DOI: https://doi.org/10.53555/nnmhs.v8i12.1466 Publication URL: https://nnpub.org/index.php/MHS/article/view/1466

CIGARETTE SMOKING AND DIABETIC PERIPHERAL NEUROPATHY : A SYSTEMATIC REVIEW

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Abstract

It is common knowledge that smoking cigarettes is associated with a wide range of detrimental effects on one's health, including the development of a number of diseases and conditions that can manifest in any organ or system of the body. Diabetes can lead to a wide variety of microvascular problems, some of which include ulcers and amputations, dysfunctions in erectile function and autonomic function, and erectile dysfunction. DPN, or diabetic peripheral neuropathy, is a microvascular complication of diabetes that is part of a larger spectrum of diabetic problems. It is also known as distal symmetrical polyneuropathy or sensorimotor neuropathy. The most common of these problems is diabetes peripheral neuropathy (DPN), which affects approximately 30 percent of persons who have diabetes types. It is largely agreed upon that oxidative stress is the final mechanism that is accountable for the cellular damage seen in diabetic neuropathy. [Citation needed] [Citation needed] It is defined by high levels of persistent generation of reactive oxygen species (ROS), which can include ozone, superoxide, hydrogen peroxide, singlet oxygen, and organic peroxides in cells. ROS can also be produced when cells are exposed to persistently high quantities of singlet oxygen. The term "peroxidative stress" can also be used to refer to this condition. Although there is inconsistency in the relationship between diabetic peripheral neuropathy and smoking cigarettes, research that reveal an association between the two show that the prevalence of the condition is greater than 10%.

Keyword: *Cigarette; Diabetes Mellitus; Peripheral Neuropathy; Smoking*

INTRODUCTION

The most prevalent use of smoking as a method of consumption is for tobacco, primarily in the form of burnt tobacco and primarily cigarettes. Although the prevalence of cigarette smoking is declining in a number of nations, it continues to pose a global hazard to public health, especially in central and south-east Asia as well as eastern Europe, which have the highest number of smokers. The World Health Organization (WHO) projects that there will be 1.5 billion smokers worldwide by 2050.[1]

It is well-known that cigarette smoking has devastating negative effects on health, causing a wide variety of diseases and disorders throughout every organ and system of the human body. The risks of acquiring cardiovascular illnesses, cancer, and chronic obstructive pulmonary diseases (COPD) are inversely proportional to the number of cigarettes smoked daily and the duration of smoking. Prolonged abstinence from smoking reduces these risks.[2,3]

Aside from the smoking epidemic, another deadly pandemic looms: diabetes mellitus (DM). Since 1980, the number of adults with diabetes in the world has quadrupled, surpassing 400 million, with a projection of roughly 650 million by 2040.[4–6] The significant rise in diabetes prevalence poses a formidable public health concern. Diabetes mellitus is defined by chronic hyperglycemia, which causes irreversible damage to blood vessels, resulting in macrovascular (coronary artery disease, stroke, peripheral arteriopathy, and erectile dysfunction) and microvascular (retinopathy, nephropathy, and diabetic neuropathy) complications.[1,7,8]

Diabetes can cause a wide range of microvascular complications, including ulcers and amputations, erectile dysfunction, and autonomic dysfunction. Diabetic peripheral neuropathy (DPN), also known as distal symmetrical polyneuropathy or sensorimotor neuropathy, is a microvascular complication of diabetes that is part of a larger spectrum of diabetic complications. DPN is the most prevalent of these complications, affecting around 30 percent of people who have diabetes types.[9,10]

Numbness, tingling, or a burning feeling can be experienced in the legs and hands, manifesting themselves commonly in a "stocking and glove" distribution 1. In the end, certain individuals with poorly controlled disease may experience muscle weakening, loss of reflexes, and foot abnormalities, which can lead to the final clinical sequelae of ulceration, the possibility of infection, and amputation.[7,10,11] To prevent the beginning of diabetes and postpone the development of its complications, public health policies and programs must address the primary modifiable risk factors. The link between cigarette smoking and diabetic peripheral neuropathy was demonstrated in this paper.

