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ABOUT COVER

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Environmental pollution and diabetes mellitus

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Abstract

Diabetes mellitus (DM) is a chromic metabolic disease that affects a large segment of the population worldwide. Physical inactivity, poor nutrition, and genetic predisposition are main risk factors for disease development. In the last decade, it was clear to the scientific community that DM development is linked to a novel disease inducer that was later defined as diabetogenic factors of pollution and endocrine disrupting agents. Environmental pollution is exponentially increasing in uncontrolled manner in several countries. Environmental pollutants are of diverse nature and toxicities, including polyaromatic hydrocarbons (PAHs), pesticides, and heavy metals. In the current review, we shed light on the impact of each class of these pollutants and the underlined molecular mechanism of diabetes induction and biological toxicities. Finally, a brief overview about the connection between coronavirus disease 2019 and diabetes pandemics is presented.

Key Words: Diabetes mellitus; Glucose; Heavy metals; Polyaromatic hydrocarbons; Pesticide; COVID-19

Core Tip: In the review we summarize the relationship between different environmental pollutants of polyaromatic hydrocarbons, pesticides and heavy metals and their association with prevalence of diabetes mellitus. Further discussion of the molecular mechanisms of these pollutants that underline diabetes pathophysiology. Finally, a brief discussion on the association of diabetes mellitus, coronavirus disease 2019 and their clinical complications.

INTRODUCTION

The metabolic disease burden is mounting globally with accelerating rate[1]. Diabetes is a chronic metabolic disorder that significantly increases global disease burden and associated mortality[2]. Around 350 million individuals are suffering from diabetes worldwide, and epidemiological studies expect that there would be up to 590 million sufferers by 2035[3]. Diabetes costs the medical sector an estimate of 1.31 trillion dollars of the global domestic product[4]. Diabetes is the 7th leading cause of death worldwide. The disease is characterized by a deficiency in insulin secretion, hyperglycemia, and insulin receptor insensitivity[5]. Secondary diabetic complications include ulcer foot, renal failure, vision impairment, and cognitive dysfunction which can be developed over a prolonged unrecognized hyperglycemia[10]. It had been confirmed for decades that diabetes is a disease of obesity, poor dietary habits, smoking, and physical inactivity[6-8] but a decade ago it was proposed that environmental pollutants can be a potent inducer to diabetes mellitus (DM)[9]. Furthermore, due to widespread industrialization, a large segment of the world population is increasingly exposed to elevated concentration of environmental pollutants[5].

Diabetes can be of type I (type I DM, T1DM) or type II (type II DM, T2DM). T1DM results from pancreatic β-cell destruction due to reactive oxygen species (ROS) overload or autoimmune self-destruction[11]. Molecular mediators of T1DM include, but are not limited to, ROS, tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), and interferon γ (INF γ)[12,13]. On the other hand, T2DM results from either reduction in insulin synthesis and secretion or insulin resistance as the main hallmark of the disease[14,15]. The burden of T2DM arouses in its associated complications affecting more than 400 million people worldwide and is increasing annually[16].

Environmental pollution is defined as the introduction of harmful substances to human into the environment. Pollutants can be solid, liquid, or gaseous in nature, and elevated concentrations of any form will affect the quality of our environment and living organisms[17]. The term diabetogen was firstly introduced by Campbell[18] in a letter submitted to the *British Medical Journal* describing his finding that excess consumption of mustard oil was the cause of increased incidence of diabetes among Natal Indians. Later, he postulated that diabetes was developed as a result of chemical chelation of sulfhydryl group that can interfere with carbohydrate metabolism. Recent reports demonstrated that environmental pollutants and endocrine disruptive chemicals can be attributed to the increased number of diabetes sufferers among different populations[7,19-24]. Following this, obesogenic chemicals, such as polychlorinated biphenyls and pesticides, also arouse on the front line of research[25].

Environmental pollutants are diverse examples of heavy metals, polycyclic aromatic hydrocarbons (PAHs), pesticides, and different dioxins. They have various health impacts on the biological systems. Recently, there is a call for minimizing human exposure to such pollutants in order to improve human health and decrease economic, coast, and disease burden worldwide[24]. Dioxins are a group of highly toxic persistent organic pollutants (POPs), released in the environment as industrial by-products. They comprise molecules such as polychlorinated dibenzo-p-dioxins, polychlorinated/polybrominated biphenyls, and polychlorinated dibenzofurans[26].

