RELATIONSHIP BETWEEN SMOKING AND DIABETIC MICROVASCULAR COMPLICATIONS

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ABSTRACT*: Examination of the association between smoking and diabetic microvascular complications in diabetic patients.*
Background-
Diabetes is among the most prevalent lifestyle diseases in the world with high mortality rates. Diabetic microvascular complications have also increased in incidence as the number of patients diagnosed with the disease continues to rise. Studies indicate that the complications are promoted by smoking which prompts research to validate the assumptions.
The aim of Study*- This study aims to establish whether smoking increases the incidence of microvascular complications among diabetic patients.*
Methods- *We conducted an incidence survey on PubMed, Embase, and Cochrane databases and cross-referenced citations on published studies on the relationship between smoking and microvascular complications.*
Results- There is a high prevalence of smoking in men than women. Current smokers have a higher prevalence of microvascular complications. The intensity of smoking determines the prevalence of complications among the patients as those who quit gradually decrease their risk level of developing complications.
Conclusions*- There is a relationship between smoking and the prevalence of microvascular complications as well as poor control of glycemia. The prevalence of microvascular complications is higher in smokers compared to non-smokers. Therefore, smoking increases the risk of complications for smokers and the stoppage of smoking leads to an effective decrease in the incidence of microvascular complications for smokers.*

Key Words- Diabetes, Microvascular complications, Neurology, Smoking.

INTRODUCTION

One of the major goals in managing microvascular complication ix among the main therapeutic goals for diabetic patients [13]. Diabetic mortality and morbidity are greatly influenced by the effect of complications. Stringent control of diabetes is one of the interventions known to restrict the progress and incidence caused by complications [1]. However, the strict measures are also associated with an increase in the frequency in occurrence of hypoglycemic attacks and gaining weight [14]. Not all the patients will find the measures easy and safe to achieve. The ability to intervene in micro-vascular complications limited due to the incomplete information associated with the condition. High complication rates associated with diabetes in patients is cigarette smoking [5]. There are numerous studies showing a strong relationship between cigarette smoking and increased frequency of microvascular complications [9]. However, some studies do not show any relationship which may be because of restrictions in methodology in earlier studies that analyzed a fairly smaller number of heterogeneous participants, lacked proper adjustments on potential confounders, and did not differentiate between current smokers and ex-smokers [10]. There is also small data that shows the association between the participant's smoking status and complications for patients who stopped smoking [6]. The data is significant to individuals who undertake the huge duty of convincing young people suffering from diabetes to quit smoking [15]. This research paper is an analysis of the association between smoking and diabetic microvascular complications taking with an emphasis on the long-term control of glycaemia.

RESEARCH DESIGN AND METHODS

SEARCH STRATEGY AND RESEARCH CRITERION

The research was done through a search on PubMed, Embase, Cochrane databases (January 2008 to November 2018) and did a search for the citations of qualified articles. The search included studies that analyze the association of impacts of smoking cigarettes and the risk level of acquiring complications. The study only included participants with diabetes at baseline due to its primary interest on the effect of smoking on diabetic microvascular complications in diabetic patients. Cigarette smoking was the determinant in most of the studies. For systematic review purposes, the studies considered included a control group of non-smoking diabetic participants.

The search results included case-control, cross-sectional and cohort studies. A minimum of 1 year follows up was implemented for cohort studies due to the assumption of a minimum of one-year latency period for smoking to have an effect on the development of diabetic neuropathy. The search considered only published studies done in the English language to avoid misinterpretation of information. Three search themes were used diabetes, smoking, and microvascular complications.

STUDY SELECTION

Based on collected titles and abstracts, a prior screening of retrieved citations was done. The screening of every citation was by two co-authors. In the first screening, the inclusion criteria were in the following order, subjects with diabetes, microvascular complication, and prospective identification, cross-sectional or cohort study. Studies that did not have exposure to smoking mentioned in their abstract or title are also included. The exclusion criteria included animal studies, non-studies (case series, case reports, editorials, and reviews), and gestational diabetes. The full-text reviews of retained citations created the basis for conducting a second screening. The exclusion criteria of the first screening were retained in the second screening with the following additional criteria: there was no assessment of the link between smoking and microvascular complications since the data did not allow

manual calculation and the inclusion of subjects without diabetes. Reviews were done by two independent reviewers who resolved any disagreements through a consensus.

