Peripheral neuropathy and diabetes: Severity, Management and Future Perspectives.

By

Ferdous Hasan warin

16326014

A thesis submitted to the Department of Mathematics and Natural Sciences in partial fulfillment
of the requirements for the degree of
Bachelor of Science in Microbiology

Mathematics and Natural Sciences
Brac University
April 2022

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

Student's Full Name & Signature:

Ferdous hasan warin

Ferdous Hasan Warin

16326014

Approval

The thesis/project titled "Peripheral neuropathy and diabetes: Severity, Management and Future Perspectives." submitted by

1. Ferdous Hasan Warin (16326014)

Spring 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Science in Microbiology on 2022.

Examining Committee:

Supervisor:
(Member)

_____
Dr. Fahim Kabir Monjurul Haque
Assistant Professor, Department of Mathematics and Natural Sciences
Brac University

Program Coordinator:
(Member)

_____
Dr. Mahbubul H. Siddiqee
Assistant Professor, Department of Mathematics and Natural Sciences
Brac University

Departmental Head:
(Chair)

_____
Professor A.F.M. Yusuf Haider
Chairperson, Department of Mathematics and Natural Sciences
Brac University

Ethics Statement

No human or animal subjects were studied in this experiment. Also no harms of any environmental substances were done by this experiment.

Abstract/ Executive Summary

Diabetic neuropathy is a heterogeneous gathering of problems with very complicated pathophysiology furthermore, influences both physical and autonomic parts of the sensory system. Neuropathy is the most common persistent inconvenience of diabetes mellitus. Metabolic interruptions in the peipheral sensory system, including changed protein kinase C action, and expanded polyol pathway action in neurons and Schwann cells coming about because of hyperglycemia assumes a vital part in the advancement of diabetic neuropathy. These pathways are connected with the metabolic and additionally redox condition of the cell and are the significant source of harm. When this metabolic pathways activates it leads to oxidative stress which also activate hyperglycemia induced injury of cells and result into diabetic neuropathy. Though the problem is very common and serious therapeutics which target one particular mechanism has a very limited success rate. The approaches which are available basically depends on agents which modulate pathogenetic mechanisms (glycemic control) and minimize diabetic neuropathy symptoms. This review discuss the pathogenesis, as of now accessible remedial methodologies and future bearings for the administration of diabetic neuropathy.

Keywords: DPN, Hereditary neuropathies, Paraneoplastic neuropathy, Toxic neuropathies, Neuralgic amyotrophy, Central nervous system, Desipramine, Timipramine

DEDICATION

I would like to dedicate my work to my beloved parents, friends and family. I appreciate all of their trust and love for me which has given me the strength to work harder every time.

Acknowledgement

I would like to start by thanking the Almighty Allah for granting us to live this long and also fulfilling me with the strength and enough patience to finish my thesis work and accomplish all the objectives successfully.

Secondly, I would like to express my utmost gratitude to Professor A.F.M. Yusuf Haider, Chairperson of the Department of Mathematics and Natural Sciences, BRAC University, Assistant Professor, Dr. Fahim Kabir Monjurul Haque for allowing and providing us with all the opportunities to conduct my thesis work.

I am really honored and also grateful to my supervisor Dr. Fahim Kabir Monjurul Haque, Assistant Professor, Department of Mathematics and Natural Sciences, BRAC University. I will forever be obliged and grateful to him for his continuous support and useful knowledge throughout my work. He was also available whenever we needed some help or assistance regarding my work and paper. He also supported me morally and gave us much strength throughout the thesis to accomplish all the objectives of this work.

Most importantly, my gratitude knows no bounds to our parents, brothers, my wife who always believed in us no matter what the situation is and what the tasks we needed to accomplish. They are the reason of our sole existence and nothing can be compared to that.

