**Name of Journal:** *World Journal of Meta-Analysis*

**Manuscript NO:** 63441

**Manuscript Type:** REVIEW

**Environmental pollution and diabetes mellitus**

El-Sikaily A *et al*. Environmental pollution and diabetes mellitus

Amany El-Sikaily, Mohamed Helal

**Amany El-Sikaily, Mohamed Helal,** National Institute of Oceanography and Fisheries (NIOF), Cairo 21513, Egypt

**Author contributions:** Helal M and El-Sikaily A wrote the paper and revised the paper.

**Corresponding author: Mohamed Helal, PhD, Assistant Professor,** National Institute of Oceanography and Fisheries (NIOF), Quaiet Bay, Al Anfoushy, Cairo 21513, Egypt. m.helalf@gmail.com

**Received:** January 28, 2021

**Revised:** March 17, 2021

**Accepted:** June 3, 2021

**Published online:** June 28, 2021

**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

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** El-Sikaily A, Helal M. Environmental pollution and diabetes mellitus. *World J Meta-Anal* 2021; 9(3): 234-256

URL: https://www.wjgnet.com/2308-3840/full/v9/i3/234.htm

DOI: https://dx.doi.org/10.13105/wjma.v9.i3.234

**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 dissociation 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.

**REFERENCES**

1 **Duan H**, Yu L, Tian F, Zhai Q, Fan L, Chen W. Gut microbiota: A target for heavy metal toxicity and a probiotic protective strategy. *Sci Total Environ* 2020; **742**: 140429 [PMID: 32629250 DOI: 10.1016/j.scitotenv.2020.140429]

2 **GBD 2017 Disease and Injury Incidence and Prevalence Collaborators**. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**: 1789-1858 [PMID: 30496104 DOI: 10.1016/S0140-6736(18)32279-7]

3 **Guariguata L**, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract* 2014; **103**: 137-149 [PMID: 24630390 DOI: 10.1016/j.diabres.2013.11.002]

4 **Bommer C**, Heesemann E, Sagalova V, Manne-Goehler J, Atun R, Bärnighausen T, Vollmer S. The global economic burden of diabetes in adults aged 20-79 years: a cost-of-illness study. *Lancet Diabetes Endocrinol* 2017; **5**: 423-430 [PMID: 28456416 DOI: 10.1016/S2213-8587(17)30097-9]

5 **Chen YW**, Yang CY, Huang CF, Hung DZ, Leung YM, Liu SH. Heavy metals, islet function and diabetes development. *Islets* 2009; **1**: 169-176 [PMID: 21099269 DOI: 10.4161/isl.1.3.9262]

6 **Satoh H**, Ohira T, Nagai M, Hosoya M, Sakai A, Yasumura S, Ohtsuru A, Kawasaki Y, Suzuki H, Takahashi A, Sugiura Y, Shishido H, Hayashi Y, Takahashi H, Kobashi G, Ozasa K, Hashimoto S, Ohto H, Abe M, Kamiya K; Fukushima Health Management Survey Group. Evacuation is a risk factor for diabetes development among evacuees of the Great East Japan earthquake: A 4-year follow-up of the Fukushima Health Management Survey. *Diabetes Metab* 2019; **45**: 312-315 [PMID: 29097002 DOI: 10.1016/j.diabet.2017.09.005]

7 **Legler J**, Fletcher T, Govarts E, Porta M, Blumberg B, Heindel JJ, Trasande L. Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab* 2015; **100**: 1278-1288 [PMID: 25742518 DOI: 10.1210/jc.2014-4326]

8 **Borisova AM**, Koev D, Kirilov G. [High-degree obesity--a risk factor for the development of diabetes mellitus]. *Vutr Boles* 1990; **29**: 74-78 [PMID: 2284804]

9 **Bowe B**, Xie Y, Li T, Yan Y, Xian H, Al-Aly Z. The 2016 global and national burden of diabetes mellitus attributable to PM2·5 air pollution. *Lancet Planet Health* 2018; **2**: e301-e312 [PMID: 30074893 DOI: 10.1016/S2542-5196(18)30140-2]

10 **Wang X**, Song Y, Chen L, Zhuang G, Zhang J, Li M, Meng XF. Contribution of single-minded 2 to hyperglycaemia-induced neurotoxicity. *Neurotoxicology* 2013; **35**: 106-112 [PMID: 23333261 DOI: 10.1016/j.neuro.2013.01.003]

11 **Kawasaki E**, Abiru N, Eguchi K. Prevention of type 1 diabetes: from the view point of beta cell damage. *Diabetes Res Clin Pract* 2004; **66 Suppl 1**: S27-S32 [PMID: 15563975 DOI: 10.1016/j.diabres.2003.09.015]

12 **Lenzen S**. Oxidative stress: the vulnerable beta-cell. *Biochem Soc Trans* 2008; **36**: 343-347 [PMID: 18481954 DOI: 10.1042/BST0360343]

13 **Kim KA**, Lee MS. Recent progress in research on beta-cell apoptosis by cytokines. *Front Biosci (Landmark Ed)* 2009; **14**: 657-664 [PMID: 19273093 DOI: 10.2741/3271]

14 **Rolo AP**, Palmeira CM. Diabetes and mitochondrial function: role of hyperglycemia and oxidative stress. *Toxicol Appl Pharmacol* 2006; **212**: 167-178 [PMID: 16490224 DOI: 10.1016/j.taap.2006.01.003]

15 **Marroqui L**, Tudurí E, Alonso-Magdalena P, Quesada I, Nadal Á, Dos Santos RS. Mitochondria as target of endocrine-disrupting chemicals: implications for type 2 diabetes. *J Endocrinol* 2018; **239**: R27-R45 [PMID: 30072426 DOI: 10.1530/JOE-18-0362]

16 **Wang CY**, Neil DL, Home P. 2020 vision - An overview of prospects for diabetes management and prevention in the next decade. *Diabetes Res Clin Pract* 2018; **143**: 101-112 [PMID: 29944968 DOI: 10.1016/j.diabres.2018.06.007]

17 **Manisalidis I**, Stavropoulou E, Stavropoulos A, Bezirtzoglou E. Environmental and Health Impacts of Air Pollution: A Review. *Front Public Health* 2020; **8**: 14 [PMID: 32154200 DOI: 10.3389/fpubh.2020.00014]