RESULTS

Based on the selection of studies, the first search entailed references from Cochrane, Embase, and PubMed databases from 2008. 994 unique references became available after exclusion of duplicates. After the first screening, further review was done for 226 citations. In the second screening, full-text review. Some of the reasons that led to exclusion of some studies included the absence of estimates or figures that could enable the manual calculation of the relationship between microvascular relationship and smoking, an outcome instead of microvascular complications, and including non-diabetic participants without diabetes. In the end, the systematic review included 33 participants and a separate meta-analysis was performed for ten prospective studies and 23 cross-sectional studies as shown in figure (1).

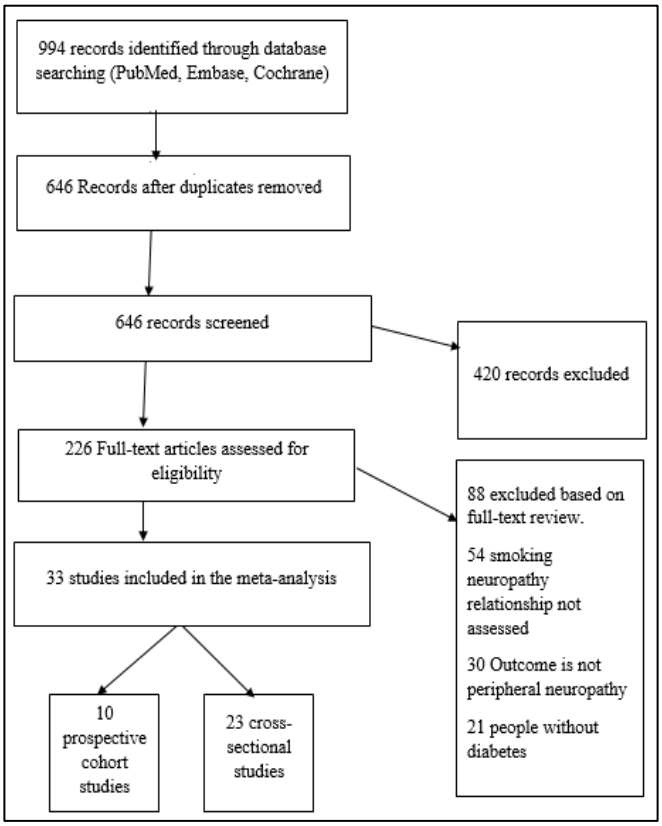


Figure (1): showing the results of the study from Cochrane, Embase, and PubMed databases from 2008 which involved 994 unique references

Experiment end: 33 participants were involved at the end, a separate meta-analysis was performed for ten prospective studies, and 23 cross-sectional studies, results were shown as in the table above.

SMOKING AND INCIDENCE OF DIABETIC PERIPHERAL NEUROPATHY

The studies comprised of 5558 participants: one study that had type 1 and 2 diabetic participants, six studies had type 1 diabetic participants, and three studies had type 2 diabetic participants.

The settings of the patients were from different areas including the community, inpatient, and outpatient. 25 to 66 years old was used as the average age of the participants while 0 to 17 years was the average duration of diabetes among the participants. Baseline neuropathy was used as an excluding factor in all the studies which led to the study being conducted between 2 and 10 years. In most of the studies, the screening was based on examination and neurological history [19]. The studies had varying definitions of smoking exposure; three of the studies did not make clear specifications of the smoking comparison groups, one study compared nonsmokers to current smokers, while six of the studies compared former smokers to current smokers.

In most of the studies, ORs (odds ratio) was provided, RRs (relative risk) were include

d in two of the studies and one of the studies provided the number of smoking and nonsmoking participants as well as the number of patients in every group who experienced the development of peripheral neuropathy [20]. All studies conducted multivariable-adjusted analyses except for one, five of the studies had control of at least A1C and duration of diabetes, while four of the studies showed adjustments for either diabetes duration or A1C and numerous other confounders. There was varied quality in the studies. Most of the studies categorized as quality studies through the use of the Newcastle-Ottawa scale [11]. Three of the studies were categorized to be of adequate quality and one study was deemed to be of low quality mainly because of bias in selection and poor definition of results.