Table of Contents

1. Background: Basic introduction, objective

Chronic diabetes mellitus is related with different problems like retinopathy, neuropathy, nephropathy, cardiomyopathy, vasculopathy, dermatopathy and encephalopathy [1]. Diabetic neuropathy has been characterized as the presence of side effects as well as indications of peripheral nerve brokenness in diabetics after prohibition of different causes (for example innate, awful, compressive, metabolic, poisonous, healthful, irresistible, invulnerable interceded, neoplastic and optional to other fundamental sicknesses) [2] [3]. Diabetic peripheral neuropathy (DPN) is portrayed by torment, paraesthesia, tangible misfortune and influences around half of individuals with significant dreariness, mortality and lessened personal satisfaction. The Toronto Agreement Panel on diabetic neuropathy as of late characterized DPN as a 'even, length-subordinate sensorimotor polyneuropathy inferable from metabolic and microvessel modifications coming about from persistent hyperglycemia and cardiovascular gamble covariates [4] . Agonizing side effects like consuming, shivering, shoot like ache or then again spearing (wounding) are supervised in around 33% of patients who are diagnose with DPN and 20% patients with diabetes diagnosis shows these symptoms [4] [5]. DPN begins in the toes furthermore, steadily moves proximally. When it is grounded in the lower appendages, it influences the upper appendages, with tangible misfortune following the average 'glove and loading' example of circulation. Huge engine shortages are not normal in the beginning phases of DPN [4]. These side effects are for the most part more regrettable around evening time and upset rest [6]. An irregularity of nerve conduction tests, which is habitually subclinical, gives off an impression of being the principal quantitative sign of the condition [7]. The patient doesn't normally grumble of shortcoming, yet when indications are available, they will quite often be tangible in nature. Indicative muscle shortcoming will in general foster later in the illness course. In addition, DPN is additionally connected with significant horribleness including gloom, weakness to foot or lower leg breaks, ulceration and lower-appendage removals [8] [9] [10] [11].

2. Epidemiology of Peripheral Neuropathy: Brief about the classification

Peripheral neuropathy is observed in different types of common and also in rare diseases. In addition, varied etiology, pathology with seriousness has been viewed. Peripheral neuropathy can be seen in one

nerve and at the same time also in multiple nerves. Further order relies upon a combination of phenomenological, obsessive, and hereditary or then again other aetiological elements. These things cause issues for disease transmission experts who, without concurred meanings of what comprises a case, find it challenging to depict examples of event of illness. Maybe it isn't extremely astonishing that data about the enlightening the study of disease transmission of peripheral neuropathy got from populace based investigations is scarce. Peripheral neuropathies are a different gathering of infections. To think about them all in all accentuate their commitment to the level of illness and inability locally, yet may darken intriguing epidemiological highlights that could prompt a superior comprehension of etiology.

2.1 Diabetic neuropathies:

Patients can suffer from multiple neuropathy for example autonomic, proximal, cranial or mono neuropathy. In some patients more than one type of neuropathy has been observed [12]. In one study concluded that they found 4% patients suffering from peripheral neuropathy along with diabetes which was conducted for 5 years of time frame. This has been now raised by 15% within time. Patients with both diabetes and cardiovascular issues showed higher mortality rates [13] [14]. In autonomic neuropathy liver disease has been observed too [15].

2.2 Hereditary neuropathies

Charcot-Marie-Tooth is a heterogeneous gathering of issues influencing the peripheral nerves and anterior horn cells of the spinal line. Together they establish the most regularly acquired type of peripheral neuropathy. Surveys have been done which show huge geological varieties in the recurrence of the condition [16]. The most common sort is the demyelinating structure, CMT1. In the others, different point transformations have been found in the PMP22, PO, and connexin 32 genes. Lastly, the X chromosome and represents X connected cases. Around 10% of families with autosomal prevailing CMT1 have once more duplications, typically, yet not continuously, emerging from duplication during male meiosis [17]. Amyloid neuropathy is the other normal reason for inherited neuropathy, being expected to statement of transthyretin, or less regularly different proteins, in the peripheral nerves, despite the fact that it might

likewise be a gained issue auxiliary to B cell dyscrasia and immunoglobulin light chain testimony. Mutation type in the transthyretin gene decides the settling amount and the introducing factors of the neuropathy.

2.3 Paraneoplastic neuropathy

Not many examinations have straightforwardly researched how generally neoplasms cause peripheral neuropathy. Lin et al [18] viewed that as 2-3% of 520 instances of peripheral neuropathy going to neurological focuses in Taiwan were because of neoplasm. Alternately between 2.5 and 5.5% of patients with lung or breast disease have clinical proof of a peripheral neuropathy [19]. Due to the influence of cancer radiculopathies which can be both focal and multifocal can be seen. In addition, plexopathy, neuropathy are also observed. They give the signal of paraneoplastic neuropathy. Specifically carcinoma in the lung causes this. Subacute tangible neuronopathy is a maybe trademark paraneoplastic condition, as around 20% of such cases truly do have a hidden carcinoma, which is generally a little cell lung carcinoma [20].