18 **Campbell GD**. Connubial Diabetes and the Possible Role of "Oral Diabetogens". *Br Med J* 1961; **1**: 1538-1539 [DOI: 10.1136/bmj.1.5238.1538-a]

19 **Song Y**, Chou EL, Baecker A, You NC, Song Y, Sun Q, Liu S. Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: A systematic review and meta-analysis. *J Diabetes* 2016; **8**: 516-532 [PMID: 26119400 DOI: 10.1111/1753-0407.12325]

20 **Sargis RM**, Simmons RA. Environmental neglect: endocrine disruptors as underappreciated but potentially modifiable diabetes risk factors. *Diabetologia* 2019; **62**: 1811-1822 [PMID: 31451869 DOI: 10.1007/s00125-019-4940-z]

21 **Ruiz D**, Becerra M, Jagai JS, Ard K, Sargis RM. Disparities in Environmental Exposures to Endocrine-Disrupting Chemicals and Diabetes Risk in Vulnerable Populations. *Diabetes Care* 2018; **41**: 193-205 [PMID: 29142003 DOI: 10.2337/dc16-2765]

22 **Priyam A**, Singh PP, Gehlout S. Role of Endocrine-Disrupting Engineered Nanomaterials in the Pathogenesis of Type 2 Diabetes Mellitus. *Front Endocrinol (Lausanne)* 2018; **9**: 704 [PMID: 30542324 DOI: 10.3389/fendo.2018.00704]

23 **Predieri B**, Bruzzi P, Bigi E, Ciancia S, Madeo SF, Lucaccioni L, Iughetti L. Endocrine Disrupting Chemicals and Type 1 Diabetes. *Int J Mol Sci* 2020; **21** [PMID: 32331412 DOI: 10.3390/ijms21082937]

24 **Kassotis CD**, Vandenberg LN, Demeneix BA, Porta M, Slama R, Trasande L. Endocrine-disrupting chemicals: economic, regulatory, and policy implications. *Lancet Diabetes Endocrinol* 2020; **8**: 719-730 [PMID: 32707119 DOI: 10.1016/S2213-8587(20)30128-5]

25 **Lind PM**, Lind L. Endocrine-disrupting chemicals and risk of diabetes: an evidence-based review. *Diabetologia* 2018; **61**: 1495-1502 [PMID: 29744538 DOI: 10.1007/s00125-018-4621-3]

26 **Pizzorno J**. Is the Diabetes Epidemic Primarily Due to Toxins? *Integr Med (Encinitas)* 2016; **15**: 8-17 [PMID: 27574488]

27 **Guo X**, Li H, Xu H, Woo S, Dong H, Lu F, Lange AJ, Wu C. Glycolysis in the control of blood glucose homeostasis. *Acta Pharmaceutica Sinica B* 2012; **2**: 358-367 [DOI: 10.1016/j.apsb.2012.06.002]

28 **Terrettaz J**, Assimacopoulos-Jeannet F, Jeanrenaud B. Inhibition of hepatic glucose production by insulin *in vivo* in rats: contribution of glycolysis. *Am J Physiol* 1986; **250**: E346-E351 [PMID: 3008568 DOI: 10.1152/ajpendo.1986.250.4.E346]

29 **Rossetti L**, Giaccari A. Relative contribution of glycogen synthesis and glycolysis to insulin-mediated glucose uptake. A dose-response euglycemic clamp study in normal and diabetic rats. *J Clin Invest* 1990; **85**: 1785-1792 [PMID: 2189891 DOI: 10.1172/JCI114636]

30 **Wu C**, Khan SA, Lange AJ. Regulation of glycolysis-role of insulin. *Exp Gerontol* 2005; **40**: 894-899 [PMID: 16157461 DOI: 10.1016/j.exger.2005.08.002]

31 **Choi IY**, Wu C, Okar DA, Lange AJ, Gruetter R. Elucidation of the role of fructose 2,6-bisphosphate in the regulation of glucose fluxes in mice using *in vivo* (13)C NMR measurements of hepatic carbohydrate metabolism. *Eur J Biochem* 2002; **269**: 4418-4426 [PMID: 12230553 DOI: 10.1046/j.1432-1033.2002.t01-1-03125.x]

32 **Huo Y**, Guo X, Li H, Wang H, Zhang W, Wang Y, Zhou H, Gao Z, Telang S, Chesney J, Chen YE, Ye J, Chapkin RS, Wu C. Disruption of inducible 6-phosphofructo-2-kinase ameliorates diet-induced adiposity but exacerbates systemic insulin resistance and adipose tissue inflammatory response. *J Biol Chem* 2010; **285**: 3713-3721 [PMID: 19948719 DOI: 10.1074/jbc.M109.058446]

33 **Kang L**, Dunn-Meynell AA, Routh VH, Gaspers LD, Nagata Y, Nishimura T, Eiki J, Zhang BB, Levin BE. Glucokinase is a critical regulator of ventromedial hypothalamic neuronal glucosensing. *Diabetes* 2006; **55**: 412-420 [PMID: 16443775 DOI: 10.2337/diabetes.55.02.06.db05-1229]

34 **Wu C**, Okar DA, Newgard CB, Lange AJ. Increasing fructose 2,6-bisphosphate overcomes hepatic insulin resistance of type 2 diabetes. *Am J Physiol Endocrinol Metab* 2002; **282**: E38-E45 [PMID: 11739081 DOI: 10.1152/ajpendo.2002.282.1.E38]

35 **Agius L**. The physiological role of glucokinase binding and translocation in hepatocytes. *Adv Enzyme Regul* 1998; **38**: 303-331 [PMID: 9762360 DOI: 10.1016/S0065-2571(97)00001-0]

36 **Würtz P**, Tiainen M, Mäkinen VP, Kangas AJ, Soininen P, Saltevo J, Keinänen-Kiukaanniemi S, Mäntyselkä P, Lehtimäki T, Laakso M, Jula A, Kähönen M, Vanhala M, Ala-Korpela M. Circulating metabolite predictors of glycemia in middle-aged men and women. *Diabetes Care* 2012; **35**: 1749-1756 [PMID: 22563043 DOI: 10.2337/dc11-1838]

