ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2021 November 15; 12(11): 1812-1968

Published by Baishideng Publishing Group Inc

World Journal of Diabetes

Contents

Monthly Volume 12 Number 11 November 15, 2021

EDITORIAL

1812 Long-term effects of metformin use in gestational diabetes mellitus on offspring health

Roy A, Sahoo J

REVIEW

1818 Organophosphate pesticides and new-onset diabetes mellitus: From molecular mechanisms to a possible therapeutic perspective

Chung YL, Hou YC, Wang IK, Lu KC, Yen TH

1832 Anti-diabetics and antimicrobials: Harmony of mutual interplay

Hegazy WAH, Rajab AAH, Abu Lila AS, Abbas HA

1856 Effect of glycemic control on markers of subclinical atherosclerosis in patients with type 2 diabetes mellitus: A review

Antoniou S, Naka KKK, Papadakis M, Bechlioulis A, Tsatsoulis A, Michalis LK, Tigas S

ORIGINAL ARTICLE

Basic Study

1875 Profilin-1 is involved in macroangiopathy induced by advanced glycation end products *via* vascular remodeling and inflammation

Xiao ZL, Ma LP, Yang DF, Yang M, Li ZY, Chen MF

1894 p66Shc-mediated oxidative stress is involved in gestational diabetes mellitus

Huang TT, Sun WJ, Liu HY, Ma HL, Cui BX

Retrospective Cohort Study

1908 Factors influencing the effectiveness of using flash glucose monitoring on glycemic control for type 1 diabetes in Saudi Arabia

Alhodaib HI, Alsulihem S

Observational Study

1917 Association between admission hemoglobin level and prognosis in patients with type 2 diabetes mellitus

Song HY, Wei CM, Zhou WX, Hu HF, Wan QJ

1928 Role of hepatitis A virus in diabetes mellitus

Lin J, Ou HY, Karnchanasorn R, Samoa R, Chuang LM, Chiu KC

1942 Adherence to Mediterranean diet and advanced glycation endproducts in patients with diabetes

Grahovac M, Kumric M, Vilovic M, Martinovic D, Kreso A, Ticinovic Kurir T, Vrdoljak J, Prizmic K, Božić J

1957 Comprehensive genetic screening reveals wide spectrum of genetic variants in monogenic forms of diabetes among Pakistani population

Rafique I, Mir A, Siddiqui S, Saqib MAN, Fawwad A, Marchand L, Adnan M, Naeem M, Basit A, Polychronakos C

LETTER TO THE EDITOR

1967 Letter to editor 'Gastroenteropathy in gastric cancer patients concurrent with diabetes mellitus'

Cheng YX, Tao W, Zhang W, Peng D

World Journal of Diabetes

Monthly Volume 12 Number 11 November 15, 2021

Contents

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INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJD* as 3.763; IF without journal self cites: 3.684; 5-year IF: 7.348; Journal Citation Indicator: 0.64□Ranking: 80 among 145 journals in endocrinology and metabolism; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Lin-YuTong Wang*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Lu Cai, Md. Shahidul Islam, Jian-Bo Xiao, Manfredi Rizzo

EDITORIAL BOARD MEMBERS

https://www.wjgnet.com/1948-9358/editorialboard.htm

PUBLICATION DATE

November 15, 2021

INSTRUCTIONS TO AUTHORS

https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS

https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS

https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT

https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE

https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS

https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION

https://www.f6publishing.com

World Journal of Diabetes

Submit a Manuscript: https://www.f6publishing.com

World J Diabetes 2021 November 15; 12(11): 1818-1831

DOI: 10.4239/wjd.v12.i11.1818

ISSN 1948-9358 (online)

REVIEW

Organophosphate pesticides and new-onset diabetes mellitus: From molecular mechanisms to a possible therapeutic perspective

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Author contributions: Chung YL and Hou YC contributed data collection and manuscript writing; Wang IK contributed data analysis; Lu KC and Yen TH contributed study design and supervision; Chung YL and Hou YC contributed equally to this work; Lu KC and Yen TH also contributed equally.

Supported by Chang Gung Memorial Hospital, Linkou, Taiwan, No. CORPG3K0191 and No. CMRPG3J1051-3.

Conflict-of-interest statement: The authors declare no conflicts of financial interest.

