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Pesticide from farm to Clinic: Possible Association between Pesticides and Diabetes Mellitus

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Abstract

Pesticides represent an increasingly widespread environmental exposure today and some of them have the potential to accumulate in human tissues either through direct exposure or through the food chain.There have been multiple findings linking diabetes and other metabolic problems to metabolic abnormalities, hyperglycemia, and oxidative stress in acute and chronic pesticide exposures. The major pesticides that are widely used include organophosphates (OP), organochlorines (OC), pyrethroids and carbamate (CB). The suppression of the enzyme acetylcholinesterase is the main mechanism of action of OP and CB (AChE) that results in signs and symptoms of excessive cholinergic stimulation. Exposure to OCs has been linked to the development of type 2 diabetes, which involves mitochondrial dysfunction, according to epidemiological research. Pyrethroid-induced oxidative stress may play a role in developing -cell pancreas dysfunction. In this report we performed a systematic review which aimed at highlighting the possible mechanisms that could lead to diabetes mellitus due long-term pesticide exposure.

Keywords: *Diabetes, organophosphates (OP), organochlorines (OC), pyrethroids, carbamate (CB)*

Introduction

Agriculture is the primary source of livelihood for about 58% of Indian population. India was the 9th largest exporter of agricultural products in 2017. India is currently the world's fourth largest producer of agrochemicals.

The area under cultivation and under the use of chemical and bio pesticides has risen from 68382000 hectares in the year 2014-15 to about 134391000 hectares as of 28th November 2019.Pesticides are chemicals meant to combat rodents, including plants. The word pesticide comprises all the following: herbicide, nematicide insecticides, molluscide, piscide, avicide, rodenticide, bactericide, repellent for humans, repellent for plants, antimicrobial and fungicide. The indigenous pesticide consumption of the nation was on a rise from 2014-15 to 2018-19.

Among the indigenous pesticides the insecticide consumption was increased from 6740.02MT in the year 2014-15 to about 9478.05MT in the year 2018-19. A similar pattern was observed in case of fungicides where about 6322.64MT of indigenous fungicide was used in the year 2014-15 which escalated to about 8962.21MT in 2018-19.

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But surprisingly a decline in indigenous weedicide consumption was observer where about 4475.85MT in 2014-15 dropped to about 3998.45MT in the year 2018-19.Taking into account the other pesticides like rodenticides, bio-pesticides and plant growth regulators the net consumption of indigenous pesticides inclined from 20800.50MT in 2014-15 to 26013.67MT in 2018-19.

The list of most widely used indigenous pesticides in the nation are given in following table

The total area under cultivation was about 167499000hectares as of 28th November 2019 in which 87957000hectares (52.5%) is under chemical pesticide use, 14636000hectares (8.7%) under bio-pesticide use and 31799000hectares (18.9%) under bio-chemical pesticides. 35993000 hectares (21.48%) were not under the use of any pesticide.

From 2014-15 to 2018-19, the use of chemical pesticides in the nation has gradually increased.The chemical pesticide consumption of the nation in the year 2014-15 was about 56268 MT which rose to 59670MT by the year 2018-19.

S.No.	Pesticide	Type	Class	2014-15 (MT)	2018-19 (MT)
1.	Quinalphos	INSECTICIDE	Organothiophosphate	498.55	509.84
2.	Fipronil	INSECTICIDE	Phenylpyrazole	380.99	545.12
3.	Butachlor	WEEDICIDE	Acetanilide	565.24	993.71
4.	Malathion	INSECTICIDE	Organophosphate	519.63	656.41
5.	Carbendazim	FUNGICIDE	Benzimidazole	556.10	668.86
6.	Glyphosate	WEEDICIDE	Organophosphorus	718.06	679.81
7.	Phorate	INSECTICIDE	Organophosphate	443.01	723.70
8.	2,4 D-Dicholrophenoxy acetic acid	WEEDICIDE	Phenoxyacetic Acid	798.02	871.51
9.	Chlorpyrifos	INSECTICIDE	Organophosphate	470.69	1105.61
10.	Mancozeb	FUNGICIDE	Dithiocarbamate	2130.68	2792.64
11.	Sulphur	FUNGICIDE	Sulphur	1548.36	3221.98

As of 28th November 2019 the top 10 consumers of chemical pesticides throughout the nation is listed below:

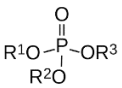
S.No.	State	2014-15 (in MT)	2018-19 (in MT)
1.	Maharashtra	8663	11746
2.	Uttar Pradesh	9736	11049
3.	Punjab	5689	5543
4.	Telangana	2806	4894
5.	Haryana	4070	4015
6.	West Bengal	3060	3190
7.	Jammu Kashmir	1921	2459
8.	Rajasthan	2694	2290
9.	Tamil Nadu	2096	1901
10.	Chattisgarh	1589	1770

According to International Diabetes Federation (IDF) in 2019, 463 million adults (20-79 yrs) were living with diabetes and by 2045 this will rise to 700 million[1].According to recent surveys (Oct 2019), India has 72.96 million persons with diabetes mellitus (DM), making it the world's second-largest diabetes mellitus (DM) population behind China. In India, the prevalence of diabetes mellitus ranges from 5 to 17 percent, with greater rates in the south and in urban regions. [2].With 53 deaths among 100,000 inhabitants, Tamil Nadu has the highest diabetes death rate among Indian states, followed by Punjab (44), and Karnataka (42), all of which are much higher than the national average(23).[3].

Diabetes is considered to have environmental as well as hereditary influences, but the environmental factors leading to its pathogenesis remains longly unknown[4].Recent reports involve certain chemicals such as organophosphate (OP) and organochlorine (OC) as potentially contributing to the diabetes development and accidental poisoning with some plant products can occur in rural area [4].People are exposed to pollutants through proximity to occupation or environment such as rural workers, greenhouse workers, workers in pesticide manufacturing, mixing, application, loading, transporting as well as through consumption of polluted food and water bodies[5].According to India environmental portal, the prevalence of diabetes is three times higher among those exposed to insecticides [6].

Organophosphate

Organophosphate pesticides are commonly used worldwide and poisoning by these agents is a major public health issue, especially in developing nations (7). Organophosphates (OPs) were originally produced in the early nineteenth century as phosphoric acid esters, amides, or thiol derivatives. (8).



There are several proposed mechanisms of organophosphate compounds resulting in abnormal glycemic levels. The organophosphates and carbamates are strong carboxylic ester hydrolases antagonists, namely acetylcholinesterase (found in nervous tissues and erythrocytes) and butyrylcholinesterase (plasma or pseudocholinesterase) (9). AChE is essentially a pervasive enzyme in vertebrates and invertebrates and is found in mammals in some regions of the central nervous system and in organs and glands regulated by the autonomous nervous system's parasympathetic division (10). AChE acts as a controlling agent for nervous transmission by reducing the concentration of ACh at the junction by catalyzing AChE hydrolysis into choline (Ch) and acetic acid (A). The postsynaptic membrane is not activated by such materials(10). The organophosphorus ester inhibition of AChE occurs by a chemical process phosphorylation of the serine hydroxyl moiety at the active enzyme cite occurs in the same way that AChE is acetylated. Unlike the acetylated enzyme, which easily breaks down to give acetic acid and the regenerated enzyme, the phosphorylated enzyme is extremely stable, though in certain instances, it is irreversibly inhibited based on the groups attached to the phosphorus atom (R though R') (11). The phosphorylated moiety inhibited serine hydroxyl group, can no longer engage in Ach hydrolysis (10). The serine hydroxyl group, blocked by a phosphorylated moiety, can no longer engage in Ach hydrolysis (12). Thus the loss of metabolic balance can also alter glucose metabolism via overstimulation and subsequent downregulation of muscarinic receptors and result in abnormal glycemic levels.

Organophosphate and Incretin Effect

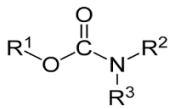
The 'incretin effect' attenuation is increasingly recognized as an significant pathophysiological process which contributes to impaired homeostasis of glucose (13,14). Incretins are a collections of metabolic hormones that cause blood sugar levels to drop. After eating, incretins are produced by a blood glucose-dependent mechanism, also by insulin released fromislets of Langerhansin the pancreatic beta cells. More insulin is produced with oral than the same IV glucose dose. This insulin rise of 40-60 per cent is assosiated to the 'incretin effect' (15,16). Glucagon like peptide-1(GLP-1) and Glucose-dependent Insulinotropic Polypeptide (GIP) are two main gastrointestinal tract-secreted incretin hormones in relation to glucose (17,18). Release of Glp-1 happens in two phases. The early secretory process of GLP-1 is regulated on L-cells in distal ileum and colon by muscarinic receptors (type 1 and 2) (19). The late secretory process is activated directly by carbohydrates that penetrate the distal ileum and colon (19). GIP secreted by K-cells of duodenum in relation to glucose, which works indirectly by afferent vagus nerve to induce the secretion of GLP-1 from human L-cells. This includes acetylcholine (Ach) (20,21). OP prevents AChE, which allows Ach to accumulate (22). A Neuroendocrine system controls the GLP-1 secretion. This includes ACH in the muscarinic receptor at distal ileum and colon on the human L-cell (20,21). Therefore, it may be speculated that acute OP toxicity results in GLP-1 secretion attenuation owing to overstimulation and eventual down-regulation of the muscarinic receptors on distal ileum and colon L-cells in humans (22).