37 **Floegel A**, Stefan N, Yu Z, Mühlenbruch K, Drogan D, Joost HG, Fritsche A, Häring HU, Hrabě de Angelis M, Peters A, Roden M, Prehn C, Wang-Sattler R, Illig T, Schulze MB, Adamski J, Boeing H, Pischon T. Identification of serum metabolites associated with risk of type 2 diabetes using a targeted metabolomic approach. *Diabetes* 2013; **62**: 639-648 [PMID: 23043162 DOI: 10.2337/db12-0495]

38 **Padberg I**, Peter E, González-Maldonado S, Witt H, Mueller M, Weis T, Bethan B, Liebenberg V, Wiemer J, Katus HA, Rein D, Schatz P. A new metabolomic signature in type-2 diabetes mellitus and its pathophysiology. *PLoS One* 2014; **9**: e85082 [PMID: 24465478 DOI: 10.1371/journal.pone.0085082]

39 **Drogan D**, Dunn WB, Lin W, Buijsse B, Schulze MB, Langenberg C, Brown M, Floegel A, Dietrich S, Rolandsson O, Wedge DC, Goodacre R, Forouhi NG, Sharp SJ, Spranger J, Wareham NJ, Boeing H. Untargeted metabolic profiling identifies altered serum metabolites of type 2 diabetes mellitus in a prospective, nested case control study. *Clin Chem* 2015; **61**: 487-497 [PMID: 25524438 DOI: 10.1373/clinchem.2014.228965]

40 **Landau BR**, Chandramouli V, Schumann WC, Ekberg K, Kumaran K, Kalhan SC, Wahren J. Estimates of Krebs cycle activity and contributions of gluconeogenesis to hepatic glucose production in fasting healthy subjects and IDDM patients. *Diabetologia* 1995; **38**: 831-838 [PMID: 7556986 DOI: 10.1007/s001250050360]

41 **Ho JE**, Larson MG, Vasan RS, Ghorbani A, Cheng S, Rhee EP, Florez JC, Clish CB, Gerszten RE, Wang TJ. Metabolite profiles during oral glucose challenge. *Diabetes* 2013; **62**: 2689-2698 [PMID: 23382451 DOI: 10.2337/db12-0754]

42 **Juraschek SP**, Shantha GP, Chu AY, Miller ER 3rd, Guallar E, Hoogeveen RC, Ballantyne CM, Brancati FL, Schmidt MI, Pankow JS, Young JH. Lactate and risk of incident diabetes in a case-cohort of the atherosclerosis risk in communities (ARIC) study. *PLoS One* 2013; **8**: e55113 [PMID: 23383072 DOI: 10.1371/journal.pone.0055113]

43 **Crawford SO**, Hoogeveen RC, Brancati FL, Astor BC, Ballantyne CM, Schmidt MI, Young JH. Association of blood lactate with type 2 diabetes: the Atherosclerosis Risk in Communities Carotid MRI Study. *Int J Epidemiol* 2010; **39**: 1647-1655 [PMID: 20797988 DOI: 10.1093/ije/dyq126]

44 **Martínez-González MÁ**, Corella D, Salas-Salvadó J, Ros E, Covas MI, Fiol M, Wärnberg J, Arós F, Ruíz-Gutiérrez V, Lamuela-Raventós RM, Lapetra J, Muñoz MÁ, Martínez JA, Sáez G, Serra-Majem L, Pintó X, Mitjavila MT, Tur JA, Portillo MP, Estruch R; PREDIMED Study Investigators. Cohort profile: design and methods of the PREDIMED study. *Int J Epidemiol* 2012; **41**: 377-385 [PMID: 21172932 DOI: 10.1093/ije/dyq250]

45 **Huang M**, Joseph JW. Metabolomic analysis of pancreatic β-cell insulin release in response to glucose. *Islets* 2012; **4**: 210-222 [PMID: 22847496 DOI: 10.4161/isl.20141]

46 **Menni C**, Fauman E, Erte I, Perry JR, Kastenmüller G, Shin SY, Petersen AK, Hyde C, Psatha M, Ward KJ, Yuan W, Milburn M, Palmer CN, Frayling TM, Trimmer J, Bell JT, Gieger C, Mohney RP, Brosnan MJ, Suhre K, Soranzo N, Spector TD. Biomarkers for type 2 diabetes and impaired fasting glucose using a nontargeted metabolomics approach. *Diabetes* 2013; **62**: 4270-4276 [PMID: 23884885 DOI: 10.2337/db13-0570]

47 **Lovejoy J**, Newby FD, Gebhart SS, DiGirolamo M. Insulin resistance in obesity is associated with elevated basal lactate levels and diminished lactate appearance following intravenous glucose and insulin. *Metabolism* 1992; **41**: 22-27 [PMID: 1538640 DOI: 10.1016/0026-0495(92)90185-D]

48 **Berhane F**, Fite A, Daboul N, Al-Janabi W, Msallaty Z, Caruso M, Lewis MK, Yi Z, Diamond MP, Abou-Samra AB, Seyoum B. Plasma Lactate Levels Increase during Hyperinsulinemic Euglycemic Clamp and Oral Glucose Tolerance Test. *J Diabetes Res* 2015; **2015**: 102054 [PMID: 25961050 DOI: 10.1155/2015/102054]

49 **Galgani JE**, Gómez C, Mizgier ML, Gutierrez J, Santos JL, Olmos P, Mari A. Assessment of the Role of Metabolic Determinants on the Relationship between Insulin Sensitivity and Secretion. *PLoS One* 2016; **11**: e0168352 [PMID: 28002466 DOI: 10.1371/journal.pone.0168352]

50 **Hui S**, Ghergurovich JM, Morscher RJ, Jang C, Teng X, Lu W, Esparza LA, Reya T, Le Zhan, Yanxiang Guo J, White E, Rabinowitz JD. Glucose feeds the TCA cycle *via* circulating lactate. *Nature* 2017; **551**: 115-118 [PMID: 29045397 DOI: 10.1038/nature24057]

51 **Brooks GA**. The Science and Translation of Lactate Shuttle Theory. *Cell Metab* 2018; **27**: 757-785 [PMID: 29617642 DOI: 10.1016/j.cmet.2018.03.008]

52 **Gaster M**, Petersen I, Højlund K, Poulsen P, Beck-Nielsen H. The diabetic phenotype is conserved in myotubes established from diabetic subjects: evidence for primary defects in glucose transport and glycogen synthase activity. *Diabetes* 2002; **51**: 921-927 [PMID: 11916908 DOI: 10.2337/diabetes.51.4.921]