METHODS

Protocol

During the entirety of the process of carrying out this systematic review, we ensured that we adhered to the guidelines that are specified in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist. On top of these principles, which served as the foundation, the regulations that governed the process of carrying out this systematic review were constructed. These guidelines were the foundation.

Eligibility Criteria

This systematic review was developed to analyze papers on "cigarette smoking" and "diabetic peripheral neuropathy". These are the subjects that were covered in depth in the research that was taken into account. The following requirements have to be met in order for your work to be taken into consideration: 1) Articles have to be written in English. 2) Articles have to have been published after 2012, but before the time this systematic review is created. The following kinds of textual contributions will under no circumstances be considered for inclusion in the anthology: 1) Editorial letters, 2) contributions that do not have a Digital Object Identifier (DOI), and 3) article reviews and submissions that are comparable to those that have previously been published in the journal.

Search Strategy

The search for studies to be included in the systematic review was carried out from December, 1st 2022 using the PubMed and SagePub databases by inputting the words"cigarette smoking" and "diabetic peripheral neuropathy". Where *("cigarette smoking"[MeSH Terms] OR ("cigarette"[All Fields] AND "smoking"[All Fields]) OR "cigarette smoking"[All Fields]) AND ("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]) AND ("peripheral nervous system diseases"[MeSH Terms] OR ("peripheral"[All Fields] AND "nervous"[All Fields] AND "system"[All Fields] AND "diseases"[All Fields]) OR "peripheral nervous system diseases"[All Fields] OR ("peripheral"[All Fields] AND "neuropathy"[All Fields]) OR "peripheral neuropathy"[All Fields])* is used as search keywords.