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Abstract

Organophosphate is a commonly used pesticide in the agricultural sector. The main action of organophosphate focuses on acetylcholinesterase inhibition, and it therefore contributes to acute cholinergic crisis, intermediate syndrome and delayed neurotoxicity. From sporadic case series to epidemiologic studies, organophosphate has been linked to hyperglycemia and the occurrence of new-onset diabetes mellitus. Organophosphate-mediated direct damage to pancreatic

Provenance and peer review: Invited article; Externally peer reviewed

Specialty type: Endocrinology and metabolism

Country/Territory of origin: Taiwan

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 25, 2021
Peer-review started: February 25, 2021
First decision: May 3, 2021
Revised: May 27, 2021
Accepted: September 22, 2021
Article in press: September 22, 2021
Published online: November 15, 2021

P-Reviewer: Mei XF
S-Editor: Gao CC
L-Editor: A
P-Editor: Wang LYT

beta cells, insulin resistance related to systemic inflammation and excessive hepatic gluconeogenesis and polymorphisms of the enzyme governing organophosphate elimination are all possible contributors to the development of new-onset diabetes mellitus. To date, a preventive strategy for organophosphate-mediated new-onset diabetes mellitus is still lacking. However, lowering reactive oxygen species levels may be a practical method to reduce the risk of developing hyperglycemia.

Key Words: Organophosphate; Pesticide; New-onset diabetes mellitus; Mechanism; Reactive oxygen species

Core Tip: Organophosphate may induce acute hyperglycemia by damaging pancreatic cells and result in new-onset diabetes mellitus after chronic exposure to organophosphate compounds. Organophosphate-mediated new-onset diabetes mellitus might be mediated by a polymorphism of paraoxonase-1, which is associated with organophosphate elimination in hepatocytes. Pancreatic beta cell damage, excessive gluconeogenesis, hepatic steatosis, systemic inflammation and possibly sarcopenia all contribute to insulin resistance and therefore hyperglycemia.

Citation: Chung YL, Hou YC, Wang IK, Lu KC, Yen TH. Organophosphate pesticides and new-onset diabetes mellitus: From molecular mechanisms to a possible therapeutic perspective. *World J Diabetes* 2021; 12(11): 1818-1831
URL: https://www.wjgnet.com/1948-9358/full/v12/i11/1818.htm
DOI: https://dx.doi.org/10.4239/wjd.v12.i11.1818

INTRODUCTION

Organophosphate is a commonly used pesticide in the agricultural sector because of its bioavailability. The main action of the organophosphate focuses on acetylcholinesterase inhibition. Because of its wide use, intoxication of organophosphate has been commonly encountered by physicians. Intoxication can be divided into acute cholinergic crisis, intermediate syndrome and delayed neuropathy[1]. Among the complications induced by organophosphates, diabetes mellitus is a common yet often overlooked metabolic complication. The aim of this review is to analyze the molecular pathogenesis mechanisms of new-onset diabetes mellitus after organophosphate exposure.

ORGANOPHOSPHATE TOXICITY: ACUTE CHOLINERGIC CRISIS AND CHRONIC OXIDATIVE STRESS GENERATION

The main action of organophosphate is to inhibit acetylcholinesterase within the nervous system, and therefore, acetylcholine overactivity exists within the synapse and neuromuscular junction[2]. Neurological manifestations are the cardinal symptoms of organophosphate intoxication through the activation of muscarinic receptors and include myosis, excessive secretions, seizures, severe muscle paralysis, cardiorespiratory depression and even death in organophosphate overdose patients [3]. The hydrophobic character of organophosphate leads to its accumulation in adipose tissue, and therefore, intermediate syndrome with delayed neurologic injury might occur through the generation of oxidative stress. Gultekin *et al*[4] demonstrated that organophosphate treatment could activate lipid peroxidase and therefore generate reactive oxygen species (ROS) by exhausting glutathione and superoxide dismutase in a dose-dependent manner. Similar oxidative stress with excessive acetylcholinesterase activity has been reported in workers with chronic exposure to organophosphate[5]. Apart from neurotoxicity, accumulation within different tissues could cause different end-organ damage in the chronic phase. The mitogen-activated protein kinase

(MAPK) signaling pathway could activate associated kinases, such as extracellular responsive kinases, c-Jun N-terminal kinase (JNK) and p38 MAPK, which could worsen downstream apoptosis[6]. The main contributor to MAPK signaling from organophosphates is mediated by oxidative stress. From *in vitro* studies, the administration of organophosphate could activate the expression of quinone oxidoreductase-1, heme oxygenase 1, paraoxonase-1, catalase or superoxide dismutase in blood mesenchymal stem cells[7] or human umbilical vein endothelial cells[8]. Therefore, distant organ damage should arouse concern in chronic organophosphate-intoxicated subjects.

