

Occupational Exposure to Pesticide: A Risk of Diabetic Neuropathy

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Abstract

Prevalence of diabetic neuropathy is increasing at high speed despite of significant progress in its pathogenesis and its etiologies suggesting the requirement of a non-traditional risk factor for the development of diabetic neuropathy. Environmental chemicals could be one of the reasons behind the development of diabetic neuropathy as many environmental chemicals are known to be positively associated with hyperglycemia and diabetes. Therefore, in this mini-review, we have listed some of the epidemiological studies which show the occurrence of diabetes on pesticide exposure. We have also listed epidemiological studies where exposures of different classes of pesticides are known to induce neuropathy in the exposed population. This study provides substantial evidence that exposure to pesticides might lead to development of diabetic neuropathy. Although, at present, there are no studies available which suggests exposure to pesticide may induce diabetic neuropathy. Therefore, future studies in this direction will be helpful in evaluating as well as elucidating the mechanism behind pesticide-induced diabetic neuropathy.

Keywords: Pesticide; Diabetic neuropathy; Epidemiology

complications are also observed in diabetic individuals like diabetic keto-acidosis (increased ketone bodies in the blood; occurs especially in extreme hyperglycemic condition) and diabetic coma (in extreme hypoglycemic condition). However, when the hyperglycemic condition persists for a longer duration; it may lead to several diabetes-associated microvascular (nephropathy, retinopathy, sexual dysfunction, neuropathy) and macrovascular (cardiomyopathy, cardiovascular disease etc.) complications [3-5]. Out of the listed diabetic complications, in this review; we are mainly focused on diabetic neuropathy, a disorder associated with the nervous system in diabetes. We have also included some organophosphate pesticides which may cause diabetes and diabetic neuropathy.

Neuropathy

Neuropathy is a disease where nerves get damaged or disrupted in the brain. In most of the cases, peripheral nerves which include motor, autonomic and sensory nerves get affected, and therefore it is also known as peripheral neuropathy. Neuropathy can be classified based on the peripheral nerves getting affected: Sensory neuropathy, motor neuropathy and autonomic neuropathy. Neuropathy can be further classified based on the number of nerves getting affected. For instance, mononeuropathy, single peripheral nerves get damaged either due to traumatic injury or polyneuropathy, nerves present in different body parts get damaged [6]. The prevalence of neuropathy is about 2.4%; however, this number increases up to 8% in the population having age more than 55 years [7]. There are different causative factors that cause neuropathy and out of which diabetes is one of the most important risk factors for neuropathy.

Diabetic neuropathy

In diabetic neuropathy, there are microvascular injuries in the small blood vessels which connect arteries with the peripheral nerves. As a result, in diabetic neuropathy, it can affect all the organs and organ systems that are innervated.

Introduction

Diabetes is a metabolic disorder affecting around 425 million people living in the world in 2017, and these number is expected to increase up to 629 million in 2045 [1]. Diabetes occurs when there is a deficiency of insulin (Type 1 diabetes) or when the body is unable to use the available insulin, i.e., insulin resistance (Type 2 diabetes). As a result, blood glucose increases and resulting in the hyperglycemic state [1,2]. As a consequence of this, first symptoms that appear in diabetic individuals are polydipsia (excessive thirst), polyphagia (increased hunger), and polyuria (excessive urination) along with hyperglycemia. Also, several short-term

The diabetic neuropathy is the most common complication and one of the prominent reasons of morbidity and mortality among the diabetic patients of the western world. Epidemiological studies suggest 30% prevalence of diabetic neuropathy across the globe implicating the seriousness the disease has over the individual life [8,9]. While the prevalence of neuropathy in non-diabetic individuals is 2% [10,11] and it increases to 15% in people having age more than 40 years [12]. These suggest diabetes has a profound effect on the occurrence of neuropathy. Therefore, it is important to understand the reason behind the cause of diabetic neuropathy, which warrants serious attention in the present time.

Pesticides and diabetic neuropathy

Pesticides are group of chemicals and used for the destruction of insects, weeds, fungi, bacteria etc. They are called as insecticides, fungicides, bactericides or rodenticides. Classification of pesticides is based on their origin: 1. chemical pesticides i.e., organochlorine, organophosphate etc., 2. biopesticides i.e., bacteria, fungi, plants, agriculture, domestic, public health etc.

Hyperglycemia is the most prominent risk factor associated with diabetic neuropathy [9]. In the current scenario, production of chemicals increases tremendously and simultaneously the prevalence of diabetes is also high suggesting a positive co-relation between the chemical exposure and prevalence of diabetes [13]. Therefore, it is important to understand the mechanism as well as preventive steps required to prevent development of diabetes and diabetic neuropathy. Various environmental chemicals are reported that may be causative agent for diabetes or increases substantial levels of glucose in the blood may also lead to the development of diabetic neuropathy [14,15]. Different classes of environmental chemicals are present in the environment, includes pesticides, chemical contaminants, nutritional ingredients, metals, organic solvents, pharmaceutical drugs and so on. Out of the available environmental chemicals, epidemiological studies conducted across the world have shown occupational exposure to the pesticide is one of environmental chemicals having a positive association with the onset of diabetes and neuropathy in the exposed populations.

Table 1 List of some epidemiological studies showing positive co-relation between pesticides exposure with diabetes.