KREBS CYCLE, GLYCOLYSIS, AND BLOOD GLUCOSE LEVEL

Glycolysis is the process of converting glucose into pyruvate/lactate following cellular uptake of glucose and glucose phosphorylation. Adenosine triphosphate (ATP) and energy required for glycogenesis and lipogenesis are also provided through glycolysis. Different cells utilize glycolysis through different regulation levels such as glucose phosphorylation, glucose uptake, and/or fructose-6-phosphate conversion into fructose-2,6-biphosphate (F2,6p2). Moreover, glycolysis rate is strictly regulated by various factors such as glucokinase (GK), glucose transporter-4 (GLUT-4), and 6-phosphofructo-1-kinase (6PFK1). Briefly, 6PFK1 activation occurs *via* F2,6p2 which is a potent activator to 6PFK1 and regulation of glycolysis rate. F2,6p2 production and breakdown are achieved through 6-phosphofructo-2-kinase/fructose-2,6-biphosphate (6PFK2/FBPase2) in different cells in response to nutritional variations in the environment[27].

Importantly, it has been demonstrated that glycolysis is closely associated with different aspects of integrative physiology, in particular, glucose production in liver, insulin secretion in the pancreas[28-30], muscle glycolysis[31], adipose tissue lipogenesis[32], and hypothalamus glycolysis[33]. Furthermore, liver glucose entrance and clearance are achieved through cycles of glycolysis and glycogenesis regulating blood glucose level[34]. Mechanistic interaction between insulin and glucose is mainly additive or synergistic for stimulating GK dissociation in hepatocytes from the inhibitory GK discoiation from its inhibitory binding to GK regulatory protein in order to improve the hepatic expression of GK and 6PFK2/FBPase2[35].

Linking glycolysis as a physiological process with diabetes can obviously be seen from the fact that decreased or dysregulated glucose phosphorylation is a glycolytic critical step contributing to elevated HGP and developed hyperglycemia[27].

Several cross-sectional and prospective studies reported the relation of blood sugar level, sugar-related metabolites, glycolysis/glucogenesis components, and tricarboxylic acid (TCA) pathway intermediates with prediabetic syndrome, insulin resistance, and diabetes[36-39]. TCA cycle is the main source of energy in cells by yielding ATP. TCA is also known as citric acid cycle or Krebs's cycle. In addition, TCA works as a precursor pathway for gluconeogenesis during fasting[40].

Among different glycolysis/glucogenesis metabolites, lactate (the endpoint of anaerobic glycolysis) showed a differential response change in its concentration during oral-glucose-tolerance test (OGTT)[41]. Moreover, lactate metabolite was a relevant predictor for T2DM incidence in some epidemiological studies[42-44]. Although TCA metabolic cycle and glycolytic pathway were altered in pancreatic β-cell lines[45], it is unlikely that lactate/pyruvate circulated in the blood directly influence insulin secretion given that lactate/pyruvate transporter monocarboxylate transporter 1 is inhibited in the β cells responsible for insulin resistance and metabolic phenotypes [46]. Plasma lactate concentration was increased upon 75-g OGTT and hyperinsulinemic-euglycemic clamps in insulin resistant objects compared to insulin sensitive objects[47-49]. In addition, there was an observed link between circulating lactate and glucose homeostasis as lactate is a precursor of hepatic gluconeogenesis enhancing the endogenous glucose production. Finally, the importance of plasma lactate in metabolism lies in its utilization as the major carbon source to mitochondrial TCA mostly in peripheral tissues[50,51].

Among diabetes clinical features, peripheral insulin resistance is a major concern where the exact molecular mechanism has not been elucidated in detail yet[52]. Researchers have described that diabetic myotubes derived from T2DM individuals experience increased basal glucose and lipid oxidation[53]. These alterations in myotubes physiology were attributed to reduced TCA cycle flux[54]. This was confirmed by TCA cycle inhibition by malonate (competitive inhibitor of TCA cycle enzyme succinate dehydrogenase) which resulted in a decline in acetate oxidation and full palmitate oxidation[55]. TCA cycle flux reduction can be responsible in part in the diabetic phenotype. An explanation to this lies in the fact that acetate, malate, citrate, pyruvate, glutamate, and isocitrate (TCA metabolites produced by anaplerosis process)[56] enter TCA cycle at different sites before their oxidation occurs which powers the conversion of ADP to ATP. The generated energy is transferred to electron transport chain complex I[57]. It was found that mitochondrial ATP production was reduced in diabetic patients due to impaired oxidative phosphorylation[58,59]. Other studies could not confirm this finding based on transcriptomic profile of diabetic myotubes[60]. Insulin resistance in type II diabetic patients has been connected to increased oxidative stress, DNA damage, and lipid and protein damage[61].

Conventional laboratory tests can be utilized for confirming the reality of toxin exposure inside animals' bodies such as γ-glutamyl transferase which is an enzyme that recycles glutathione for POPs detoxification[26], determination of pollutant metabolites in urine by using gas chromatography mass spectrometry[62-64], complete blood counts, alanine transaminase, and high-sensitivity C-reactive protein.