CLINICAL STUDIES OF NEW-ONSET DIABETES MELLITUS AFTER ORGANOPHOSPHATE EXPOSURE

Previous studies revealed that organophosphate exposure could increase the risk of new-onset diabetes mellitus (Tables 1 and 2). Moore and James[9] first noticed that acute organophosphate ingestion was associated with hyperglycemia, and hyperglycemia required insulin intervention for blood sugar control (Table 1). Serial studies also demonstrated that organophosphate-mediated acute pancreatic injury might induce hyperglycemia[10,11]. In 2008, Montgomery *et al*[12] provided epidemiologic data to link chronic exposure to organophosphate with diabetes mellitus (Table 2). Within the 5-year follow-up, the incidence of diabetes mellitus increased in organophosphate users. The study conducted by Liu *et al*[13] demonstrated that acute exposure to organophosphate led to hyperglycemia, but the effect on the development of diabetes mellitus was only marginal. In a meta-analysis study conducted by Lakshmi *et al*[14], hyperglycemia was common. A recent study by Panda *et al*[15] demonstrated that organophosphate exposure was associated with higher insulin resistance and higher plasma glycated hemoglobin levels. From the clinical study, acute organophosphate exposure was associated with hyperglycemia and then regressed after atropine treatment. From the study published by Leonel Javeres *et al* [16], red blood cell acetylcholinesterase activity decreased within the organophosphate exposure group, and the plasma concentrations of lipase/amylase and insulin increased in the organophosphate-exposed group. Such evidence demonstrated the effect of organophosphate on insulin resistance and direct damage to pancreatic cells in clinical investigations.

Clinical studies have shown that acute hyperglycemia develops in acute organophosphate-intoxicated subjects and that such hyperglycemia is associated with poor clinical patient outcomes. However, hyperglycemic status was mostly observed in animals with chronic or subchronic exposure[17,18]. Several *in vivo* studies demonstrated the acute effect of organophosphate on the variation of blood sugar. Rodrigues *et al*[19] reported variations in blood sugar after acute organophosphate exposure. For rats receiving a single intraperitoneal injection of malathion, blood glucose increased within 2 h, followed by hypoglycemia 8 h after injection[19]. In brain tissue, organophosphates can decrease the storage of glycogen within the brain by activating glycogenolytic enzymes such as glycogen phosphorylase and phosphoglucomutase[20]. Glycolytic enzymes, such as phosphofructokinase and hexokinase, might decrease in the acute exposure of organophosphate[21]. Collectively, these mechanisms could explain the occurrence of acute hyperglycemia following organophosphate exposure.

MECHANISMS OF NEW-ONSET DIABETES MELLITUS AFTER ORGANOPHOSPHATE EXPOSURE: DYSFUNCTION OF PANCREATIC BETA CELLS

Nagaraju and Rajini[22] reported that rats receiving chronic organophosphate had higher insulin secretion from pancreatic islet cells and associated pancreatic hypertrophy. Insulin plays an important role in activating glucose transporter 9-mediated glucose transport into cells. Therefore, the regulation of insulin secretion is important in mediating the plasma concentration of glucose. Acetylcholinesterase lies within the pancreas either within acinar cells or insulin-secreting beta cells[23,24]. In insulin-secreting beta cells, acetylcholine binds to the muscarinic receptors of beta cells and then increases the cytosolic calcium concentration and enhances the efficiency of calcium-mediated exocytosis, which activates insulin-secreting activity[24]. Acetylcholinesterase also occurred within the alpha cells of the pancreas. Alpha cells

Table 1 Published human studies on the association between acute organophosphate exposure and the development of new-onset diabetes mellitus

Ref.	Area	Pesticide	Exposure	Sample size	Association
Moore and James[9], 1980	Australia	Coumaphos	Acute	1	Hyperglycemia
Hui[10], 1983	Hong Kong	Organophosphate	Acute	2	Hyperglycemia
Weizman and Sofer [11], 1992	Israel	Organophosphate and carbamate	Acute	17	Hyperglycemia in 29.4% of patients
Yurumez *et al*[98], 2007	Turkey	Organophosphate	Acute	220	Hyperglycemia in 67.7% of patients
Liu *et al*[13], 2014	Taiwan	Organophosphate	Acute	118	Hyperglycemia after poisoning was not associated with higher mortality
Moon *et al*[99], 2016	South Korea	Organophosphate	Acute	184	Hyperglycemia after poisoning was associated with higher mortality

Table 2 Published human studies on the association between chronic organophosphate exposure and the development of new-onset diabetes mellitus

Ref.	Area	Pesticide	Exposure	Sample size	Association
Montgomery *et al* [12], 2008	United States	Organophosphate and organochlorine	Chronic	33457	Positive association with diabetes
Raafat *et al*[100], 2012	Egypt	Malathion	Chronic	98	Positive associations among blood malathion concentration, waist circumference and insulin resistance
Velmurugan *et al* [30], 2017	India	Organophosphate	Chronic	3080	Positive association between blood organophosphate residues and glycated hemoglobin levels
Velmurugan *et al* [90], 2020	India	Organophosphate and arsenic	Chronic	865	Positive associations of organophosphate and arsenic with diabetes, prediabetes and atherosclerosis