DISCUSSION

SMOKING AND DIABETES INCIDENCE

There is a lot of evidence that shows smoking increases the risk of diabetes. Numerous cohort studies around the world indicate a strong association in smoking and an increase in the risk of developing diabetes [21]. There is an increased risk of both type 1 and 2 diabetes for past and current smokers. As the number of cigarette smokers increases, so does the risk of acquiring diabetes. Participants who smoked 20 cigarettes or more daily have increased risk levels of acquiring diabetes in comparison to that of participants who smoked fewer cigarettes daily [18]. Therefore, there is a positive relationship between cigarette consumption and the risk level in the acquisition of diabetes [22]. The number of studies on the risk level of acquiring diabetes in women who smoke are few due to the lower prevalence of smoking among women compared to men [7].

The incidence of hypertension, hyperinsulinemia, and hyperglycemia increase based on the frequency of smoking cigarettes [3]. The threat of contracting diabetes in men is higher than in women. On the other hand, the risk level of acquiring diabetes is significantly high for women who smoke more 40 cigarettes daily. The risk goes as high as 75% in comparison to women who do not smoke. For men and women who quit smoking, the level of risk reduces [19], as shown in the table (1).

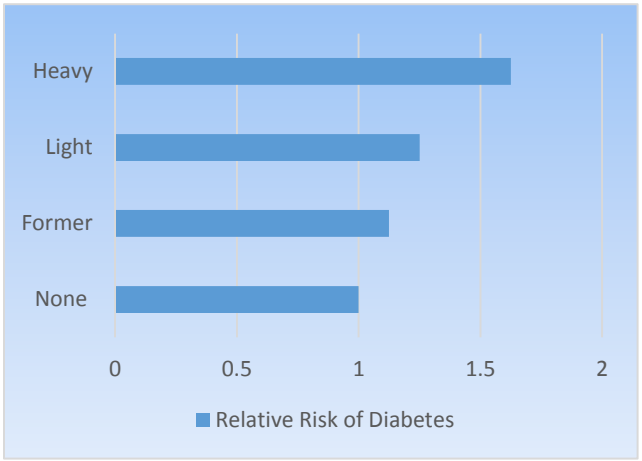
Table (1): Table showing the relative risk as a result of smoking cigarettes from four different studies

First author	Publication year	Total Case (gender)	Cigarettes/day	RR (95% CI)
Park et al.	2008	1717 (men)	1-9 10-19 >19	1.47 (0.71-3.04). 1.84 (0.92-3.04). 1.87 (1.13-3.67).
Cho et al.	2009	4041 (men)	1-20 >20	2.06 (1.35-3.16). 2.41 (1.48-3.93).
Akter et al.	2015	20,579	>20	1.31 (1.16-1.47).
Hilawe et al.	2015	3338 (men)	1-19 20-29 >30	1.35 (0.79-2.32). 168 (1.10-2.58). 2.30 (1.47-3.60).

RR-relative risk, CI- confidence interval, RR and cigarettes for each day for the 4 citations were indicated

There is a measured responsive behavior between cigarette smoking and diabetes. According to the meta-analysis from studies examining the relationship between diabetes incidence and smoking, it is established that the risk level of development of type 2 diabetes increases in active smokers in comparison to non-smokers [25]. In addition, the meta-analysis investigated analyzed the relationship's effect through the division of the respondents based on their frequency of smoking. The quantitative summary below is an indication that as the intensity of smoking increases, there is an increase in the RR of diabetes based on a dose-dependent factor. The RR of light smokers is 1.25 (95% CI: 1.14-1.37) while the RR of heavy smokers is 1.54 (95% CI: 1.40–1.68). This is in comparison to non-smokers. In addition, the meta-analysis indicates that the level of risk drops for smokers who quit compared to current smokers [23], as shown in graph (1).

Graph (1): showing the relative risk of Diabetes for Heavy, Light, Former smokers as well as non-smokers



Heavy drinkers have the highest relative risk of diabetes, followed by light smokers, previous smokers and last non-smokers

Based on published studies, there is a good relationship between the risk level in the development of diabetes and the intensity of smoking. The studies indicate a significant reduction in the risk of acquiring diabetes for those who quit smoking [18].