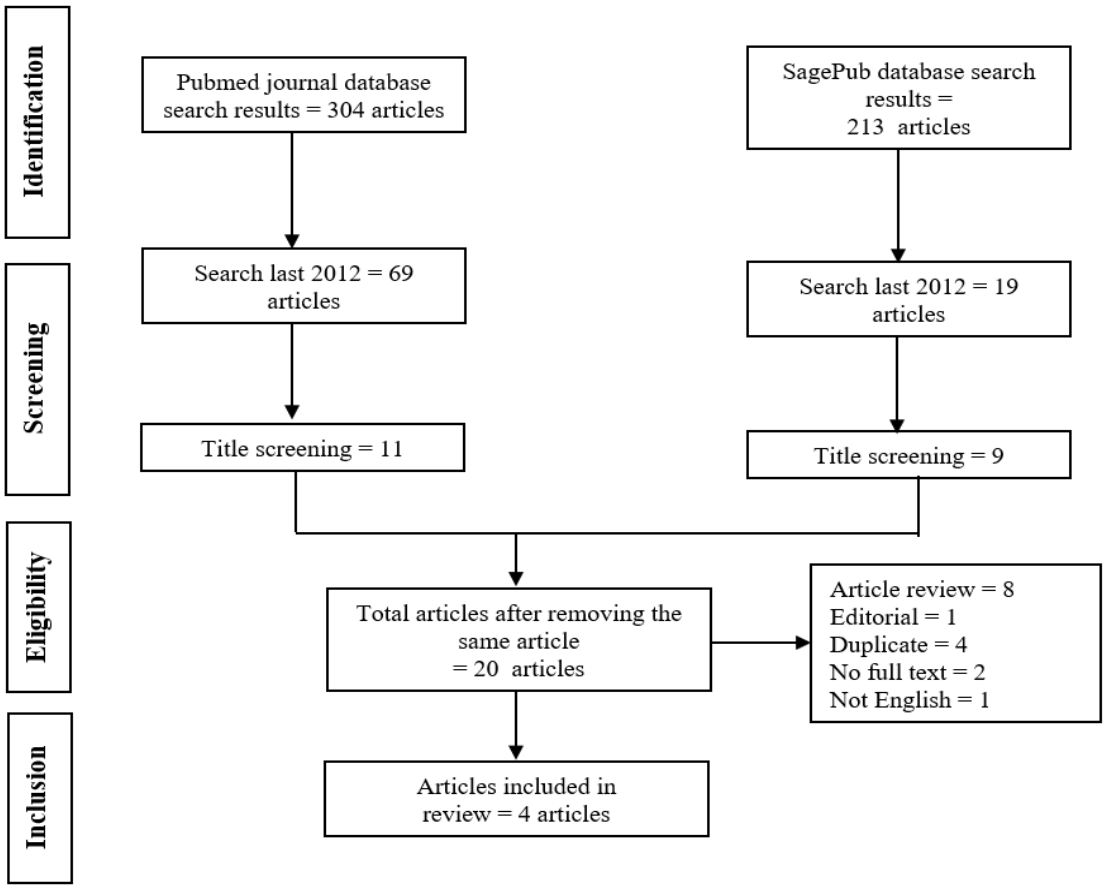

Figure 1. Article search flowchart

Data retrieval

After conducting a literature analysis and examining the titles and abstracts of previously published research, the author of the study revised the criteria for what should and should not be included in the study. This update was made after the author examined previously published research. This was done in order to establish what should be included in the study and what should not be included in it. The author made these adjustments after doing a thorough review of other studies that had been presented in prior publications.

During the process of compiling the systematic review, the only research projects that were deemed to be relevant were those that satisfied each and every condition. These studies were the only ones that were regarded to be relevant. In order to guarantee that the evaluation is as comprehensive as it potentially can be, this step was taken. It is feasible to collect information about each individual study, such as the title of the study, the author of the study, the publication date of the study, the place of origin of the study, the research design, and the research variables. This information may be found online. It is possible for this information to be transmitted to the recipient in any one of a number of different formats.

Quality Assessment and Data Synthesis

In order to determine which studies could be taken into consideration, the authors conducted their own independent reviews of a subset of the research that was listed in the titles and abstracts of the papers. After this step, the full texts of the studies that satisfy the inclusion criteria for the systematic review will be read in order to determine which studies can be used as final inclusions for the purposes of the review. This will be done so as to ensure that the review is as accurate as possible.

RESULT

A study in 2022 showed prevalence of DPN was 26.6%, in which mild grade was 17.3%, moderate grade was 8.2% and severe grade was 1.1% in total. Age (OR = 1.73, 95% CI 1.12– 2.67, p = 0.012), smoking (OR = 1.64, 95% CI 1.03– 2.62, p = 0.037), poor control HbA1c (OR = 2.66, 95% CI 1.23– 5.76, p = 0.01), 24-h urinary albumin (24hUA) (OR = 2.49, 95% CI 1.26– 4.94, p = 0.007), and diabetic retinopathy (OR = 3.17, 95% CI 1.46– 6.89, p = 0.002) significantly increased the risk for DPN. In multivariate logistic regression analysis, hypertension (OR = 2.96, 95% CI 1.16– 7.55, p = 0.023), triglyceride (OR = 1.50, 95% CI 1.11– 2.03, p = 0.009), albumin (OR = 0.85, 95% CI 0.75– 0.95, p = 0.005), and fGLP-1 (OR = 0.79, 95% CI 0.67– 0.93, p = 0.005) correlated with DPN. The fGLP-1 concentrations were reduced significantly in DPN ($p < 0.001$). In particular, male patients with DPN had a significantly lower fGLP-1 levels than those without DPN ($p < 0.001$).[12]

Prevalence of peripheral neuropathy was 10.4% based on the MNSI-history score of ≥7 and 25.6% based on the MNSI-sign score of ≥3. Logistic regression analysis revealed that HbA1c [OR=3.41, 95% CI; 1.15– 10.16] and physical activity [OR=4.99, 95% CI; 2.21–11.29] were significant predictors of the MNSI-history score. Age [OR=1.06, 95% CI; 1.03–1.09], height [OR=1.06, 95% CI; 1.02–1.10], systolic blood pressure [OR=1.03, 95% CI; 1.01–1.06] and duration of diabetes [OR=1.08, 95% CI; 1.04–1.13] were significant predictors of the MNSI-sign score.[13]