stimulate insulin secretion in a paracrine manner within the pancreas[25]. Bendayan and Gisiger[23] also reported that acetylcholinesterase existed within acinar cells. Acinar cells are commonly regarded as governing lipase, but insulin secretion ability has been noted in several human studies beyond alpha and beta islet cells[26]. Case series studies showed that organophosphate overdose could induce pancreatitis and elevation of serum amylase[27]. Such clinical studies have provided evidence of organophosphate-mediated pancreatic damage. In addition, the acetylcholinergic receptor also governs the viability of pancreatic cells. The study conducted by Pfitzinger *et al*[28] demonstrated that cholinergic activation slowed the progression of pancreatic cancer. On the other hand, Zhang *et al*[29] presented evidence in a type I diabetes mellitus animal model mediated by streptozotocin that an acetylcholinesterase inhibitor protected pancreatic beta cells against apoptosis. Therefore, organophosphates might disrupt insulin secretion directly by dysregulating acetylcholinesterase activity (Figure 1).

MECHANISMS OF NEW-ONSET DIABETES MELLITUS AFTER ORGANOPHOSPHATE EXPOSURE: DYSFUNCTION OF GLUCONEOGENESIS

Organophosphate-mediated gluconeogenesis by disrupted lipolysis

The pathogenesis of diabetes mellitus involves impaired regulation of hepatic gluconeogenesis. Hypersensitive glucose production in response to gluconeogenic stimuli poses organophosphate exposure as a risk factor for prediabetes[30,31]. As organophosphates are ingested *via* the intestine, the conversion of organophosphates by cytochrome 450 enhances cholinergic inhibition up to 70%[32]. As organophosphate accumulates within hepatocytes, the activation of adenylyl cyclase produces excessive cyclic adenosine monophosphate[31], which increases hepatic glucose production and