2.4 Toxic neuropathies

The peripheral nervous system is caused by numerous poisonous substances. Before, weighty metals, particularly Pb (lead), As (arsenic), represented instances of neuropathy. Those who are exposed to solvents like CS_2 (carbon disulphide), $C_6H_{12}O$ (methyl-nbutyl ketone) has been also showed complications.

2.5 Neuralgic amyotrophy

In one investigation 11 cases were found which has a yearly rate of 1.6 for 100000 population which was done for 12 years of a time frame involving neuralgic amyotrophy [21]. Retrospective investigation proposed different precursor occasions: different irresistible ailments, immunisations, medical procedure, intravenous medication abuse, intravenous organization of radiological difference medium [22]. More vulnerability has been observed in patients with

central injury and injured joints. This condition is considered as autosomal prevailing characteristic which has linkage with chromosome number 17 (Long arm) [23]. Transformation in a crucial gene which is PMP22 is also related [24].

3. Diabetic Peripheral neuropathy: Introduction about peripheral neuropathy

Persistent diabetes mellitus is related with different entanglements like retinopathies, neuropathies, nephropathies, cardiomyopathies, vasculopathies, dermatopathies and encephalopathies [25]. Diabetic neuropathy has been characterized as the presence of side effects and additionally indications of fringe nerve brokenness in diabetics after avoidance of different causes (for example innate, horrendous, compressive, metabolic, harmful, healthful, irresistible, resistant interceded, neoplastic and auxiliary to other fundamental sicknesses) [26]. DPN is described by torment, tactile misfortune and influences roughly half of individuals with extensive grimness, mortality and reduced personal satisfaction. The Toronto Agreement Panel on diabetic neuropathy as of late characterized DPN as a 'balanced, length-subordinate sensorimotor polyneuropathy owing to metabolic and microvessel changes coming about from ongoing hyperglycemia and cardiovascular gamble covariates [27]. Agonizing side effects like consuming, shivering, shoot like ache or then again spearing (wounding) are supervised in around 33% of patients who are diagnose with DPN and 20% patients with diabetes diagnosis shows these symptoms . DPN begins in the toes and then continuously it progress to nearest parts. If first affects the lower parts of the body and then proceed to upper parts. Huge engine deficiencies are not normal in the beginning phases of DPN [28]. These side effects are by and large more regrettable around evening time and upset rest. An irregularity of nerve conduction tests, which is every now and again subclinical, gives off an impression of being the primary quantitative sign of the condition [29] [30]. The patient doesn't normally gripe of shortcoming, however when side-effects are available, they will generally be tangible in nature. Indicative muscle shortcoming will in general foster later in the sickness course. In addition, DPN is likewise connected with significant dreariness including discouragement, defenselessness to foot or lower leg cracks, ulceration and lower-appendage removals.

4. Clinical Feature of Diabetic Peripheral neuropathy: Analysis about patients from different studies

People who are suffering from diabetes also commonly suffer from DPN. By doing nerve tests this condition can be primarily identified [31]. Mostly one cranial nerve is affected and also central nerve is affected which shows symptoms in leg like weakness and pain[32]. Critical motor deficiencies are not normal in the beginning phases of DPN [32]. The patient doesn't ordinarily whine of shortcoming, however when side effects are available, they will more often than not be tangible in nature. Indicative muscle shortcoming will in general foster later in the sickness course. Agonizing side effects like consuming, shivering, shoot like ache or then again spearing (wounding) are supervised in around 33% of patients who are diagnose with DPN and 20% patients with diabetes diagnosis shows these symptoms [32]. These side effects are by and large more terrible around evening time and upset rest [33]. Along with agonizing side effects during the day, this frequently prompts a decrease in person's capacity to perform everyday exercises [33]. The weight of agonizing DPN was accounted for to be significant in one review, which brought about a diligent uneasiness in spite of polypharmacy and high asset use, and prompted constraints in everyday exercises and unfortunate fulfillment with medicines that were frequently considered to be unseemly [34]. Constant diligently difficult DPN can be very troubling and may be related with significant wretchedness along with nervousness [34]. Critically, side effects are not a solid mark of the seriousness of the nerve harm. A few patients who shows numbness in their foot are at high risk for toe or foot ulcers which results in not recovering from lesions. They can't detect temperature and regularly consume themselves while, for instance, cooking or pressing, and furthermore experience issues taking care of little objects. People with loss of sensation frequently support stabbings, rubbing injury and at most they can lead to removal due to infection. Nonetheless, if proper care is taken in lot of times this situation can be treated [35].