Sarihin, et al (2013) conducted a study with 102 male and 100 female. Their age ranged from 16 to 88 years (M = 56.19 ± 14.31 years). The mean duration of diabetes was 10.69 ± 8.24 years. The overall prevalence of diabetic PN was (54.45 ± 49.92). The prevalence of diabetic PN was higher in women than men (55 ± 50 VS 53.92 ± 50.09). There were significant increase in prevalence of PN among DM patients with non target glycosylated hemoglobin (HbAIc) ($p < 0.05$), age ≥ 65 years ($p < 0.05$), duration of diabetes ≥10 years and body Mass index (BMI) ≥ 25 kg/m2 ($p < 0.05$).[14]

Bansal, 2014 showed KDM had a greater frequency than NDDM, 33.7% (95% CI: 31.42–36.01) versus 9.2% (95% CI: 6.3–12.2; P 0.001). The prevalence of mild, moderate, and severe neuropathies were, respectively, 8.06, 14.55, and 6.63 percent. Age (P 0.001), duration of diabetes (P 0.001), dyslipidemia (P = 0.03), glycated hemoglobin (P 0.001), presence of additional microvascular problems (P 0.001), macrovascular complications (P = 0.003), and alcoholic status (P 0.033) were found to be linked in a regression analysis. No gender-specific differences were identified in the mean age at diabetes diagnosis, the mean age at neuropathy diagnosis, or the length of DPN development in females and males.[15]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Dinh, 2022[12]	Vietnam	Cross-sectional descriptive study	473	The prevalence of DPN was 26.6%, in which mild grade was 17.3%, moderate grade was 8.2% and severe grade was 1.1% in total. Age (OR = 1.73, 95% CI 1.12– 2.67, p = 0.012), smoking (OR = 1.64, 95% CI 1.03–2.62, p = 0.037), poor control HbA1c (OR = 2.66, 95% CI 1.23– 5.76, p = 0.01), 24-h urinary albumin (24hUA) (OR = 2.49, 95% CI 1.26– 4.94, p = 0.007), and diabetic retinopathy (OR = 3.17, 95% CI 1.46– 6.89, p = 0.002) significantly increased the risk for DPN. In multivariate logistic regression analysis, hypertension (OR = 2.96, 95% CI 1.16– 7.55, p = 0.023), triglyceride (OR = 1.50, 95% CI 1.11– 2.03, p = 0.009), albumin (OR = 0.85, 95% CI 0.75– 0.95, p = 0.005), and fGLP-1 (OR = 0.79, 95% CI 0.67– 0.93, p = 0.005) correlated with DPN. The fGLP-1 concentrations were reduced significantly in DPN ($p < 0.001$). In particular, male patients with DPN had a significantly lower fGLP-1 levels than those without DPN ($p < 0.001$).
Al-Kaabi, 2014[13]	Uni Emirates Arab	Cross-sectional descriptive study	394	Peripheral neuropathy prevalence was 10.4% based on an MNSI-history score of ≥7 and 25.6% based on an MNSI-sign score of ≥3. HbA1c [OR=3.41, 95% CI; 1.15–10.16] and physical activity [OR=4.98, 95% CI; 2.21–11.29] were significant predictors of the MNSI-history score, as determined by logistic regression analysis. Significant predictors of the MNSI-sign score were age [OR=1.06, 95% CI; 1.03–1.09], height [OR=1.06, 95% CI; 1.02–1.10], systolic blood pressure [OR=1.03, 95% CI; 1.01–1.06], and duration of diabetes [OR=1.08, 95% CI; 1.04–1.13].
Sarihin, 2013[14]	Jordan	Cross-sectional descriptive study	202	The sample consisted of 102 male and 100 female patients. Their age ranged from 16 to 88 years (M = 56.19 ± 14.31 years). The mean duration of diabetes was 10.69 ± 8.24 years. The overall prevalence of diabetic PN was (54.45 ± 49.92). The prevalence of diabetic PN was higher in women than men (55 ± 50 VS 53.92 ± 50.09). There were significant increase in prevalence of PN among DM patients with non target glycosylated hemoglobin (HbAIc) ($p < 0.05$), age ≥ 65 years ($p < 0.05$), duration of diabetes ≥10 years and body Mass index (BMI) ≥ 25 kg/m2 ($p < 0.05$).
Bansal, 2014[15]	India	Cross-sectional descriptive study	586	KDM had a greater frequency than NDDM, 33.7% (95% CI: 31.42–36.01) versus 9.2% (95% CI: 6.3–12.2; P <0.001). The prevalence of mild, moderate, and severe neuropathies were, respectively, 8.06, 14.55, and 6.63 percent. Age (P <0.001), duration of diabetes (P <0.001), dyslipidemia (P = 0.03), glycated hemoglobin (P <0.001), presence of additional microvascular problems (P <0.001), macrovascular complications (P = 0.003), and alcoholic status (P <0.033) were found to be linked in a regression analysis. No gender-specific differences were identified in the mean age at diabetes diagnosis, the mean age at neuropathy diagnosis, or the length of DPN development in females and males.