53 **Gaster M**, Rustan AC, Aas V, Beck-Nielsen H. Reduced lipid oxidation in skeletal muscle from type 2 diabetic subjects may be of genetic origin: evidence from cultured myotubes. *Diabetes* 2004; **53**: 542-548 [PMID: 14988236 DOI: 10.2337/diabetes.53.3.542]

54 **Gaster M**. Insulin resistance and the mitochondrial link. Lessons from cultured human myotubes. *Biochim Biophys Acta* 2007; **1772**: 755-765 [PMID: 17482433 DOI: 10.1016/j.bbadis.2007.03.007]

55 **Gaster M**. Reduced TCA flux in diabetic myotubes: A governing influence on the diabetic phenotype? *Biochem Biophys Res Commun* 2009; **387**: 651-655 [PMID: 19615969 DOI: 10.1016/j.bbrc.2009.07.064]

56 **Aghelan Z**, Kiani S, Nasiri A, Sadeghi M, Farrokhi A, Khodarahmi R. Factors Influencing Mitochondrial Function as a Key Mediator of Glucose-Induced Insulin Release: Highlighting Nicotinamide Nucleotide Transhydrogenase. *Int J Mol Cell Med* 2020; **9**: 107-122 [PMID: 32934948 DOI: 10.22088/IJMCM.BUMS.9.2.107]

57 **Gaster M**. Reduced TCA Flux in Diabetic Myotubes: Determined by Single Defects? *Biochem Res Int* 2012; **2012**: 716056 [PMID: 22506116 DOI: 10.1155/2012/716056]

58 **Patti ME**, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S, Miyazaki Y, Kohane I, Costello M, Saccone R, Landaker EJ, Goldfine AB, Mun E, DeFronzo R, Finlayson J, Kahn CR, Mandarino LJ. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of PGC1 and NRF1. *Proc Natl Acad Sci U S A* 2003; **100**: 8466-8471 [PMID: 12832613 DOI: 10.1073/pnas.1032913100]

59 **Mootha VK**, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J, Puigserver P, Carlsson E, Ridderstråle M, Laurila E, Houstis N, Daly MJ, Patterson N, Mesirov JP, Golub TR, Tamayo P, Spiegelman B, Lander ES, Hirschhorn JN, Altshuler D, Groop LC. PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. *Nat Genet* 2003; **34**: 267-273 [PMID: 12808457 DOI: 10.1038/ng1180]

60 **Frederiksen CM**, Højlund K, Hansen L, Oakeley EJ, Hemmings B, Abdallah BM, Brusgaard K, Beck-Nielsen H, Gaster M. Transcriptional profiling of myotubes from patients with type 2 diabetes: no evidence for a primary defect in oxidative phosphorylation genes. *Diabetologia* 2008; **51**: 2068-2077 [PMID: 18719883 DOI: 10.1007/s00125-008-1122-9]

61 **Abdul-Ghani MA**, Jani R, Chavez A, Molina-Carrion M, Tripathy D, Defronzo RA. Mitochondrial reactive oxygen species generation in obese non-diabetic and type 2 diabetic participants. *Diabetologia* 2009; **52**: 574-582 [PMID: 19183935 DOI: 10.1007/s00125-009-1264-4]

62 **Khosravipour M**, Khosravipour H. The association between urinary metabolites of polycyclic aromatic hydrocarbons and diabetes: A systematic review and meta-analysis study. *Chemosphere* 2020; **247**: 125680 [PMID: 32069705 DOI: 10.1016/j.chemosphere.2019.125680]

63 **Farzan SF**, Chen Y, Trachtman H, Trasande L. Urinary polycyclic aromatic hydrocarbons and measures of oxidative stress, inflammation and renal function in adolescents: NHANES 2003-2008. *Environ Res* 2016; **144**: 149-157 [PMID: 26610293 DOI: 10.1016/j.envres.2015.11.012]

64 **Aquilina NJ**, Delgado-Saborit JM, Meddings C, Baker S, Harrison RM, Jacob P 3rd, Wilson M, Yu L, Duan M, Benowitz NL. Environmental and biological monitoring of exposures to PAHs and ETS in the general population. *Environ Int* 2010; **36**: 763-771 [PMID: 20591483 DOI: 10.1016/j.envint.2010.05.015]

65 **He B**, Ni Y, Jin Y, Fu Z. Pesticides-induced energy metabolic disorders. *Sci Total Environ* 2020; **729**: 139033 [PMID: 32388131 DOI: 10.1016/j.scitotenv.2020.139033]

66 **Popp J**, Pető K, Nagy J. Pesticide productivity and food security. A review. *Agron Sustain Dev* 2013; **33**: 243-255 [DOI: 10.1007/s13593-012-0105-x]

67 **Czajka M**, Matysiak-Kucharek M, Jodłowska-Jędrych B, Sawicki K, Fal B, Drop B, Kruszewski M, Kapka-Skrzypczak L. Organophosphorus pesticides can influence the development of obesity and type 2 diabetes with concomitant metabolic changes. *Environ Res* 2019; **178**: 108685 [PMID: 31479978 DOI: 10.1016/j.envres.2019.108685]

68 **Rahimi R**, Abdollahi M. A review on the mechanisms involved in hyperglycemia induced by organophosphorus pesticides. *Pestic Biochem Physiolo* 2007; **88**: 115-121 [DOI: 10.1016/j.pestbp.2006.10.003]

69 **Leonel Javeres MN**, Raza S, Judith N, Anwar F, Habib R, Batool S, Nurulain SM. Mixture of Organophosphates Chronic Exposure and Pancreatic Dysregulations in Two Different Population Samples. *Front Public Health* 2020; **8**: 534902 [PMID: 33194944 DOI: 10.3389/fpubh.2020.534902]

70 **Thayer KA**, Heindel JJ, Bucher JR, Gallo MA. Role of environmental chemicals in diabetes and obesity: a National Toxicology Program workshop review. *Environ Health Perspect* 2012; **120**: 779-789 [PMID: 22296744 DOI: 10.1289/ehp.1104597]

71 **Evangelou E**, Ntritsos G, Chondrogiorgi M, Kavvoura FK, Hernández AF, Ntzani EE, Tzoulaki I. Exposure to pesticides and diabetes: A systematic review and meta-analysis. *Environ Int* 2016; **91**: 60-68 [PMID: 26909814 DOI: 10.1016/j.envint.2016.02.013]