Neuropathic torment is one of the most common side effects in DPN patients. This condition is very difficult to treat. DNP creates in 10% to 20% of the diabetic populace generally speaking, and can be seen as in 40% to 60% with archived neuropathy [36] [37] [38]. Like different sorts of neuropathic torment, DNP is portrayed by copying, electric, and wounding sensations regardless of deadness. Every now and

again, patients create allodynia (difficult sensations to harmless improvements) and hyperalgesia (expanded aversion to excruciating boosts). Notwithstanding, not exactly half are treated for torment, in spite of numerous accessible powerful therapies [38]. There are various processes to identify if patients are getting benefit from these therapies [39].

5. Risk Factor

In different studies it has found that patients who are suffering from type 1 or 2 diabetes they are at risk to affect by DPN. However, there are many different factors also working behind this. In one study which involved 3250 patients who were found with type 1 diabetes was done. They concluded that diabetes is linked with the DPN [40]. Mostly the connection between DPN and diabetes stays at 28%, however due to other factors the percentage shows difference which can raise up to 41%. However even with lower diabetes some people shows symptoms related to DPN [40]. One study that involved type 1 diabetic patients shows only 25% of the patients suffered from DPN and particularly those who have poor control over their diabetes [51]. This can be improved if patients focus on a good lifestyle by quitting smoking and taking care of hyper tension and other cardiovascular problems [41]. Also taking care of obesity [42] and consumptions of fat sources [42] should be maintained. High level of TGA in the patients are also observed [43]. Block in the veins and arteries due to TGA, fat has showed raised level of mortality [44].

6. Neuropathic pain in Diabetes

There are some theories of which explains neuropathic pain but mostly this is still unexplainable [45]. Other potential systems remember the relationship of expanded blood glucose unstability for the beginning of neuropathic trauma [46] [47], an expansion in peripheral nerve epineurial blood stream, adjusted foot skin microcirculation [47], decreased intraepidermal nerve fiber thickness with regards to right on time neuropathy [48], an expansion in thalamic vascularity [49] and autonomic brokenness [11].

Some broad research are saying that total sensory system can be affected because of diabetes which later can cause multiple problems which includes infection or decay in cerebrum [50]. CNS or central nervous system can be affected further.

7. Central nervous system and spinal cord

In many studies spinal cord collusion has been observed but most of these researches were not particularly focused on DPN patients [51]. Symptoms where patients feel electrical tingling type of sensation in their spinal cord has raised the chance of spinal cord collusion [52]. Utilizing a painless MR imaging strategy, patients with both diabetes and DPN and patients without diabetes and with DPN [53] has been observed [54]. When the result was observed it showed that patients with DPN and diabetes together has spinal cord collusion and mostly they showed symptoms related to these [67].

8. Treatment management:

Treatment process can be divided into three phases:

1. Slow progression: Consistent maintenance of diabetes can slower the progression of peripheral neuropathy
2. Relieving the pain: There are few medicines that can help to minimize the nerve pain which in some cases suggested to start with Pregabalin (Lyrica) along with other options such as Gabapentin. Though side effects like incorporate sleepiness, dazedness and enlarging can be observed. A few antidepressants ease nerve pain. Some examples are Tricyclic antidepressants amitriptyline, desipramine (Norpramin) etc. However dry mouth and spleepiness can be observed.
3. Complication Management: Along with diabetic peripheral neuropathy some complication like urinary tract infection, digestive problems, low blood pressure on standing (orthostatic hypotension and dysfunction can occur. Thus consultation with doctor for these symptoms is also needed.

9. Conclusion:

DPN has now become very common in patients who are suffering from diabetes and if we talk about numerical value it can go up to 50%. It can lead to pain, grimness and even death. Most researchers believe

that controlling glucose level is the best solution of this problem. However there are other aligning factors. In diabetic patients cardiovascular diseases are also observed and they are also linked to DPN. Thus these type of diseases are also advised to control. Prevention is the main theory here because if the DPN with excoriating pain cannot be solved easily. TCA, the SNRIduloxetine and the anticonvulsant pregabalin are used for the 1st line of treatment. Combination of treatment may be helpful with more sseverepain. However, more studies need to be done. Studies of treatments which have long effects result in the trial is needed.

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