PESTICIDES

Pesticides are a group of natural or chemical compounds utilized in the agriculture field to fight insects and enhance plant growth[65]. Pesticides are receiving more attention recently because they are the most commonly used compound nowadays with more than 2.3 billion kgs used worldwide[66]. Pesticides include both organochlorine (OC) and organophosphorus (OP). OP pesticides can degrade easily and have a short half-life cycle. Hence, most studies related to OP are designed to comply with

their nature[67,68]. OP pesticide exposure was associated with diabetes prevalence in two different Pakistani and Cameroonian populations through dysregulation of pancreatic function of β cell[69].

Data linking pesticides and diabetes is scare, and more research and epidemiological studies are needed[70]. The first reported and largest systematic review of observational analysis linking diabetes association and pesticides was conducted by Evangelou *et al*[71]. In their study, they summarized the finding of their analysis as there is an association between OC (chlordane, trans-nonachlor, oxylchlordane, heptachlor, DDE, DDT, HCB, and dieldrin) and T2DM.

In a large-scale population study applied on 33457 pesticide applicators in the US initiated by Agriculture Health Study, an association was found between OC compounds, such as chlordane, aldrin, dichlorvos, heptachlor, alachlor, cyanazine, and trichlorfon, and diabetes[72]. When the study was extended to include wives of those pesticide applicators, more diabetic linked compounds were identified such as fonofos, phorate, and parathion (organophosphate) and one OC as dieldrin[73]. Furthermore, pesticides (mevinphos, endosulfan, carbaryl/sevin and benlate) as a major agriculture chemical waste were reported to be significantly associated with diabetes occurrence among Thai farmers[74]; the same finding was reported in Korean farmers in a cohort study comprising 2559 farmers[75]. Egyptian diabetic children showed a correlation between CD4%, CD4/CD8 ratio, and HLADR% and lindane and malathion (organophosphate compound), highlighting the need for further studies to reduce pesticide use in Egypt[76]. A US large-scale screening of pesticide applicators of non-Hispanic white males found that chlordane, aldrin, and heptachlor pesticides specifically correlated with increased diabetes risk[72]. Moreover, diabetes-associated mortality was higher in Australian individuals exposed to pesticides than the general population[77]; the same finding was reported among Indian farmers[78]. Finally, in a recent and pioneering study, OCs compounds (chordane, trans-nonachlor, p,p'-DDT, β-HCH, *trans*-chordan, and mirex/kepone) were detected in sera of more than 75% of Chinese participants in a nationwide Chinese study. It was reported that the associated mechanism may be disrupted lipid metabolism, elevated hemoglobin A1c, triglycerides, and lactate dehydrogenase[79].

A recently published research article studied the diabetogenic impact of dichlorvos and atrazine in Drosophila melanogaster. In this study, the authors utilized a fly model with conserved insulin/insulin growth factor-like signaling (IIS) and exposed the embryonic stages to various concentrations of either the pesticide (dichlorvos) or the herbicide (atrazine). Dichlorvos induced T1DM, while atrazine induced T2DM. The associated mechanism included excess oxidative stress, altered JNK, and AKT phosphorylation[80]. Acute and chronic rat exposure to dichlorvos caused hyperglycemia associated with UDP glucose synthesis inhibition that was reversed by insulin administration[80].

Secondary diabetic nephropathy is a common secondary manifestation of diabetes. Various pesticide compounds were detected in sera samples of individuals with chronic nephropathy. It was found that the six chemicals were *p,p'*-DDT (dichlorodiphenyltrichloroethane), *p,p'*-DDE (dichlorodiphenyltrichloroethylene), beta-hexachlorocyclohexane, oxychlordane, trans-nonachlor, and heptachlor epoxide to be loaded excessively in their blood sera. It was also demonstrated that androstane receptor/pregnane X receptor and aryl hydrocarbon receptor pathway are the main indulged pathways in diabetic secondary manifestation[81].

Trichlorfon insecticide is broadly utilized in aquaculture farms for reducing fish parasitic infection. Silver cat fish *Rhamdia quelen* exposed to an acute dose of trichlorfon exhibited reduced activity of creatine kinase and complexes II-III and IV in muscle, lower content of polyunsaturated fatty acids (Omega 3 and Omega 6), and altered fatty acid profile in comparison to the control group[82].

Nonobese diabetic mice (NOD) mice exposed to chronic high dose of DDE suffered significantly from T1DM development and hyperglycemia because of the irregular activity of T-cell and suppressed cytokine secretion such as IL-4 and IL-10[83].

Gestational DM (GDM) is a form of diabetes that develops during pregnancy affecting 1%-14% of the United States population[84]. GDM is considered a predisposition for T2DM development. The main risk factors for GDM include older maternal age, obesity, previous macrosomic infant, and diabetes history[85]. Wistar rats exposed to imidacloprid (IMI) and chlorpyrifos (CPF) during gestation resulted in striking results where female rats developed diabetes and their offspring also developed diabetes over the long term of life indicating intergenerational adverse effect. Diabetes developed in those Wistar rats showed signs of increased fasting blood glucose, decreased GLUT4 and NFkβ, and reduced high-density lipoproteins (HDL)[86].