72 **Montgomery MP**, Kamel F, Saldana TM, Alavanja MC, Sandler DP. Incident diabetes and pesticide exposure among licensed pesticide applicators: Agricultural Health Study, 1993-2003. *Am J Epidemiol* 2008; **167**: 1235-1246 [PMID: 18343878 DOI: 10.1093/aje/kwn028]

73 **Starling AP**, Umbach DM, Kamel F, Long S, Sandler DP, Hoppin JA. Pesticide use and incident diabetes among wives of farmers in the Agricultural Health Study. *Occup Environ Med* 2014; **71**: 629-635 [PMID: 24727735 DOI: 10.1136/oemed-2013-101659]

74 **Juntarawijit C**, Juntarawijit Y. Association between diabetes and pesticides: a case-control study among Thai farmers. *Environ Health Prev Med* 2018; **23**: 3 [PMID: 29374457 DOI: 10.1186/s12199-018-0692-5]

75 **Park S**, Kim SK, Kim JY, Lee K, Choi JR, Chang SJ, Chung CH, Park KS, Oh SS, Koh SB. Exposure to pesticides and the prevalence of diabetes in a rural population in Korea. *Neurotoxicology* 2019; **70**: 12-18 [PMID: 30367900 DOI: 10.1016/j.neuro.2018.10.007]

76 **Abdel-Rahman RH**, El Morsi DA, Abd El-Aziz SM, El-Sharkawy AA. Immunotoxicity of Some Pesticides in Egyptian Diabetic Children. *Manso J Forensic Med Clin Toxicol* 2012; **20**: 1-15 [DOI: 10.21608/mjfmct.2012.47724]

77 **Beard J**, Sladden T, Morgan G, Berry G, Brooks L, McMichael A. Health impacts of pesticide exposure in a cohort of outdoor workers. *Environ Health Perspect* 2003; **111**: 724-730 [PMID: 12727601 DOI: 10.1289/ehp.5885]

78 **Swaminathan K**, Thangavel G. Pesticides and human diabetes: a pilot project to explore a possible link. *Practic Diabetes* 2015; **32**: 111-113 [DOI: 10.1002/pdi.1937]

79 **Han X**, Zhang F, Meng L, Xu Y, Li Y, Li A, Turyk ME, Yang R, Wang P, Zhang J, Zhang Q, Jiang G. Exposure to organochlorine pesticides and the risk of type 2 diabetes in the population of East China. *Ecotoxicol Environ Saf* 2020; **190**: 110125 [PMID: 31887706 DOI: 10.1016/j.ecoenv.2019.110125]

80 **Gupta HP**, Jha RR, Ahmad H, Patel DK, Ravi Ram K. Xenobiotic mediated diabetogenesis: Developmental exposure to dichlorvos or atrazine leads to type 1 or type 2 diabetes in Drosophila. *Free Radic Biol Med* 2019; **141**: 461-474 [PMID: 31319158 DOI: 10.1016/j.freeradbiomed.2019.07.013]

81 **Everett CJ**, Thompson OM. Association of DDT and heptachlor epoxide in human blood with diabetic nephropathy. *Rev Environ Health* 2015; **30**: 93-97 [PMID: 25822320 DOI: 10.1515/reveh-2015-0003]

82 **Baldissera MD**, Souza CF, Parmeggiani B, Vendrusculo RG, Ribeiro LC, Muenchen DK, Zeppenfeld CC, Meinhart AD, Wagner R, Zanella R, Prestes OD, da Silva AS, Leipnitz G, Baldisserotto B. Protective effects of diet containing rutin against trichlorfon-induced muscle bioenergetics disruption and impairment on fatty acid profile of silver catfish Rhamdia quelen. *Ecotoxicol Environ Saf* 2020; **205**: 111127 [PMID: 32846293 DOI: 10.1016/j.ecoenv.2020.111127]

83 **Cetkovic-Cvrlje M**, Olson M, Schindler B, Gong HK. Exposure to DDT metabolite p,p'-DDE increases autoimmune type 1 diabetes incidence in NOD mouse model. *J Immunotoxicol* 2016; **13**: 108-118 [PMID: 25721050 DOI: 10.3109/1547691X.2015.1017060]

84 **Gilmartin AB**, Ural SH, Repke JT. Gestational diabetes mellitus. *Rev Obstet Gynecol* 2008; **1**: 129-134 [PMID: 19015764]

85 **Plows JF**, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The Pathophysiology of Gestational Diabetes Mellitus. *Int J Mol Sci* 2018; **19** [PMID: 30373146 DOI: 10.3390/ijms19113342]

86 **Ndonwi EN**, Atogho-Tiedeu B, Lontchi-Yimagou E, Shinkafi TS, Nanfa D, Balti EV, Katte JC, Mbanya A, Matsha T, Mbanya JC, Shakir A, Sobngwi E. Metabolic effects of exposure to pesticides during gestation in female Wistar rats and their offspring: a risk factor for diabetes? *Toxicol Res* 2020; **36**: 249-256 [PMID: 32685429 DOI: 10.1007/s43188-019-00028-y]

87 **Jin C**, Zeng Z, Wang C, Luo T, Wang S, Zhou J, Ni Y, Fu Z, Jin Y. Insights into a Possible Mechanism Underlying the Connection of Carbendazim-Induced Lipid Metabolism Disorder and Gut Microbiota Dysbiosis in Mice. *Toxicol Sci* 2018; **166**: 382-393 [PMID: 30496565 DOI: 10.1093/toxsci/kfy205]

88 **Agus A**, Planchais J, Sokol H. Gut Microbiota Regulation of Tryptophan Metabolism in Health and Disease. *Cell Host Microbe* 2018; **23**: 716-724 [PMID: 29902437 DOI: 10.1016/j.chom.2018.05.003]

89 **Sevim Ç**, Çomaklı S, Taghizadehghalehjoughi A, Özkaraca M, Mesnage R, Kovatsi L, Burykina TI, Kalogeraki A, Antoniou MN, Tsatsakis A. An imazamox-based herbicide causes apoptotic changes in rat liver and pancreas. *Toxicol Rep* 2019; **6**: 42-50 [PMID: 30560060 DOI: 10.1016/j.toxrep.2018.11.008]