Pesticides	Population	Location	References
Herbicides (2,4,5-T; 2,4,5-TP; atrazine; or butylate) and insecticides (diazinon, phorate, or carbofuran)	Pesticide applicators women	Iowa and North Carolina	Saldana et al. [16]
Aldrin, chlordane, heptachlor, dichlorvos, trichlorfon, alachlor, and cyanazine	Pesticide applicators non-Hispanic White males	Iowa and North Carolina	Montgomery et al. [17]
PCBs (15), p,p'-DDE, p,p'-DDT	People from the heavily polluted areas recruited by the primary care physicians	Slovakia	Ukropec et al. [18]
PCB-153, p,p'-DDE	WHILA cohort (1995–2000)	Sweden	Rignell-Hydbom et al. [19]
PCB-153, p,p'-DDE	Fishermen and their wives from the Swedish east coast	Sweden	Rylander et al. [20]
Total PCB	Yu Cheng cohort (1993–2003)	Taiwan	Wang et al. [21]
Total PCB, PCB-153, PCB-74, DDE, HCB	Mohawk adults (one adult/household)	USA	Codru et al. [22]
p,p'-DDT, p,p'-DDE, β -HCH, oxychlordane, trans-nonachlor	HHANES (1982–1984), Hispanic Americans	USA	Cox et al. [23]
PCB-126, p,p'-DDT	NHANES (1999–2002)	USA	Everett et al. [24]
Organophosphate pesticides (fonofos, phorate and parathion), organochlorine pesticide (dieldrin) and Herbicide (2,4,5-T)	Agricultural Health Study: Eives of farmers	Iowa and North Carolina	Starling et al. [25]
Organophosphates (OPs), organosulfurs (OSs), organonitrogens (ONs) and pyrethroids (PYRs)	Farmer	China	Huang et al. [26]

Table 2 List of pesticides having a positive association with the occurrence of neuropathy based on epidemiological studies.

Pesticide	Population	Location	References
Organophosphate pesticides	Agricultural workers	Italy	Lotti and Moretto [28]

Malathion (Organophosphate insecticide)	Suicides	Turkey	Ergun et al. [29]
Organophosphorous agents	Chemical warfare	Iran	Holisaz et al. [30]
Sarin (Organophosphorous agent)	Terrorist activity	Japan	Yokoyama et al. [31]
Ortho-cresyl phosphate (Organophosphorous agent)	Cooking oil	Morocco	Smith and Spalding [32]
Tri-ortho-cresylphosphate (Organophosphorous agent)	Cooking oil	South Africa	Susser and Stein [33]
Tri-ortho-cresylphosphate (Organophosphorous agent)	Cooking oil	Sri Lanka	Senanayake and Jeyaratnam [34]
Tri-ortho-cresylphosphate (Organophosphorous agent)	Beverage production (alcohol during Prohibitionera)	United States	Aring [35]; Morgan and Penovich [36]; Woolf [37]

Epidemiological studies conducted in China, it was found that exposures to various pesticides were associated with hyperglycemia as well as damage in the nerves was observed in the farmers exposed to pesticides [26]. The epidemiological studies mentioned in the table as well as pesticides have ability to induce hyperglycemia, diabetes and ultimate cause diabetic neuropathy. Although, detailed experimental studies are required to validate the role of pesticides exposure in inducing diabetic neuropathy.

Probable mechanisms behind pesticide-induced diabetic neuropathy

In general, for the occurrence of a diabetic complication, these are five proposed pathway which hyperglycemia induces: activation of increased polyol pathway flux, increased advanced glycation end-product (AGE) formation; activation of protein kinase C (PKC) isoforms, increased oxidative stress and increased hexosamine pathway flux [38]. And, these pathways are also implicated in the development of diabetic neuropathy [39,40]. Therefore, in this review, we have briefly described two pathways mostly studied in diabetic neuropathy.

Polyol pathway activation: It is the most studied mechanism in diabetic neuropathy. In this, excess glucose present in the circulation is taken up by the nerve cells, and it converts glucose into sorbitol through an enzyme, aldose reductase. Since sorbitol cannot cross cytoplasm, it accumulates inside the cytoplasm and increases intracellular hyperosmolarity and thereby cell lysis [41,42]. However, this is not observed in all diabetic neuropathy cases [43]. Later, it was also observed that for the compensation of osmotic imbalances, efflux of myoinositol, adenosine and taurine take place. Since, myoinositol is a required for adenosine triphosphate (ATP) production, and if myoinositol is not available, then there will be decrease ATP production leading to reduce activity of sodium/potassium (Na/K) ATPase and protein kinase C (PKC) [44,45]. Hence, increased polyol pathway flux will impair normal nerve physiology [46].

Advanced glycation end-product (AGE) formation: In hyperglycemic condition, there is the non-enzymatic reaction in which glucose gets attached to amino groups of protein to form Amadori products, through Maillard reaction [47]. As a consequence of this, it impairs the biological function of proteins and may cause cellular damage [48]. Extracellular

AGEs bind with it cell surface receptor RAGE (Receptor for AGE) and activates inflammatory signaling and NADPH oxidases, and thereby generates oxidative stress [49]. While in a chronic condition, it also activates nuclear factor- κ B (NF- κ B) [50] AGE accumulation is reported in the peripheral nerves of diabetic neuropathy patients [51].

Till date, very limited mechanistic studies and even the limited number of pesticides have been examined to see the influence of pesticide exposure on the development of diabetes-induced neuropathy and therefore it warrants detail investigation.

Future Directions

In this diabetic era, each environmental chemical might have the ability to cause diabetes and thereby diabetic neuropathy. As the occurrence of diabetic neuropathy is increasing tremendously, it is utmost essential to evaluate and elucidate the mechanism behind environmental chemicals induced diabetic neuropathy as the data reviewed here suggest only a plausible factor behind increase prevalence of diabetic neuropathy. Once the mechanism is identified, it will be helpful to decrease the burden of diabetic neuropathy.

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