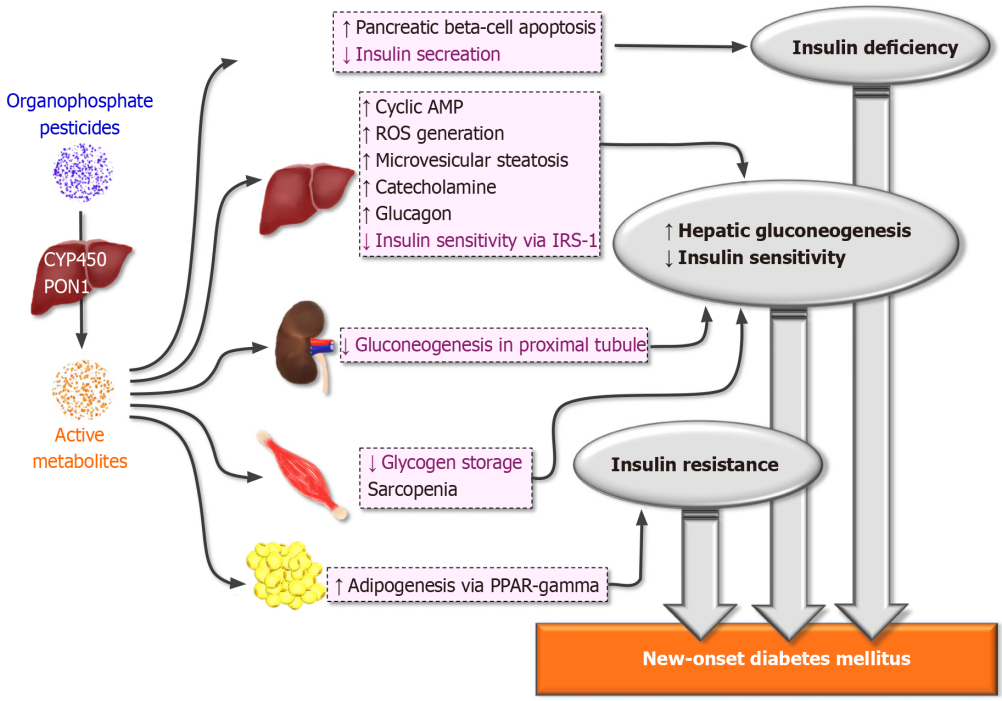

Figure 1 Postulated molecular mechanisms of new-onset diabetes mellitus after organophosphate pesticide exposure. Organophosphate pesticides are metabolized in the liver to toxic derivatives *via* cytochrome P450 *via* a first-pass effect. Paroxonase isoform 1 serves as the enzyme handling hydroxylation and cleavage of the toxic form. The active metabolite might induce new-onset diabetes mellitus *via* pancreatic beta cell damage and disturb the homeostasis of gluconeogenesis and insulin sensitivity. Organophosphates could directly induce apoptosis of pancreatic beta cells by activating nuclear factor-kappa beta, and therefore, insulin secretion may be hampered. Beyond pancreatic cells, gluconeogenesis within the liver could be activated by reactive oxidative species generation and inflammation induced by microvesicular steatosis, enhanced cyclic adenosine monophosphate generation, excessive catecholamine and abated insulin sensitivity of hepatocytes *via* insulin receptor substrate-1. Distal organ damage by organophosphates may also disturb the homeostasis of gluconeogenesis. In organophosphate-related acute kidney injury, gluconeogenesis within the proximal tubules is disturbed. Decreased proximal gluconeogenesis exacerbates excessive hepatic gluconeogenesis. In skeletal muscle, sarcopenia mediated by intermediate syndrome might reduce glycogen storage within skeletal muscle, which may induce hyperglycemia. Organophosphates also deposit within adipose tissue and therefore exacerbate adipogenesis by activating peroxisome proliferator-activated receptor-gamma. Excessive adipose tissue might enhance insulin resistance and further hasten the development of new-onset diabetes mellitus. CYP450: Cytochrome P450; PON1: Paroxonase isoform 1; ROS: Reactive oxidative species; AMP: Adenosine monophosphate; IRS-1: Insulin receptor substrate-1; PPAR: Peroxisome proliferator-activated receptor.

therefore increases body weight along with adipose tissue[33]. In a study conducted by Velmurugan *et al*[30], acetic acid increased hepatic glucose-6 phosphate and citric acid production after inducing inflammation. Apart from activation of cyclic adenosine monophosphate, the organophosphate itself also increases oxidative stress within hepatocytes by exhausting enzymes that reverse oxidative stress[34], and such oxidative stress may disrupt membranous lipids by activating lipid peroxidation[35]. Hepatic injury also occurs in organophosphate intoxication, and therefore, sequential sinusoidal dilatation and microvesicular steatosis impair glycogen synthesis[36]. Insulin mediates the suppression of adipose lipolysis physiologically and therefore downregulates gluconeogenesis[37]. Ince *et al*[38] demonstrated that lipid metabolism was disturbed in organophosphate-treated mice, with excessive end-products of lipid peroxidation. As excessive acetylcholinesterase leads to subjects having chronic hypercholinergic status, dietary habits are altered. From the study by Slotkin *et al*[39], neonatal rats exposed to organophosphate had hyperactive acetylcholine function within the neuron body, and such activity could be ameliorated only by a high-fat diet.

Organophosphate-mediated gluconeogenesis mediated by impaired glycogen storage

Under hyperglycemic conditions, glycogen storage could lower circulating glucose and enhance the anabolism process rather than catabolism. Glycogen phosphorylase, which counteracts glycogen storage, is activated by organophosphates[40]. Dichlorvos, as an example, increased the messenger ribonucleic acid expression of glycogen phosphorylase and decreased glycogen storage[41]. However, the different organophosphates had diverse actions on glycogen-storing proteins. Malathion, while activating the gluconeogenesis process, decreased glycogen phosphorylase but resulted in compensatory hepatomegaly[42,43]. The modulation of organophosphate

on glycogen storage could contribute to the gluconeogenesis process.

Organophosphate-mediated gluconeogenesis mediated by altered hormone regulation

Glucagon and catecholamine are the major hormones regulating gluconeogenesis[37]. Glucagon and catecholamine could directly enhance hepatic gluconeogenesis by activating cyclic adenosine monophosphate *via* phosphorylation of protein kinase A activity[44] and bifunctional enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2 (PFK2/FBPase-2)[45]. Glucagon activity also decreased glycogen storage by coupling with the inhibitory G protein[46]. Catecholamine, on the other hand, also activates gluconeogenesis *via* cyclic adenosine monophosphate activity[47]. Stress-associated catecholamine release can increase the gluconeogenesis process and therefore insulin resistance, and organophosphate itself activates catecholamine release after inhibiting acetylcholinesterase activity[42]. Organophosphate could activate catecholamine release within neurons, and unbalanced catecholamine release might prolong the gluconeogenesis process.

MECHANISMS OF NEW-ONSET DIABETES MELLITUS AFTER ORGANOPHOSPHATE EXPOSURE: INSULIN RESISTANCE MEDIATED BY INFLAMMATION OR DYNAMIC CHANGES IN THE MICROBIOTA

Insulin resistance, excessive gluconeogenesis and insufficient glucose uptake in the presence of insulin place subjects as hyperglycemia status and therefore invoke sequential adipose tissue formation. Physiologically, insulin activates the insulin receptor by tyrosine phosphorylation of insulin receptor substrate-1[48], and serine phosphorylation inhibits the insulin receptor and offsets insulin activity[49]. Insulin resistance is common in chronic organophosphate exposure subjects. From the *in vivo* study conducted by Nagaraju and Rajini[22], insulin hypertrophy and the increased secretion of insulin were accompanied by circulating insulin-like growth factor 1, free fatty acids, corticosterone, and paraoxonase activity. As organophosphate increases excessive cholinergic activity, insulin resistance is associated with systemic inflammation. From the study reported by Liang *et al*[50], organophosphates could induce an increase in body weight in experimental mice treated with a high-fat diet. In organophosphate mice treated with a high-fat diet, systemic inflammation mediated by lipopolysaccharide might occur. Systemic inflammation mediated by the intestinal barrier might activate systemic inflammation. In addition, the lipid peroxidation end product malondialdehyde (MDA) increased in organophosphate-treated rats, and the oxidative end product was associated with a higher level of inflammation[38].