Carbendazim (fungicide) administration to mice for 14 wk caused elevation in the levels of triglycerides in their feces as an indication of dysregulated lipid absorption in intestine[87]. Pesticide may have an effect on energy absorption in intestine by regulating gut microbiota[88]. Evidence of rat exposure to pesticides showed a deteriorative effect on pancreatic β cell by imazamox (36 mg/b.w.) treatment[89] and change of pancreas size and glucose homeostasis by IMI (1 mg/kg) treatment[90]. Meanwhile, rats treated with dimethoate at dose of 200 mg/kg b.w. showed signs of pancreas fibrosis and profibrotic cytokines such as transforming growth factor β1[91]. Pesticides affected not only pancreas cytotoxicity but also hormone secretion. Malathion treatment at 400 ppm resulted in an elevated secretion of insulin[92]. On the other hand, both amitraz (10 μmol/L)[93] and diazinon (60 g/kg b.w.)[94] reduced insulin secretion in rat pancreas. Furthermore, pesticide mixture of pirimicarb, quinoclamine, thiram, and ziram in rats led to overexpression of glucagon in pancreatic α cells which is an indicator of increased glucogenesis[95].

Insulin resistance and dysglycemia are also associated with pesticides exposure. Permethrin, CPF, and IMI treatment in mice led to an elevation in blood glucose level [96-98]. Additionally, obesogenic effects of pesticides have been documented in different studies. CPF treated rats (3 mg/kg b.w.) had increased body weight without affecting animal appetite or food consumption[99]. Opposite effect was noticed when pesticide mixture of pirimicarb, quinoclamine, thiram, and ziram treated rats led to decreased body weight[95].

Several mechanisms were proposed explaining the effect of pesticides on diabetes [68]. OC pesticides have variable molecular weights and cellular targets which imply that not a single mechanism can define their mode of action. The underlying mechanisms of T2DM development include adipose tissue inflammation, liver lipotoxicity, ectopic lipid accumulation in liver, pancreas, and muscle, and finally mitochondria dysfunction[100]. *In vivo* study indicated that rats fed salmon oil enriched with OC pesticides had insulin resistance, dyslipidemia, visceral obesity, and non-alcoholic inflammatory fatty liver[101]. Oxychordane, trans-nonachlor, and p,p'-DDE exhibited strong inhibitory effect on pancreatic β-cell dysfunction[101], decreased cell metabolism, and induced obesity[102] or affected insulin release and action and dysregulated glucose homeostasis[103] or increased oxidative stress and inhibited cholinesterase activity[104]. Humans' OC background exposure (long term-low dose) alongside their lipophilicity and hydrophilicity and resistance to metabolic degradation indulges them into tissue toxicity and bioaccumulation through lifetime [100].

So far, the results of different studies demonstrated a contradictory finding regarding the exact effect and firm association between different classes of pesticides and incidences of different classes of diabetes. Further studies are still in need to decipher the exact mechanism and underlying effector[105].

PAHS

PAHs are a group of lipid soluble environment-related pollutants that are characterized by the presence of aromatic ring in their chemical structure. They are generated from the incomplete combustion of organic materials including wood, gasoline, and coal during cooking process of contaminated food and industrial production processes [106-108]. PAHs include several members such as naphthalene (NAP), fluorene, anthracene, phenanthrene (PHEN), fluoranthene, pyrene, benzo[a] anthracene, chrysene, benzo[a]pyrene (BaP), benzo[b] fluoranthene, benzo[e]pyrene, benzo[j]fluoranthene, benzo[k]fluoranthene, dibenzo[a,h]anthracene, indo[1,2,3-cd]pyrene, and dibenzo[al]pyrene[26].

PAHs are ubiquitously toxic with high melting and boiling points and low vapor pressure[109]. PAHs are listed among the top ten priority list of hazardous materials according to their characters[110]. They enter the human body *via* food consumption, cigarette smoking, and aquatic and air pollution[17,64,111-113]. Once inside the body, they are metabolized into mono hydroxylated PAHs (OH-PAHs) and excreted *via* urine route. Thus, it is anticipated to consider urinary metabolites of PAHs as a good biomarker for environment pollution associated with certain diseases[114].

One of the earliest studies to investigate the association between urinary metabolites of PAHs in non-Western population was done by Nam and Kim[115]. In a national wide scale study in Korean population, it was found that the urinary metabolites of PAHs were closely associated with diabetes prevalence in men and women (diabetes prevalence was 6.5% among participants). The most commonly diabetic associated

PAHs were 2-naphthol (2-NAP) and 2-hydroxyflourene with geometric mean value of 4.11 and 0.45, respectively, in men, while 2-NAP was only associated with diabetes development in women with geometric mean value of 1.81[115]. Another retrospective study among Chinese population indicated a dose-dependent association between urinary OH-PAHs and prevalence of diabetes especially in female participants[111]. In addition, another cohort study among Chinese cooking females in Wuhan demonstrated that female exposure to OH-PAHs and fraction exhalation of nitric oxide during cooking were positively associated with diabetes prevalence among them[107]. An elegant study was published recently to investigate the association between OH-PAHs and incidence of DM development by analyzing the reported research output in different databases like Scopus, PubMed, and Web of Science. Meta-analysis of more than 668 research articles reported a significant association between diabetes and urinary NAP, total OH-PAH, and fluorine (FLU)[62].