90 **Khalil SR**, Awad A, Mohammed HH, Nassan MA. Imidacloprid insecticide exposure induces stress and disrupts glucose homeostasis in male rats. *Environ Toxicol Pharmacol* 2017; **55**: 165-174 [PMID: 28850943 DOI: 10.1016/j.etap.2017.08.017]

91 **Martínez-Morcillo S**, Pérez-López M, Soler-Rodríguez F, González A. The organophosphorus pesticide dimethoate decreases cell viability and induces changes in different biochemical parameters of rat pancreatic stellate cells. *Toxicol In Vitro* 2019; **54**: 89-97 [PMID: 30243730 DOI: 10.1016/j.tiv.2018.09.011]

92 **Pournourmohammadi S**, Ostad SN, Azizi E, Ghahremani MH, Farzami B, Minaie B, Larijani B, Abdollahi M. Induction of insulin resistance by malathion: Evidence for disrupted islets cells metabolism and mitochondrial dysfunction. *Pestic Biochem Physiol* 2007; **88**: 346-352 [DOI: 10.1016/j.pestbp.2007.02.001]

93 **Abu-Basha EA**, Yibchok-Anun S, Hopper DL, Hsu WH. Effects of the pesticide amitraz and its metabolite BTS 27271 on insulin and glucagon secretion from the perfused rat pancreas: involvement of alpha2D-adrenergic receptors. *Metabolism* 1999; **48**: 1461-1469 [PMID: 10582558 DOI: 10.1016/S0026-0495(99)90160-9]

94 **Jamshidi HR**, Ghahremani MH, Ostad SN, Sharifzadeh M, Dehpour AR, Abdollahi M. Effects of diazinon on the activity and gene expression of mitochondrial glutamate dehydrogenase from rat pancreatic Langerhans islets. *Pestic Biochem Physiol* 2009; **93**: 23-27 [DOI: 10.1016/j.pestbp.2008.09.002]

95 **Svingen T**, Ramhøj L, Mandrup K, Christiansen S, Axelstad M, Vinggaard AM, Hass U. Effects on metabolic parameters in young rats born with low birth weight after exposure to a mixture of pesticides. *Sci Rep* 2018; **8**: 305 [PMID: 29321614 DOI: 10.1038/s41598-017-18626-x]

96 **Peris-Sampedro F**, Cabré M, Basaure P, Reverte I, Domingo JL, Teresa Colomina M. Adulthood dietary exposure to a common pesticide leads to an obese-like phenotype and a diabetic profile in apoE3 mice. *Environ Res* 2015; **142**: 169-176 [PMID: 26162960 DOI: 10.1016/j.envres.2015.06.036]

97 **Sun Q**, Xiao X, Kim Y, Kim D, Yoon KS, Clark JM, Park Y. Imidacloprid Promotes High Fat Diet-Induced Adiposity and Insulin Resistance in Male C57BL/6J Mice. *J Agric Food Chem* 2016; **64**: 9293-9306 [PMID: 27960282 DOI: 10.1021/acs.jafc.6b04322]

98 **Xiao X**, Kim Y, Kim D, Yoon KS, Clark JM, Park Y. Permethrin alters glucose metabolism in conjunction with high fat diet by potentiating insulin resistance and decreases voluntary activities in female C57BL/6J mice. *Food Chem Toxicol* 2017; **108**: 161-170 [PMID: 28757463 DOI: 10.1016/j.fct.2017.07.053]

99 **Li J**, Pang G, Ren F, Fang B. Chlorpyrifos-induced reproductive toxicity in rats could be partly relieved under high-fat diet. *Chemosphere* 2019; **229**: 94-102 [PMID: 31078036 DOI: 10.1016/j.chemosphere.2019.05.020]

100 **Lee DH**, Porta M, Jacobs DR Jr, Vandenberg LN. Chlorinated persistent organic pollutants, obesity, and type 2 diabetes. *Endocr Rev* 2014; **35**: 557-601 [PMID: 24483949 DOI: 10.1210/er.2013-1084]

101 **Ruzzin J**, Petersen R, Meugnier E, Madsen L, Lock EJ, Lillefosse H, Ma T, Pesenti S, Sonne SB, Marstrand TT, Malde MK, Du ZY, Chavey C, Fajas L, Lundebye AK, Brand CL, Vidal H, Kristiansen K, Frøyland L. Persistent organic pollutant exposure leads to insulin resistance syndrome. *Environ Health Perspect* 2010; **118**: 465-471 [PMID: 20064776 DOI: 10.1289/ehp.0901321]

102 **Dirinck E**, Jorens PG, Covaci A, Geens T, Roosens L, Neels H, Mertens I, Van Gaal L. Obesity and persistent organic pollutants: possible obesogenic effect of organochlorine pesticides and polychlorinated biphenyls. *Obesity (Silver Spring)* 2011; **19**: 709-714 [PMID: 20559302 DOI: 10.1038/oby.2010.133]

103 **Sargis RM**. The hijacking of cellular signaling and the diabetes epidemic: mechanisms of environmental disruption of insulin action and glucose homeostasis. *Diabetes Metab J* 2014; **38**: 13-24 [PMID: 24627823 DOI: 10.4093/dmj.2014.38.1.13]

104 **Hectors TL**, Vanparys C, van der Ven K, Martens GA, Jorens PG, Van Gaal LF, Covaci A, De Coen W, Blust R. Environmental pollutants and type 2 diabetes: a review of mechanisms that can disrupt beta cell function. *Diabetologia* 2011; **54**: 1273-1290 [PMID: 21442161 DOI: 10.1007/s00125-011-2109-5]

105 **Claessens J**, Charlier C. [Type 2 diabetes and endocrine disrupting environmental chemical pollutants]. *Rev Med Liege* 2021; **76**: 105-110 [PMID: 33543856]

106 Ferreira MM. Polycyclic aromatic hydrocarbons: a QSPR study. Quantitative structure-property relationships. *Chemosphere* 2001; **44**: 125-146 [PMID: 11444294 DOI: 10.1016/S0045-6535(00)00275-7]

107 **Hou J**, Sun H, Zhou Y, Zhang Y, Yin W, Xu T, Cheng J, Chen W, Yuan J. Environmental exposure to polycyclic aromatic hydrocarbons, kitchen ventilation, fractional exhaled nitric oxide, and risk of diabetes among Chinese females. *Indoor Air* 2018; **28**: 383-393 [PMID: 29444361 DOI: 10.1111/ina.12453]