Chronic exposure to organophosphate could directly enhance systemic inflammation. In a study by Ince *et al*[38], organophosphate-treated rats had higher proinflammatory cytokines, such as interferon gamma, interleukin 1 beta, tumor necrosis factor alpha, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), than control rats. Hepatocytes are the major cells confronting proinflammatory cytokines. As NF-κB is activated by inflammatory cytokines, IκB kinase-β might be activated and therefore hamper the downstream action of insulin[51]. In addition to IκB kinase-β, JNK signaling was also activated in organophosphate intoxication. When endoplasmic reticulum stress is enhanced after organophosphate-mediated excessive oxidative stress, JNK is activated under conditions of proinflammatory cytokine release *via* NF-κB[52]. Based on the evidence above, organophosphates might induce inflammation and produce proinflammatory cytokines mediating insulin resistance.

MECHANISMS OF NEW-ONSET DIABETES MELLITUS AFTER ORGANOPHOSPHATE EXPOSURE: INSULIN RESISTANCE MEDIATED BY ROS

Excessive oxidative stress is associated with insulin resistance. Polyunsaturated fatty acids are the main source of oxidative stress. Low concentrations of ROS mediate the proliferative signals of insulin by phosphatidylinositol 3-kinase and protein kinase B [53]. In acute or chronic organophosphate intoxication, ROS regeneration is common as the exhaustion of endogenous antioxidant species occurs. The MDA level and superoxide dismutase increased in organophosphate intoxication, and reduced

glutathione was depleted[5]. Possamai *et al*[54] showed that both acute and chronic exposure to malathion could generate ROS within the kidney and brain acutely and liver and skeletal muscle chronically. The study performed by Aly *et al*[55] also demonstrated that the liver serves as the reservoir in chronic organophosphate exposure with the generation of ROS. To enhance the elimination of ROS, adenosine triphosphate is generated from the activated gluconeogenesis process within the liver [56]. In addition, ROS also directly disturb insulin receptor signaling. Morino *et al*[57] demonstrated that ROS activated serine residues on insulin receptor substrate 1 and therefore inhibited glucose transporter type 4. From the aspect above, the ROS generated by organophosphate could disturb insulin signaling and therefore worsen insulin resistance.

MECHANISMS OF NEW-ONSET DIABETES MELLITUS AFTER ORGANOPHOSPHATE EXPOSURE: DYSFUNCTION OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA

Peroxisome proliferator-activated receptor (PPAR) is a transcriptional receptor within the nucleus, and its main action governs the proliferation of peroxisomes within the nucleus. PPARs regulate the metabolism of carbohydrates, lipids and proteins along with insulin sensitivity. The role of organophosphates in lipid metabolism has been demonstrated. Since organophosphate is a highly fat-soluble component, accumulation within adipose tissue could prolong its toxicity and generate oxidative stress within adipose tissue[58]. Smith *et al*[59] demonstrated that diazinon induces adipogenesis within preadipocytes by activating PPAR gamma receptors along with the transcription factor CCAAT-enhancer-binding protein α (C/EBPα).

MECHANISMS OF NEW-ONSET DIABETES MELLITUS AFTER ORGANOPHOSPHATE EXPOSURE: GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST AND DIPEPTIDYL PEPTIDASE-4 INHIBITOR

Incretin secreted from the intestine is important for insulin secretion. As carbohydrates enter the duodenum, the K cells within the duodenum secrete glucose-dependent insulinotropic polypeptides into the brain *via* the vagus nerve. Activated vagal tone enhances acetylcholine release to M cells within the distal ileum and therefore increases glucagon-like peptide 1 (GLP-1). GLP-1 could therefore increase insulin release and lower blood glucose. Organophosphates might increase the acetylcholine concentration within the neural cleft and therefore downregulate muscarinic receptors. Downregulated muscarinic receptors attenuate GLP-1 release and therefore further insulin release[60]. From the study by Rathis *et al*[61], the GLP-1 response was attenuated in subjects with acute exposure to organophosphate with atropine treatment. Chronic exposure to organophosphate might downregulate the incretin-mediated glucose-lowering effect.