Male Kunming mice that received different doses of PHEN for 28 wk exhibited elevated levels of insulin resistance and hyperinsulinemia as interpreted by homeostasis model assessment-insulin resistance (HOMA-IR) and HOMA β cell. Moreover, insulin receptor signaling pathway was inhibited in skeletal muscles, accompanied with glucose intolerance and a disruption in adipocytokine secretion[116]. The effects of PHEN can also extend to offspring until adult stages. Maternal exposure to PHEN during mice gestation period disrupted glucose homeostasis machinery and caused diabetes in adult stages of their offspring[117].

Normoglycemic (normal glucose level) and diabetic rats induced by intraperitoneal injection of streptozotocin (STZ) when treated with BaP exhibited increased kidney weights and blood urea nitrogen compared to the other group treated with STZ only. Authors concluded that BaP increased kidney weight and renal injury as a secondary complication to DM[118]. Resveratrol drug could attenuate BaP-induced pancreatic β-cell dysfunction by decreasing oxidative stress and apoptosis in those cells[119].

Several urinary OH-PAHs of 2-hydroxynaphthalene, 2-hydroxyfluorene, 9-hydroxyfluorene, and 2-hydroxyphenanthrene showed a positive correlation with diabetes occurrence among adults in the United States[120]. Single OH-PAHs have been reported to be connected with diabetes prevalence in different studies. NAP metabolites, 1-NAP[121,122] and 2-NAP[121,123], were found to be significantly associated with diabetes in western populations. FLU metabolites, 2-FLU, 3-FLU, and 9-FLU, were also strongly correlated with diabetes occurrence[111,120,121]. In addition, PHEN metabolites, 1-PHEN, 2-PHEN, 4-PHEN, and 0-PHEN, were reported to be conjugated with increased risk of diabetes occurrence[63,111]. Furthermore, pyrene metabolite, 1-OHP, was found to be significantly associated with diabetes in the same reported studies[111,121,124].

The exact mechanism by which PAHs induce diabetes is under investigation; however, it has been proposed that PAHs exposure can interrogate either insulin sensitivity or decreased insulin production[26] through modulating oxidative stress, systemic inflammation, and induction of pancreatic β-cell dysfunction[63,122,125-127]. Some reports indicated that PAHs can induce either a systemic disturbance in the antioxidant system leading to elevated oxidative stress[128] or increased inflammation and release of proinflammatory markers such as CRP and IL[122]. Furthermore, disruption of the endocrine system is a main theme of PAHs-induced diabetes resulting in an increase in estrogen hormone level[129].

HEAVY METALS

Heavy metals are a group of chemical elements of high atomic weight and superior toxicity at low concentrations[130]. They originate either from natural sources of volcanic eruption and metal-bearing rocks or from anthropogenic sources of various agricultural and industrial activities. Both sources potentiate heavy metals concentration in the environment due to their persistence nature causing a public health problem affecting more people worldwide[131]. Heavy metal pollution has increased tremendously in developing countries[1], and increasing body of evidence linked heavy metal toxicity with hepatic, renal, neurological, and hematological adverse health problems[132].

Metals can be categorized into toxic metals, such as arsenic (As), Pb, cadmium (Cd), and Hg, and essential metals, such as copper (Cu), chromium (Cr), nickel (Ni), Se, and cobalt (Co), which are also metalloestrogens, and both kinds increase cardiovascular and diabetic risks[133].

Heavy metal load in the body exaggerates the progression and severity of DM by altering islet function of the pancreas. Toxic metals either directly disrupt glucose uptake or interfere with glucose regulation leading to development of T1DM or T2DM [5]. Exposure to heavy metals occurs through ingestion of contaminated food, drinking water, and ambient air[134]. In terms of heavy metals toxicity, it should be mentioned that single heavy metals have different rates of toxicity on pancreatic islet cells[135, 136]. Some trace metals under specific concentrations exert various biological functions in which glucose hemostasis is involved[137], and any imbalance in its concentration will impact pancreas biology and insulin synergy production leading to dysglycemia [138].

Metals are involved in many biological aspects of muscle contraction, nerve impulse, and kidney function. They may either function as prosthetic groups of many proteins or be an integral part of other proteins as metalloproteinase/metalloenzymes [139,140]. Diet with low content of nutritive essential metals forces the body to absorb and make use of toxic metals instead. Body substitution of scare essential metals with available toxic metals [zinc (Zn), iron, and potassium] will disrupt various endocrine pathways[141]. Abundance of metal toxicity in the body interferes with the physiological functions of the body[136]. For example, Zn deficiency induces the body to absorb more Fe and use it instead of Zn[142].