108 **Boström CE**, Gerde P, Hanberg A, Jernström B, Johansson C, Kyrklund T, Rannug A, Törnqvist M, Victorin K, Westerholm R. Cancer risk assessment, indicators, and guidelines for polycyclic aromatic hydrocarbons in the ambient air. *Environ Health Perspect* 2002; **110 Suppl 3**: 451-488 [PMID: 12060843 DOI: 10.1289/ehp.02110s3451]

109 **Scott LT**. Chemistry at the interior atoms of polycyclic aromatic hydrocarbons. *Chem Soc Rev* 2015; **44**: 6464-6471 [PMID: 25740101 DOI: 10.1039/c4cs00479e]

110 ATSDR fact sheets on hazardous substances. Agency for Toxic Substances and Disease Registry. *Public Health Rep* 2001; **116**: 271 [PMID: 12269227]

111 **Yang L**, Zhou Y, Sun H, Lai H, Liu C, Yan K, Yuan J, Wu T, Chen W, Zhang X. Dose-response relationship between polycyclic aromatic hydrocarbon metabolites and risk of diabetes in the general Chinese population. *Environ Pollut* 2014; **195**: 24-30 [PMID: 25194268 DOI: 10.1016/j.envpol.2014.08.012]

112 **Sun Y**, Chen C, Ding C, Liu G, Zhang G. Distribution Pattern, Emission Characteristics and Environmental Impact of Polycyclic Aromatic Hydrocarbons (PAHs) in Download Ash and Dust from Iron and Steel Enterprise. *Molecules* 2019; **24** [PMID: 31601043 DOI: 10.3390/molecules24203646]

113 **Buha-Marković JZ**, Marinković AD, Nemoda SĐ, Savić JZ. Distribution of PAHs in coal ashes from the thermal power plant and fluidized bed combustion system; estimation of environmental risk of ash disposal. *Environ Pollut* 2020; **266**: 115282 [PMID: 32799176 DOI: 10.1016/j.envpol.2020.115282]

114 **Gunier RB**, Reynolds P, Hurley SE, Yerabati S, Hertz A, Strickland P, Horn-Ross PL. Estimating exposure to polycyclic aromatic hydrocarbons: a comparison of survey, biological monitoring, and geographic information system-based methods. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 1376-1381 [PMID: 16835339 DOI: 10.1158/1055-9965.EPI-05-0799]

115 **Nam YJ**, Kim SH. Association of Urinary Polycyclic Aromatic Hydrocarbons and Diabetes in Korean Adults: Data from the Korean National Environmental Health Survey Cycle 2 (2012-2014). *Diabetes Metab Syndr Obes* 2020; **13**: 3993-4003 [PMID: 33149638 DOI: 10.2147/DMSO.S276658]

116 **Fang L**, Guo J, Wang Q, Ou K, Zou M, Lv L, Chen M, Wang C. Chronic Exposure to Environmental Level Phenanthrene Induces Non-Obesity-Dependent Insulin Resistance in Male Mice. *Environ Sci Technol* 2020; **54**: 15225-15234 [PMID: 33171048 DOI: 10.1021/acs.est.0c04171]

117 **Guo J**, Huang J, Wang Q, Fang L, Zhang S, Li B, Lv L, Chen M, Wang C. Maternal exposure to phenanthrene during gestation disturbs glucose homeostasis in adult mouse offspring. *Chemosphere* 2021; **270**: 128635 [PMID: 33757275 DOI: 10.1016/j.chemosphere.2020.128635]

118 **Valentovic MA**, Alejandro N, Betts Carpenter A, Brown PI, Ramos K. Streptozotocin (STZ) diabetes enhances benzo(alpha)pyrene induced renal injury in Sprague Dawley rats. *Toxicol Lett* 2006; **164**: 214-220 [PMID: 16460892 DOI: 10.1016/j.toxlet.2005.12.009]

119 **Çelik S**, Baysal B, Şen S. Resveratrol Attenuates Benzo(a)pyrene-Induced Dysfunctions, Oxidative Stress and Apoptosis in Pancreatic Beta-Cells. *Adv Biosci Biotechnol* 2019; **10** [DOI: 10.4236/abb.2019.1011029]

120 **Stallings-Smith S**, Mease A, Johnson TM, Arikawa AY. Exploring the association between polycyclic aromatic hydrocarbons and diabetes among adults in the United States. *Environ Res* 2018; **166**: 588-594 [PMID: 29982146 DOI: 10.1016/j.envres.2018.06.041]

121 **Alshaarawy O**, Zhu M, Ducatman AM, Conway B, Andrew ME. Urinary polycyclic aromatic hydrocarbon biomarkers and diabetes mellitus. *Occup Environ Med* 2014; **71**: 437-441 [PMID: 24638887 DOI: 10.1136/oemed-2013-101987]

122 **Alshaarawy O**. The Association of Urinary Polycyclic Aromatic Hydrocarbons Biomarkers and Markers of Inflammation, Diabetes Mellitus and Cardiovascular Disease. *WVU* 2013: 1-77

123 **Hou J**, Sun H, Xiao L, Zhou Y, Yin W, Xu T, Cheng J, Chen W, Yuan J. Combined effect of urinary monohydroxylated polycyclic aromatic hydrocarbons and impaired lung function on diabetes. *Environ Res* 2016; **148**: 467-474 [PMID: 27136672 DOI: 10.1016/j.envres.2016.03.038]

124 **Cenni A**, Sciarra G, Sartorelli P, Pappalardo F. Environmental and biological monitoring of polycyclic aromatic hydrocarbons (PAHs) in coke plants and other workplaces. *Med Lav* 1993; **84**: 379-386 [PMID: 8114651]

125 **Shang Y**, Zhou Q, Wang T, Jiang Y, Zhong Y, Qian G, Zhu T, Qiu X, An J. Airborne nitro-PAHs induce Nrf2/ARE defense system against oxidative stress and promote inflammatory process by activating PI3K/Akt pathway in A549 cells. *Toxicol In Vitro* 2017; **44**: 66-73 [PMID: 28633978 DOI: 10.1016/j.tiv.2017.06.017]