MECHANISMS OF NEW-ONSET DIABETES MELLITUS AFTER ORGANOPHOSPHATE EXPOSURE: RENAL HANDLING OF GLUCOSE

From clinical observations, victims of organophosphate exposure had transient glycosuria, which was relevant to euglycemia[62]. Based on the evidence, acute tubular necrosis might be noticed in organophosphate intoxication subjects. From the study reported by Kaya *et al*[63], acute organophosphate intoxication could mediate the vacuolization of tubular epithelial cells and tubular structure approaching atrophy within the proximal tubules. The oxidative stress mediated by organophosphates worsened proximal tubular damage in an *in vitro* study performed by Poovala *et al* [64]. The activation of the MAPK signaling pathway within nephron precursor cells demonstrated direct nephrotoxicity after activating JNK and caspase-3[65]. Proximal tubular cells primarily serve as gluconeogenic cells through the utilization of adenosine triphosphate, and therefore, damaged proximal tubules might impair endogenous gluconeogenesis[66] and are associated with higher mortality and the need for dialysis in critically ill patients[67,68], including organophosphate in-

toxication subjects[69]. Since acute kidney injury and stress-mediated inflammation might contribute to insulin resistance and new-onset diabetes mellitus[70], preserving kidney function during acute kidney injury status through organophosphate intoxication should be important in managing these patients to hamper the development of diabetes mellitus.

MECHANISMS OF NEW-ONSET DIABETES MELLITUS AFTER ORGANOPHOSPHATE EXPOSURE: INTERMEDIATE SYNDROME

As described in the previous sections, the major clinical manifestation of cholinergic crisis was the overactivation of the parasympathetic tone with tachycardia, myosis or neurologic complications such as seizures. From a previous study by Liu *et al*[13], acute organophosphate intoxication was minimally predictive of new-onset diabetes mellitus. Intermediate syndrome by organophosphate could induce myopathy, especially in the proximal skeletal muscle and respiratory muscle[71]. Although the direct mechanism is still unknown, necrosis of skeletal muscle and associated myopathy might be an entity in chronic organophosphate intoxication subjects[72]. In addition, organophosphate-mediated peripheral motor neuropathy is accompanied by weakness after acute intoxication[73]. From a review of the literature, a correlation between organophosphate intoxication and sarcopenia was rare. However, in patients with diabetic neuropathy, sarcopenia was more obvious than in those without neuropathy[74]. Persistent muscle weakness in intermediate syndrome might lead to sarcopenic status in organophosphate patients, and sarcopenia alone might enhance the risk of developing diabetes mellitus. In the study by Hong *et al*[75], skeletal muscle mass was negatively associated with the development of type 2 diabetes mellitus. Since skeletal muscle serves as the pool of glucose mediated by insulin, the decreased skeletal mass would reduce glucose disposal and therefore worsen the inflammation of skeletal muscle and insulin resistance[76].

POSSIBLE THERAPEUTIC PERSPECTIVE IN PREVENTING ORGANOPHOSPHATE-MEDIATED NEW-ONSET DIABETES MELLITUS

In acute organophosphate intoxication, the application of atropine is the mandatory therapeutic strategy in treating cholinergic crises. The association between atropine and insulin secretion has been discussed. In 1978, cholinergic blockade by atropine was known to decrease insulin secretion mediated by gastric inhibitory polypeptides and gastrin release[77,78]. The action of atropine on gastric inhibitory polypeptides lowered postprandial insulin secretion. From the study published by Schafer *et al*[79] and Afonso *et al*[80], atropine inhibited the release of hepatic insulin-sensitizing substances, which therefore lessened insulin sensitivity during feeding. The parasympathetic nerves directly stimulate postprandial insulin secretion; therefore, atropine might play an inhibitory role in blood sugar control. However, a study by Svensson *et al*[81] showed that atropine improved insulin sensitivity in both lean and obese subjects. In the atropine-treated group, glucose uptake was higher than that in the subjects treated with saline alone. In summary, parasympathetic blockade might directly decrease insulin secretion mediated by gastric inhibitory polypeptides and delay intestinal emptying under cellular dehydration conditions[82]. However, atropine might improve insulin sensitivity based on the clinical trial mediated by Svensson *et al*[81]. Since atropine might only be given in the acute intoxication of organophosphate conditions, the acute adverse effect might not be potentiated.

ROLE OF ROS GENERATION IN ORGANOPHOSPHATE-MEDIATED NEW-ONSET DIABETES MELLITUS

From the evidence mentioned above, the oxidative stress generated by organophosphate increased gluconeogenesis and decreased insulin sensitivity. Therefore, interventions to lessen ROS generation have been proposed to prevent the development of organophosphate-mediated diabetes mellitus. N-Acetylcysteine is a widely used scavenger for ROS due to its regeneration of glutathione. From clinical trials, N-acetylcysteine has been applied to treat acute organophosphate intoxication.