Cd, Ni, As, and mercury are examples of toxic metals that induce pancreatic cell death, alter pancreas function, and increase diabetes risk. On the other hand, Co, lead, manganese (Mn), mercury, and Cd were reported to be endocrine disruptive elements contributing to DM development[143,144]. Because of the rapid and uncontrolled industrialization in several countries, heavy metals concentration in the environment is rapidly increasing leading to elevated accumulation in the biological systems[5]. Up till now, the association of environmental exposure to different metals with diabetes development has not been fully covered[134].

Cd belongs to trace elements that occupy Earth's crust in concentrations ranging from 0.1 ppm to 0.5 ppm[145]. Cd toxicity in animals results from its accumulation in the internal organs of the animal and interruption of the common metabolic pathways in kidneys, lungs, bone marrow, pancreas, and liver[131,146]. Some studies could not prove a strong and significant connection between Cd and diabetes prevalence[147, 148], but other studies indicated that Cd exposure can increase the risk of T2DM development especially in older individuals above 50 years by increasing insulin resistance in their bodies[149,150]. Additionally, several studies have reported the significant association between Cd levels and T2DM[151-153] mainly through downregulation of glucose transporter protein GLUT4 and pancreatic β-cell dysfunction[5]. A recent review work was published and indicated an emerging role of Cd in the pathology of various diseases especially T2DM. Hence, Cd was regarded as a hyperglycemic metal that increases glucose levels in blood *via* decreasing insulin production mainly by β-cell destruction[154].

Chromium (Cr) biological activity is confined to regulation of glucose transporter (GLUT4) activity. Cr upregulates GLUT4 translocation into muscle cells which regulates insulin signaling pathway and metabolism[155]. It has been utilized for reducing diabetes risk and decreasing blood glucose level. Prolonged deficiency of dietary Cr may lead to diabetes[156]. Several studies assure the importance of Cr supplementation through diet in reducing oxidative stress, improving cardiometabolic function, and decreasing risk of DM development[157-159].

Iron (Fe) is another example of essential transition metal that is involved in the synthesis of hemoglobin and myoglobin proteins responsible for oxygen transport during respiration[160]. In addition, ferritin, the main protein responsible for Fe carriage, was found to elevate in newly diagnosed diabetic individuals[161,162]. Furthermore, it was found that women with gestational diabetes had higher index of iron dysregulated metabolism under pregnancy stress adaptive disorder[163]. Momeni *et al*[164] proposed that serum ferritin is a good indicator for diabetes development and response to therapy as its level increased and decreased, respectively, alongside HbA1c level. Other studies also supported this postulation assuring ferritin level as a surrogate marker for disease onset[165,166]. Iron overload in tissues led to hemochromatosis which was found to be tightly associated with T2DM in several studies[167-170]. About 11 case control and cohort studies described the association between serum ferritin level and soluble transferrin receptor-to-ferritin ration and DM while no significant association was found in case of serum ferritin receptor[171]. Meta-analysis study of hematological parameter indices and iron metabolism in T2DM patients showed that iron profile and total iron binding capacity were significantly higher in T2DM patients than normal individuals[172].

Zn is also a trace metal that is integrated in cellular processes of cell division and apoptosis. Zn importantly maintains the integrity of pancreatic β cells and can be used as a possible treatment of diabetes[5,173-175]. Fasting blood glucose level was found to be associated with urinary levels of Co, Zn, and Ni as a prognostic indicator[176]. T2DM patients have hypozincemia (lower serum levels of Zn) and hyperzincuria (urinary Zn levels)[177]. Decreased Zn serum level adversely affected the ability of pancreatic islet cells to synthesize and secret insulin[178-180]. A mutation in Zn transporter protein ZnT8 has been connected to T2DM development and progression [181]. Mitigation effect of Zn supplementation on relieving DM secondary complications and glucose homeostasis has been proposed in a number of different studies and meta-analysis cohort studies[182-186].

Ni belongs to ferromagnetic elements, silver-white in color and used in alloy manufacturing and production of Ni-Cd batteries[187]. Ni is widely distributed in nature as a mixture with other elements such as sulfur, As, and iron[188]. Ni concentration was found to be significantly connected with T2DM prevalence[176]. In a Chinese survey of adult male and female individuals, elevated concentration of urinary Ni was found among those with T2DM[189]. To the best of our knowledge, no cohort studies have been conducted to study its association with female gestational diabetes development[190].