MICROVASCULAR COMPLICATIONS

Microvascular complications: retinopathy, nephropathy, and neuropathy, are highly associated with smoking [4]. However, serious smoking effects on renal conditions might be independent of glycemic effect. Over the years, there has been an increase in the incidence levels of diabetic kidney disease among active smokers compared to diabetic non-smokers [17]. Low glomerular filtration (GFR) and micro-or macro-albuminuria is more likely to develop in patients who smoke compared to patients who do not smoke. Patients who had been smoking for more than 30 years were more likely to have the development of proteinuria 2.78 (95% CI: 1.34–5.76) and 3.20 (95% CI: 1.74–5.86) respectively compared to diabetic non-smoking patients. This is accompanied with good control of blood pressure, short duration of diabetes, and young individuals3. The progress of microalbuminuria to avoid the contraction of proteinuria and consequent chronic renal failure is increases for smokers compared to non-smokers. The case applies to both types of diabetes. Moreover, the relationship between the renal injury and cigarette smoking is more evident in type 1 diabetic patients. The progress of chronic kidney disease for both forms of diabetic patients is fast. The understanding of how the function of the renal excretory is impaired by the renal excretory function is still low. The general assumption is that the contents of tobacco have a higher likelihood of having negative impacts on the structure and function of the glomerulus. According to recent studies, heavy metals like lead tend to accumulate in the blood and smoking damages the glomeruli. The components of tobacco cigarettes are linked with free radial processes, that have already been proven to lead to dysfunction of the endothelial characterized by a decrease in production of nitric oxide availability which is responsible for the overproduction of endothelin-1 (ET-1) [16].

A lack of balance between endothelin and nitric oxide caused by inhalation of cigarette smoke leads to an increase in vascular inflammation that consequently leads predisposition to atherosclerosis [24]. Recent studies indicate that type 2 diabetes can be determined by elevated levels of IL-6 in the blood. Moreover, some studies indicate a relationship between type 2 diabetes and the IL-6 C-174G single-nucleotide-598G polymorphism [8]. Lipid peroxidation of cellular structures which are caused by increased free radical activity is responsible for the damage in the organs of

diabetic patients. For type 1 diabetic patients who smoke, the level of malondialdehyde in plasma which is produced by peroxidation tends to be higher compared to non-smoking type 1 diabetic patients. Another study shows that the F2-isoprostanes which is a contributor to renal damage in smokers tend to be higher than that of non-smokers. The relationship between retinopathy and smoking is mainly linked to glycaemia [12].

However, in some studies, the negative relationship between smoking and glycaemia is evident. According to the United Kingdom Prospective Diabetes Study (UKPDS), glycaemia, as well as, blood pressure and the incidence of retinopathy have a strong relationship [2]. However, the relationship with smoking is inverse. The two types of diabetes have a different effect on diabetic neuropathy. Based on the diagnosis of symptoms and signs, smoking is not a risk factor with the involvement of sensory neuropathy or polyneuropathy in type 2 diabetic patients. Another study shows that type 1 diabetic patients both current and non-smokers have a more likelihood of having neuropathy compared to participants who have never smoked [8]. On the other hand, the incidence of neuropathy increases with the patient's frequency of smoking over the years.

CONCLUSION

Both experimental and clinical show a resilient association between diabetic pathogenesis and the development of microvascular complications. Smoking leads to adjustments in the secretion of insulin by pancreatic β cell which may trigger the resistance of insulin leading to an impairment in the metabolism of glucose that eventually leads to diabetes. In addition, the development of vascular complications is highly affected by smoking-induced endothelial dysfunction. Despite the convincing numbers on the harm caused by smoking for diabetic patients, it is hard to establish why the patients continue to smoke with the same intensity as those who are not diabetic. This is attributed to unhealthy lifestyle choices or a lack of proper education of patients within this category. A gradual decrease in susceptibility to developing diabetes or microvascular complications in patients diagnosed with diabetes is achieved through quitting smoking. Therefore, there is a need for more emphasis on high-risk diabetic patient groups to stop smoking despite the lack of determination of the most effective strategy to quit smoking.

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