Organophosphate and Oxidative Stress

If the antioxidants present in the body are unable to overpower the created free radicals, free radical activity may result in cell damage, called oxidative stress (23). OPs have been documented to cause oxidizing stress in humans (24). The liver plays an important role in homeostasis of blood glucose through maintaining a balance between taking and storing glucose through glycogenesis and releasing glucose via glycogenolysis and gluconeogenesis (25,26). Studies also established that acute diazinon exposure raises blood glucose and induces hepatic GP and PEPCK actions related to the oxidative stress in hepatic cells (27). The present results support the assumption that hepatic cells are correlated with activation of oxidative stress and impaired glucose metabolism following exposure to diazinone. There is proof that glucose is needed by antioxidants for their activity against free radicals. Glucose-6-phosphate dehydrogenase catalyzes the initial stage of the pentose phosphate cycle, the most important function of which is to convert nicotinamide adenine dinucleotide phosphate (NADP) to NADPH, which is used to reduce oxidized glutathione to a reduced state (GSH) and to reduce mixed GSH and cellular protein disulphides (28). Thus the first concept that comes to mind is that hepatic glycogenolysis and gluconeogenesis pathways are stimulated to provide more glucose and retain a supply of energy for cellular antioxidants in response to triggered free radicals caused by diazinon. Altered glucose metabolism may be considered a detoxification process for the body to combat sensitivity to diazinone (27). Because of the massive work of mitochondria and microsomes, ROS like superoxide anion, hydrogen peroxide, and hydroxyl radicals are produced at a low rate under normal conditions. A decreased ability of the body's antioxidant mechanism, however, contributes to insufficient oxygen removal and, thus, elevated production of ROS (29,30). OP and OC raise levels of biomarkers of ROS (F2-isoprostans and F4-neuroprostans) and RNS (citrulline), possibly attributable to cytochrome P450 induction. They also transform enzymes like antioxidants, catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reducctase (GR). Oxidative stress induces harm to the DNA and influences genes engaged in body metabolism that express cytochrome P450s and UDP-glucuronosyl / UDP-glucosyltransferases (31,32,33,34). In rats, diazinon induced hyperglycemia linked to oxidative/nitrosative stress induction(35).

Carbamate

Carbamate pesticides are generated from carbamic acid which destroy insects in a similar way to insecticides containing organophosphates.



The toxicity in animals with insecticidally active carbamateandorganophosphorus esters is due to their capacity to suppress acetylcholinesterase (AChE, choline hydrolase, EC 3.1.1.7), a family in enzymes that catalyzes the neurotransmitting agent acetylcholine (ACh) hydrolysis (10). For an organophosphorus ester, inhibition of AChE by a carbamate insecticide occurs by a process nearly similar to the one mentioned earlier. The first step in the inhibition cycle includes the creation of the enzyme-inhibitor complex with corresponding hydroxyl seine carbamylation)] culminating in the enzyme inhibition (36). AChE inhibition contributes to aggregation of ACh in the synapses resulting in cholinergic over stimulation and neurotoxicity accompanied by metabolic function failure (13). Thus the lack of metabolic equilibrium can also change the processing of glucose by over-stimulation and eventual down-regulation of muscarinic receptors, contributing to excessive glycemic rates. One reason for their high acute toxicity is that they are direct inhibitors of AChE, and there is no need for metabolic activation as is the case with many safe organophosphorus insecticides, such as malathion. (10)

Organochlorine

Organochlorine pesticides (OCPs) are classified as insecticides and agricultural compounds, a category of chronic synthetic contaminants. They are lipophilic so minimally degradable, and they can quickly accumulate in the human body and environment (37). OCPs are lipophilic materials, which mainly collect in adipose tissue and are distributed across the body with lipids. This may contribute to metabolic disorders, indicating that such compounds are triggering metabolic disorders (38,39). Various epidemiological studies showed a strong correlation between POPs, body mass index and diabetes (40). Quantitative correlations between serum POPs and the prevalence of metabolic syndrome (insulin, triacylglycerol, glucose impairment) and mitochondrial dysfunction, which lead to Type 2 diabetes have been documented (T2D) (41).