As is a toxic metalloid that is naturally occurring as organic or inorganic form in the environment. It is mainly used in insecticide, herbicides, and pesticide production. It can be solubilized in ground water with a concentration up to 10 µg/L[191]. Chronic exposure to As is firmly connected with cancer development[192-194], vascular diseases[195,196], and neurological disorders[197]. As direct contact through diet and contaminated water was found to directly affect pancreatic β cell and decrease insulin production[198]. Available data on the connectivity between As and diabetes is not conclusive and the need for more accurate measurable studies is demanding[199]. Yet some reports highlighted that As-induced diabetes can be initiated through altering TNF-α, GLUT4, and mitogen-activated protein kinase[5]. Ramdas *et al*[200] indicated that pancreatic miR-2909 was significantly higher in NOD mice than control ones upon exposure to low dose of As. miR 2909 control expression of genes coding for pancreatic duodenal homeobox 1 and phosphatidylinositol-3 kinase (PI3k) regulated insulin synthesis and release. STZ diabetic mice model showed higher level of expression of trivalent inorganic As with consequent increase in As accumulation in their bodies and susceptibility to As-induced systemic toxicity[201]. In a Swedish children cohort study, researcher found that children with T1DM tend to have higher levels of aluminum and As metals which were traced back to their accumulation in their pregnant mothers too [202]. In a cross-sectional study in the United States covering 429 children and adolescents diagnosed with T1DM, they found higher level of As metabolites associated with higher odds of T1DM[203]. Furthermore, a Canadian community level screening indicated that higher levels of fluoride and As in drinking water were linked to higher T1DM incidence[204].

Magnesium (Mg) is known as the most important macronutrient essential for proper health maintenance through its integration with more than 300 enzymes in the body involved in nerve transmission, glucose homeostasis, and DNA and RNA synthesis[205-209]. Mg is another example of essential regulators of insulin-mediated glucose uptake in the body. A large prospective cohort study indicated an association between Mg diet level and T2DM development risk[210-214]. Dietary supplement of Mg was found to reduce T2DM risk[215]. A number of studies supported the dietary supplementation of Mg to enhance general health status and decrease risk of T2DM development[185,211,216,217].

Mn acts as a cofactor in several enzymes involved in the metabolism of carbohydrates, proteins, and lipids[218,219]. In addition, it is essential for proper utilization of vitamins (C and E), biotin, and choline[220]. More importantly, Mn is a cofactor of pyruvate carboxylase (enzyme indulged in conversion of non-carbohydrates compounds into glucose *via* gluconeogenesis), hence indirectly implicated in diabetes development as reported by Forte and his research group[177]. Dietary Mn was found to decrease inflammation and reduce risk of T2DM development in postmenopausal women[221]. Inclusion of Mn-enriched diet may decrease the risk of DM in several reported studies and cohort studies[222,223].

Copper (Cu) is crucial for various biological functions as it was found to be integrated in regulating activity of superoxide dismutase (free radical defense system) [224]. Excess Cu induces oxidative stress leading to β-cell dysfunction. Hence, abnormal Cu levels may accelerate DM development and associated complications [225]. Imbalanced Cu complications can result from its association with low-density lipoproteins and HDL imbalances due to elevated cholesterol level in the body[226].

Carbohydrates-enriched diet interferes with Cu metabolism and availability in diabetic patient sera[227]. On the other hand, in a large scale cohort study including more than 70,000 women, it was found that low dietary intake of Cu-Zn ration is associated with lower T2DM risk among women[228].

Cr and calcium (Ca) play a vital role in carbohydrate and lipid metabolism, thus controlling insulin synthesis and release *via* indirect route[137,155]. Co overload will increase the expression of GLUT-1 and inhibit gluconeogenesis[229].

Low levels of antimony, uranium, tungsten, and molybdenum were consistently associated with diabetes prevalence in the United States general population, while cesium, thallium, barium, and lead were not evidenced[141]. Antimony is used in ceramics, metal alloys, and fire-retardant[230]. Ingestion of large quantities of antimony not only induces substantial gastrointestinal effects including nausea, diarrhea, and vomiting but also increases diabetes risk[231]. Uranium is commonly used in munitions, and the studies linking urinary uranium levels with diabetes are limited[232,233].

A nationwide association study on US midlife women showed that there was a higher urinary concentration of lead, As, and Zn in diabetic high-risk group than normal group[134].

Single heavy metals can increase the risk of T2DM development through various mechanisms. First, some toxic metals (Pb, Hg, As, and Cd) can increase the oxidative stress burden in the pancreas by increasing the concentration of free radicals (hydrogen peroxide, superoxide, and nitric oxide)[234]. Alongside the weak biological ability of pancreatic islet cells of antioxidant defense system and their high expression of metal transporter proteins, islets cells become extremely sensitive and rapidly deteriorate resulting in cell damage and apoptosis[5]. Second, heavy metal-induced oxidative stress was found to be firmly connected with reduced insulin gene activity and insulin mRNA expression in β cells of the pancreas[235,236]. The change in pancreas gene expression activity was found to be accompanied with insulin receptor impairment, glucose uptake dysfunction, induced gluconeogenesis, hepatic glycolysis, and pancreatic glucan secretion[237,238]. Third, some heavy metals at certain concentration play a key role in glucose hemostasis as they are part of the metabolic pathway of glucose, cofactors in glucose hemostasis, and pancreatic β-cell function[5,137]. Finally, toxic heavy metals (Cd, Pb, Hg, and As) and essential elements (Cu, Cr, Se, Ni, and Co) can act as endocrine disruptive agents *via* interfering with PKB/AKT-mediated GLUT4 expression *in vitro*, glucose hemostasis, and disruption of lipogenesis [5,231,239,240].