DISCUSSION

Diabetic peripheral neuropathy is one of the most prevalent consequences that can arise from diabetic foot ulcers. It affects roughly 30 percent of people who have diabetes, and more than 50 percent of those with type 2 diabetes who are over the age of 60. Seventy-eight percent of patients who have foot ulcerations also have peripheral neuropathy. There are many different kinds of nerve damage that can occur in diabetic patients, such as distal symmetrical polyneuropathy, small-fiber predominant neuropathy, autonomic neuropathy, diabetic amyotrophy, mononeuritis multiplex, and so on.[13,16,17]

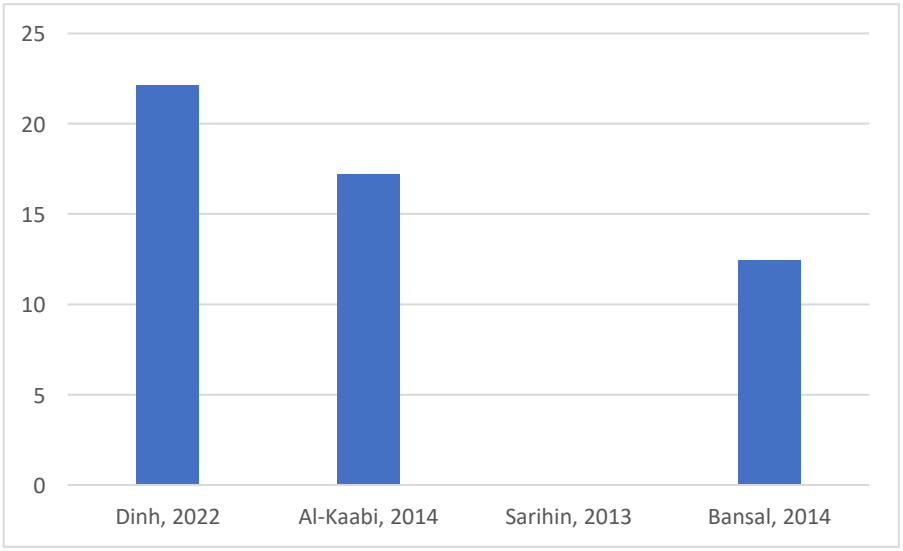

Figure 2. Prevalence DPN and cigarette smoking in this study, *Sarihin et al (2013) not showed a signifficant association

Among these, distal symmetrical polyneuropathy affects the longest nerve fibers first, and small-fiber sensory neuropathy primarily affects pain and temperature sensations, both of which are closely related to the beginning of foot ulceration. Axonal degeneration, demyelination of the nerve fibers, proliferation of Schwann cells, remyelination, hypertrophy of the basal lamina, and other pathologies are all part of the pathology of diabetic neuropathy. It is common for distal symmetrical sensory loss to be the initial step on the road to foot ulceration.[16,17]