OCP-treated mitochondria displayed irregular modulation of the ion relative to untreated mitochondria, indicating identical effects on ion channels in insect nerve cells and mitochondrial ion channels in OCP mixtures.
Studies indicate that mitochondrial complex I, II, and IV activities were enhanced by a lack of mitochondrial ion control, especially calcium control; based on this, citrate synthase function, as an entry enzyme into the TCA process, was assessed following OCP exposure to verify that this irregular calcium regulation is equal to enha As expected, mitochondrial citrate synthase exposed to OCP exhibited increased activity compared to untreated mitochondria enhanced oxidative phosphorylation. Therefore, OCPs function on the mitochondrial ion channels, including the calcium receptor, and induce enhanced calcium absorption as a signaling molecule for oxidative phosphorylation, resulting in increased production of citrate synthase and mitochondrial complexes I, II, and IV Complex III function was decreased in OCP treated mitochondria compared with untreated mitochondria. Study results suggested T2D may be evoked by mitochondrial dysfunction (37).

Pyrethtroids

Pyrethroids are widely used in China as pesticide materials, and are generally considered the safest group of insecticides available (42). Chronic effects of pyrethroid exposure cannot be excluded, as opposed to the safest group of insecticides available. Continuous human contact to pyrethroids over prolonged periods of time may have negative health consequences. (43,44)Earlier research indicated toxicity of blood glucose (45,46) as well as the chance of elevated risk of gestational diabetes and hypertensive pregnancy issues in the first trimester of pregnancy by agricultural pesticides (47,48).

The primary target of a pyrethroid insecticide in the insect nervous system by blocking the voltage-sensitive sodium channels in activated nerve cells, resulting in repeated nerve impulses with varying intensities based on the chemical composition of the pyrethroid (49).Animal studies demonstrate that sensitivity to such pyrethroids such as cypermethrin and deltamethrin used in public vector systems will change blood glucose rates. (50).

From previous studies of glucose metabolism and insulin resistance, several potential pathways of the pyrethroid effects on diabetes development can be inferred. First, pyrethroids can modify key regulators in lipid metabolism with corresponding adipogenesis and lipogenesis in adipose tissues, and alter the signals of key mediators in insulin signaling pathways, resulting in substantial reduction in insulin-stimulated glucose uptake in the muscle and adipose tissues (51). Second, pyrethroid-elevated oxidative stress can contribute in causing dysfunction of the β-cell pancreas. Several rodent experiments have shown overgeneration of free radical species and reduced antioxidants in lipid peroxidation following exposure to cypermethrin or deltamethrin (52,53,54). Oxidative stress has been proposed to exert detrimental effects on mitochondria, change the composition of the plasma membrane and raise the concentration of intracellular Ca2 +; such changes in pancreatic cell function result in insulin secretion and insulin response deficiencies (55, 56). Third, exposure to pyrethroids may induce physiological stress to which the sympathetic nervous system reacts. An animal experiment with rats recorded rise concentrations of corticosterone, noradrenaline, and adrenaline after deltamethrin was given intravenously (57). These increased releases of catecholamines and glucocorticoids could potentially disturb homeostasis of glucose (58,59).

Conclusion

According to an Indian environmental portal**,** Diabetes is three times more common among individuals exposed to pesticides, [60].According to recent findings, some chemicals such as OP and OC may have contributed to the development of diabetes, and when exposed to high quantities of organophosphates, acetylcholine accumulates, leading to downregulation of muscarinic acetylcholine receptors in pancreatic beta cells.[61] , [62]OPP is a community health and environmental problem due to its toxicity to humans and animals,. The EPA forbidden most household use of organophosphates, although their agricultural usage as pesticides on fruits and vegetables, as well as their application in mosquito abatement in public spaces like parks, remains legal.[28]. As per The Pesticide-Induced Disorders Database, the universal pesticide-related diseases affecting public health include asthma, autism and learning impairments, birth defects and reproductive dysfunction, diabetes, Parkinson's, Alzheimer's, and various forms of cancer.The dose-response association between POP proportions in blood and diabetes was significant.Hence, a prospective study is required to reveal the extent of relationship between pesticides exposureand diabetes.

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