The curative characters of some trace elements to antagonize the toxic effects of toxic metals are very crucial in keeping the integrity and biological function of the pancreas for the prevention of DM development[241]. Additionally, it was demonstrated that hyperglycemia led to abnormal metabolism of trace elements and associated proteins in various organs[151,242-246].

Furthermore, deficiency or overload of heavy metal concentration in the pancreas can cause pancreatic cell dysfunction. For instance, Zn at normal levels plays an important part in pancreatic cell function, insulin synthesis, storage, and secretion[136, 175]. On the other hand, Zn deficiency decreases insulin synthesis and secretion[247], while its overload leads to oxidative damage and cellular toxicity[248,249]. Decreased insulin sensitivity, glucose intolerance, and mitochondrial distortion of pancreatic acinar cells are remarkable examples of Cu deficiency[250]. For selenium, high level of selenium was found to be a strong diabetogenic inducer possibly through impairing insulin responsiveness, increasing glycolysis, and glucagon release stimulation resulting in hyperglycemia and obesity[251,252].

DM *VS* CORONAVIRUS DISEASE 2019

The newly surged coronavirus disease 2019 (COVID-19) is a respiratory infectious disease that was first detected in Wuhan city in China[253]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to positive single stranded RNA viruses naturally mutated genetically to infect human through its intermediate hosts (pangolins and bats)[254,255]. Clinical symptoms of COVID-19 patients include dyspnea, lymphopenia, severe respiratory distress, cytokine storm (awry and excessive uncontrolled), and blood micro-clotting in lungs and different body organs [256-258].

Diabetic individuals are at high susceptible risk of COVID-19-induced adverse outcomes and medical complications[259,260]. For instance, the early reports from Chinese hospitals in Wuhan reported that people with diabetes admitted to ICU due to

COVID-19 contradiction had greater rates of mechanical ventilation and death rates than non-diabetics[261]. On the other hand, other reports did not support this finding, such as the study by the multicenter French Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO)[262] and that in the United Kingdom[263].

Poor glycemic control is reported to be a high-risk factor for death-related mortalities among hospitalized COVID-19[264,265]. Interestingly, COVID-19 can induce hyperglycemia in patients without diabetes and induce elevated blood glucose level[266]. Diabetes-associated comorbidities include hyperglycemia, nephropathy, hypertension, obesity, and dyslipidemia[267], which predispose them to poorer and decreased effective medications. Women infected with COVID-19 with developed gestational diabetes can develop severe COVID-19 infection; however, the study results are not confirmed and need further analysis[268,269]. The toxic impact of elevated glucose titer in blood affects various cellular pathways collectively known as glucotoxicity[270]. Although it was not confirmed conclusively, it was suggested that COVID-19 induces tissue injuries within the diabetic milieu. Codo *et al*[271] reported that DM favored COVID-19 infection *via* tissue hypoxia and increased angiotensin II, fibrinogen, D-dimer, insulin resistance, and oxidative stress[272,273]. Concurrent tissue damage in several organs due to COVID-19 infection and DM subject those patients to maximum risk of mortality[260].

Both COVID-19 and diabetes pathways intersect in a number of common pathologies of inflammation (acute *vs* chronic, respectively), tissue damage (acute *vs* slowly progression, respectively), hyperglycemia, hypercoagulation, endothelia dysfunction, and tissue fibrosis[259]. The multifactorial nature and pathway complexity of both COVID-19 and DM make those patients in need of urgent critical care to increase their survival outcome[274].

CONCLUSION

Recent report over the last decade implied the diabetogenic effect of different environmental pollutants. Each category has its own mechanism of induction, and link was further confirmed by an array of different cohort and meta-analysis studies by several researchers all over the world. Pesticides, PAHs, and toxic heavy metals are all implicated in the progression and severity of DM mostly through dysregulated antioxidant machinery, elevated oxidative stress in pancreatic β cells, interferences in insulin synthesis, storage, and release from pancreas. On the other hand, dietary supplementation of some metals, such as Mg, Mn, and Zn, has been shown to decrease risk of DM development. Further studies are inevitably demanding to achieve several goals as follows: (1) Different population assessment of their history and current diabetic status in order to generate an up-to-date informatics on disease prevalence and spread; (2) Dissecting the exact molecular mechanism and identifying the molecular players included in disease development; and (3) Finally, introducing novel therapeutic regimes to treat the disease and its associated complications.

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