intensity, and acceleration to the related metabolic pathways. Van Tienen *et al.* reached this conclusion after a cross-section study of the skeletal muscles following a one-year interpersonal supervised PE program on both prediabetics and DM patients [69]. Similarly, Phielix, Esther, *et al.*, confirmed the same findings not only on the DM patients but also on the control group. This is the typical outcome of regular exercise by increasing the anaerobic respiration capacity to meet the high need for more Oxygen [70].

Available data goes with fact of PE is protecting the tissue damage in DM patients by reducing oxidative effect. Several studies had shown that the number of free radicals was increased after PE. Where it is greatly utilized by the mitochondria for oxidative phosphorylation. Nevertheless, around (2-5%) of Oxygen used is converted into free radicals.

Physical exercise with moderate intensity positively modifies the oxidative homeostasis of tissues, via diminishing the basal levels of oxidative damage and increasing resistance to oxidative stress. Thus, PE is major adaptations factor in the antioxidant capacity, protecting body tissues from the effects of oxidative stress, thus preventing cellular damage [71-74].

Further metabolic explanation the effect of PE is by limitation of polyol pathway which is well known to lead to tissue damage in DM patients including nerves. Polyol pathway is metabolic process to convert the glucose into sorbitol and finally fructose, thus also called sorbitol-aldose reductase pathway [75, 76].

Robinson J. reported the healthy outcome of regular PE in reducing the pathogenic pathway of Polyol in both animal models and human trials. This was critically linked to the improvement of neuropathy symptoms due to the re-growth of cutaneous small-diameter nerve fibers [77].

Another mechanism of regular PE on improving the DPN is by reducing the advanced glycation end products, which are outcomes of exposure to hyperglycemia. They are considered as important biomarkers in development and tissue damage in DM patients. They could be proteins or lipids that become glycated. The best example is HbA_1 c, which is used to diagnose and monitor glycemic control in DM. Studies concluded they are essential causative factors in the DPN as well as other diseases like cardiac and Alzheimer's disease [78, 79].

A possible explanation of the effect of PE on DPN comes from the accumulative research, which indicated the protective role of regular PE on advanced glycation end products effect. Regular PE helps greatly in the reduction of the overall of advanced glycation end products [80-82].

Effect of Physical Exercise on Cardiopulmonary Functions

The acute and chronic effect of the regular PE on the cardiopulmonary system is well documented. It is not strict with the improvement in heart rate, systolic blood pressure, peripheral resistance, VO_2 Max, lung capacity, O_2 delivery & consumption, anaerobic capacity, and peripheral blood flow.

It includes improvement on the vascular walls, reduction in arterial stiffness, microcirculation on the deep tissues, reconstruction of the inner vascular compartment, and lowering the risk for micro ischemic events at the peripheral circulation level. These effects are also supported by lowering other risks associated with DM, such as improvement of lipid profile, weight reduction, over all physical fitness and loss of visceral fat [83].

The sensible explanation for the cardiopulmonary effect of PE in DM patients are the followings [84-86]:

- Reduction on resting heart rate is due to the cardiac muscles'

training on more significant needs, which leads to a relative physiological increase in the left ventricular muscle mass.

- Improvement in the blood pressure is due to increased sensitivity of aortic baroreceptors, which contributes to the regulation of systolic blood pressure. Furthermore, diastolic blood pressure is improved due to decreased peripheral resistance due to the PE associated vasodilatation effect. Reduced action of the sympathetic nervous system and the renin-angiotensin system were also documented.
- There is a parallel improvement in overall pulmonary function as a response to the demands of Oxygen and cardiac function. All the related lung volumes are increased on patients with DM following eight weeks PE program as studied by Saki *et al*., Where the diabetics had three sessions a week of moderate intensity exercise of (45-60) minutes length. The improvement in the pulmonary function was due to increase in forced vital capacity and forced expiratory volume [87].

Further evidence is going at the endothelial level. Many data considered PE as one vital cause of improving the endothelial function via an increase in NO activity, which exerts the anti-atherosclerosis effect. Such a result is due to the effect of PE induced catecholamines. Additionally, many molecules like Beclin1 and Autophagy-Related Gene 3 (Atg3) increases versus reduction in p62 a classical receptor for autophagy, which collectively boosted autophagy regulation on vessel's endothelium [88-90].

Another significant influencer on the effect of PE on the DPN is the noticeable decrease of oxidative stress. It is well documented to have great implications in the pathogenesis of vascular disease at both the micro and macro levels among DM patients. Regular exercisers develop long term adaptation by a hyper-regulation of basal nitric oxide (NO) production and increasing the body protection capacity against oxidative stress by increasing NO production [91].

Effect of Physical Exercise on Inflammatory Functions

There is accumulated evidence that regular PE improves antioxidant, immune capacities, preventing the onset and progression of chronic diseases that present low-grade systemic inflammation like DM [92, 93].

Further knowledge indicates that PE stimulates the production of many anti-inflammatory chemicals like interleukins, mainly Interleukin-6 (IL-6) by the skeletal muscles, C-reactive protein (CRP), (IL-1ra), and (IL-10). This leads into inhibition of Tumor Necrosis Factor-a (TNF-a), which is a proinflammatory mediator and insulin resistance enhancer.

Furthermore, IL-6 is known as stimulants for lipolysis, fat oxidation, and turnover. IL-10 inhibits the production of many other interleukins like IL-1a, IL-1b, IL-8, and macrophage inflammatory protein-a and TNF-a as well as other white cells activation chemicals. Such chemicals antagonize the chronic inflammatory characteristics of DM [94, 95].

The overall effect is a more anti-inflammatory status which comprehensively improves endoneurial oxygen tension in the sural nerves, reduces oxidative stress, and decreases neurotrophic factors. All the metabolic, cardiopulmonary, and inflammatory changes exert combined and PE dose-related effects to maintain healthy peripheral nerves function & associated vascular structure and ultimately improve overall DPN [96, 97].

Conclusion

Diabetic Peripheral Neuropathy is a very prevalent chronic DM complication with no definitive treatment. The pathophysiology of DPN is multifactor and complicated that is antagonized by PE. Recent evidence makes regular PE is very cost-effective attractive management modality for DPN.

There is agreement on the comprehensive antagonizing effect of the PE on metabolic, glycemic, cardiovascular, and inflammatory disturbance associated with DM.

Future research directions would be to investigate which exercise type is superior to improving DPN. Exercise alone is sufficient to alter DPN progression without other lifestyle modifications. Finally, is medication pulse PE more modifying the course of DPN than either one alone.

Conflict of Interest

Authors have no financial interest, arrangement, or affiliation with anyone in relation to this narrative review that could be perceived as a real or apparent conflict of interest in the context of the subject of this study.

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