From the clinical trial reported by El-Ebiary *et al*[83], n-acetylcysteine could achieve less atropine use and shorter hospitalization stays in acute organophosphate intoxication subjects. Falach-Malik *et al*[84] demonstrated that in diabetes-prone mice treated with a high-fat diet, n-acetylcysteine alleviated glucose intolerance by lessening hepatic steatosis. Charron *et al*[85] also demonstrated that in high-fat diet-fed maternal mice, n-acetylcysteine supplementation in the maternal stage decreased diabetes mellitus development in offspring. A similar effect was also demonstrated in a type 1 diabetes mellitus animal model under insulin deficiency[86]. N-Acetylcysteine also lessened organophosphate-mediated toxicity *in vivo*. A report from Yurumez *et al*[87] demonstrated that N-acetylcysteine could rescue antioxidative glutathione, nitrite and nitrate and decrease MDA generation in organophosphate-treated mice. The study conducted by Bayir *et al*[88] demonstrated that in organophosphate-poisoned mice, n-acetylcysteine alone could restore the cholinesterase concentration within erythrocytes, and the liver MDA level was lessened in n-acetylcysteine-treated mice rather than pralidoxime-atropine-treated mice or sham mice. From the aspect of decreasing organophosphate-mediated oxidative stress and the sequential development of diabetes mellitus, a therapeutic strategy for lowering ROS should be considered.

FUTURE PERSPECTIVES ON THE PREVENTION OF ORGANOPHOSPHATE-MEDIATED NEW-ONSET DIABETES MELLITUS: RISK FACTOR STRATIFICATION

Since the development of diabetes mellitus is common in organophosphate-exposed subjects, risk stratification should be emphasized. The specific brand of organophosphate pesticide could influence the development of diabetes mellitus. Juntarawijit and Juntarawijit[89] noticed that endosulfan, mevinphos, carbamate and one fungicide (benlates) contributed to the development of diabetes mellitus in the Thai population. Apart from the specific insecticides, the environmental heavy metal content might play a synergistic role in the development of diabetes mellitus. From the study by Velmurugan *et al*[90], arsenics could synergize with organophosphate-mediated diabetes mellitus. At the same time, genetic polymorphisms should play a role in the development of organophosphate-induced diabetes mellitus. As the previous section mentioned, organophosphates could be metabolized by hepatic cytochrome p450, and metabolites might generate genotoxicity if the polymorphism existed within the subjects[91]. The first pass effect of cytochrome p450 generates toxic oxon organophosphate, which would be further oxidatively cleaved by cytochrome or hydroxylated by paraoxonase-1[92,93]. From the study by Al-Hakeem *et al*[94], the polymorphism in paraoxonase-1 with glutamine 192 to arginine made the subject vulnerable to gestational diabetes mellitus. The evidence shows a link between the polymorphism and organophosphate-mediated diabetes mellitus. In addition to diabetes mellitus development, lipid metabolism might be altered by paraoxonase-1 polymorphisms. The study conducted by Onat and *et al*[95] Leonel Javeres *et al*[96] demonstrated that the paraoxonase-1 polymorphism with the rs662 genotype was associated with ApoA1 and ApoB, which also reflected dyslipidemia in metabolic syndrome. Finally, personal protective equipment plays an important role in moderating the organophosphate metabolites associated with insulin resistance. Seesen conducted a study analyzing urinary organophosphate metabolites in pesticide sprayers and nonfarm workers[97]. In this study, the pesticide sprayer had a higher incidence of insulin resistance, and the only different organophosphate metabolite was diethylthiophosphate. No correlation was identified between diethylthiophosphate and the severity of insulin resistance. However, personal protection equipment lowered organophosphate metabolite generation. Personal protective equipment might play a preventive role in alleviating insulin resistance in organophosphate intoxication subjects.

CONCLUSION

Organophosphate pesticides have been linked to both acute and chronic intoxication. In acute intoxication, organophosphate-mediated cholinergic crisis might sequentially be followed by intermediate syndrome. Intermediate syndrome might hamper chronic muscle wasting and sarcopenia, therefore increasing the risk of diabetes mellitus. With chronic exposure to organophosphates, diabetes mellitus might develop by direct

damage to the pancreas and insulin resistance mediated by lipolysis, oxidative stress and chronic inflammation. Distal organ damage, such as acute kidney injury, might worsen possible organophosphate-mediated diabetes mellitus. The standard therapeutic strategy for cholinergic crisis may play a controversial role in managing organophosphate-mediated diabetes mellitus. However, reducing ROS might be a possible therapeutic strategy. In addition, elucidating the possible genetic polymorphisms to predict the development of diabetes mellitus with organophosphate intoxication might be essential.

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