If a person is unable to feel pain in response to an injury, this may eventually lead to the development of chronic plantar ulcers. In addition, diabetic autonomic neuropathy can lead to the development of arteriovenous shunting, neuropathic edema, and dry skin in the foot. Claw foot is a form of motor neuropathy that is characterized by a clawing of the toes and plantar flexion of the metatarsal heads. These autonomic and motor neuronal changes are typical contributors to the production of callus and ulceration.[16,17]

It is generally accepted that the ultimate mechanism responsible for the cellular damage seen in diabetic neuropathy is oxidative stress. It is distinguished by high levels of persistent formation of reactive oxygen species (ROS), which can include ozone, superoxide, hydrogen peroxide, singlet oxygen, and organic peroxides in cells. This condition is also known as peroxidative stress. Damage caused by oxidation is especially susceptible to occurring in the neurological system. A number of signaling pathways that might lead to oxidative stress in nerve fibers could be activated if hyperglycemia, hyperlipidemia, and decreased insulin sensitivity are present. Demyelination and damage to axons are the results of excessive ROS, which ultimately leads to diabetic neuropathy.[11,18]

Oxidative stress is one of the mechanisms that could be exacerbated by cigarette smoking, which could make diabetic neuropathy worse. It has been established that smoking cigarettes is a contributory factor in the development of diabetic neuropathy. Cigarette smoke is a source of free radicals as well as oxidants, and this can cause oxidative stress in the cells of many organs, including the nervous system and blood vessels. This can result in cellular damage and even apoptosis in some cases. There is evidence both in vitro and in vivo that cigarette smoke contains substances known as "glycotoxins".[19,20]

These glycotoxins are extremely reactive glycation products, and they have the potential to rapidly cause the production of advanced glycation end-products (AGE) outside of the cells. The increased levels of modified proteins and lipids in the circulation of smokers bind to the receptor for AGE, which in turn activates nicotinamide adenine dinucleotide phosphate oxidase and induces expression of pro-inflammatory cytokines and chemokines. This results in the induction of oxidative stress. The excessive ROS that is created by smoking cigarettes leads to the creation of nitric oxide synthase as well as an overload of glutamate in the synapses.[19,20]

The subsequent influx of Ca2+ causes mitochondrial dysfunction, damage to dna, inflammation, and even death in some cases. Additionally, cigarette smoking induces insulin resistance, which is another factor that makes neuropathy worse. Chronic cigarette smokers are insulin resistant and have elevated levels of insulin in their blood. Cigarette smoking is a risk factor for decreased insulin secretion. It is possible that nicotine is partially responsible for this action via acting on skeletal muscle cells via the mechanistic target of rapamycin pathway.[19,20]

Nicotine was shown to activate adenosine monophosphate-activated protein kinase a2 in adipocytes, which is another essential cell type in insulin resistance. This resulted in an increase in the amount of circulating free fatty acid as well as an induction of insulin resistance. The nitrosamine ketone that is produced from nicotine has the potential to block the

insulin receptor as well as the Akt pathway in neurons. This could result in the loss of insulin-mediated neurotropism as well as neuronal malfunction. In addition to this, smoking cigarettes blocks the pathway known as NF-E2-related factor 2– anti-oxidant responsive element (Nrf2-ARE).[21]

The transcription factor Nrf2, which is known as the master regulator of the cellular response to oxidants and which upregulates the expression of ARE-regulated genes in a wide variety of cell types, is often regarded as having this role. When someone smokes, the anti-oxidative benefits produced by the Nrf2-ARE pathway become less effective. This leaves astrocytes and neurons more vulnerable to harm, including oxidative glutamate toxicity and calcium disturbances.[21,22]

CONCLUSION

Although there is inconsistency in the relationship between diabetic peripheral neuropathy and smoking cigarettes, research that reveal an association between the two show that the prevalence of the condition is greater than 10%.

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