126 **Zhang H**, Han Y, Qiu X, Wang Y, Li W, Liu J, Chen X, Li R, Xu F, Chen W, Yang Q, Fang Y, Fan Y, Wang J, Zhang H, Zhu T. Association of internal exposure to polycyclic aromatic hydrocarbons with inflammation and oxidative stress in prediabetic and healthy individuals. *Chemosphere* 2020; **253**: 126748 [PMID: 32464779 DOI: 10.1016/j.chemosphere.2020.126748]

127 **Alalaiwe A**, Lin YK, Lin CH, Wang PW, Lin JY, Fang JY. The absorption of polycyclic aromatic hydrocarbons into the skin to elicit cutaneous inflammation: The establishment of structure-permeation and in silico-in vitro-in vivo relationships. *Chemosphere* 2020; **255**: 126955 [PMID: 32416390 DOI: 10.1016/j.chemosphere.2020.126955]

128 **Tang Y**, Donnelly KC, Tiffany-Castiglioni E, Mumtaz MM. Neurotoxicity of polycyclic aromatic hydrocarbons and simple chemical mixtures. *J Toxicol Environ Health A* 2003; **66**: 919-940 [PMID: 12825237 DOI: 10.1080/15287390306455]

129 **Archibong AE**, Inyang F, Ramesh A, Greenwood M, Nayyar T, Kopsombut P, Hood DB, Nyanda AM. Alteration of pregnancy related hormones and fetal survival in F-344 rats exposed by inhalation to benzo(a)pyrene. *Reprod Toxicol* 2002; **16**: 801-808 [PMID: 12401509 DOI: 10.1016/S0890-6238(02)00058-8]

130 **Wu X**, Cobbina SJ, Mao G, Xu H, Zhang Z, Yang L. A review of toxicity and mechanisms of individual and mixtures of heavy metals in the environment. *Environ Sci Pollut Res Int* 2016; **23**: 8244-8259 [PMID: 26965280 DOI: 10.1007/s11356-016-6333-x]

131 **Ali H**, Khan E, Ilahi I. Environmental Chemistry and Ecotoxicology of Hazardous Heavy Metals: Environmental Persistence, Toxicity, and Bioaccumulation. *J Chem* 2019; **2019**: 1-14 [DOI: 10.1155/2019/6730305]

132 **Briffa J**, Sinagra E, Blundell R. Heavy metal pollution in the environment and their toxicological effects on humans. *Heliyon* 2020; **6**: e04691 [PMID: 32964150 DOI: 10.1016/j.heliyon.2020.e04691]

133 **Yang AM**, Lo K, Zheng TZ, Yang JL, Bai YN, Feng YQ, Cheng N, Liu SM. Environmental heavy metals and cardiovascular diseases: Status and future direction. *Chronic Dis Transl Med* 2020; **6**: 251-259 [PMID: 33336170 DOI: 10.1016/j.cdtm.2020.02.005]

134 **Wang X**, Karvonen-Gutierrez CA, Herman WH, Mukherjee B, Harlow SD, Park SK. Urinary metals and incident diabetes in midlife women: Study of Women's Health Across the Nation (SWAN). *BMJ Open Diabetes Res Care* 2020; **8** [PMID: 32747380 DOI: 10.1136/bmjdrc-2020-001233]

135 **Tchounwou PB**, Yedjou CG, Patlolla AK, Sutton DJ. Heavy metal toxicity and the environment. *Exp Suppl* 2012; **101**: 133-164 [PMID: 22945569 DOI: 10.1007/978-3-7643-8340-4\_6]

136 **Khan AR**, Awan FR. Metals in the pathogenesis of type 2 diabetes. *J Diabetes Metab Disord* 2014; **13**: 16 [PMID: 24401367 DOI: 10.1186/2251-6581-13-16]

137 **Siddiqui K**, Bawazeer N, Joy SS. Variation in macro and trace elements in progression of type 2 diabetes. *ScientificWorldJournal* 2014; **2014**: 461591 [PMID: 25162051 DOI: 10.1155/2014/461591]

138 **Edwards J**, Ackerman C. A Review of Diabetes Mellitus and Exposure to the Environmental Toxicant Cadmium with an Emphasis on Likely Mechanisms of Action. *Curr Diabetes Rev* 2016; **12**: 252-258 [PMID: 26264451 DOI: 10.2174/1573399811666150812142922]

139 **Rittle J**, Field MJ, Green MT, Tezcan FA. An efficient, step-economical strategy for the design of functional metalloproteins. *Nat Chem* 2019; **11**: 434-441 [PMID: 30778140 DOI: 10.1038/s41557-019-0218-9]

140 **Lu Y**, Yeung N, Sieracki N, Marshall NM. Design of functional metalloproteins. *Nature* 2009; **460**: 855-862 [PMID: 19675646 DOI: 10.1038/nature08304]

141 **Wong WP**, Wallia A, Edwards JR, El Muayed M. Comment on Menke *et al* Metals in Urine and Diabetes in U.S. Adults. Diabetes 2016;65:164-171. *Diabetes* 2016; **65**: e31 [PMID: 27555580 DOI: 10.2337/db16-0555]

142 **Duruibe JO**, Ogwuegbu MOC, Egwurugwu JN. Heavy metal pollution and human biotoxic effects. *Int J Physic Sci* 2007; **2**: 112-118

143 **Leyssens L**, Vinck B, Van Der Straeten C, Wuyts F, Maes L. Cobalt toxicity in humans-A review of the potential sources and systemic health effects. *Toxicology* 2017; **387**: 43-56 [PMID: 28572025 DOI: 10.1016/j.tox.2017.05.015]

144 **Hendryx M**, Luo J, Chojenta C, Byles JE. Exposure to heavy metals from point pollution sources and risk of incident type 2 diabetes among women: a prospective cohort analysis. *Int J Environ Health Res* 2021; **31**: 453-464 [PMID: 31533451 DOI: 10.1080/09603123.2019.1668545]

145 **Cuypers A**, Plusquin M, Remans T, Jozefczak M, Keunen E, Gielen H, Opdenakker K, Nair AR, Munters E, Artois TJ, Nawrot T, Vangronsveld J, Smeets K. Cadmium stress: an oxidative challenge. *Biometals* 2010; **23**: 927-940 [PMID: 20361350 DOI: 10.1007/s10534-010-9329-x]

146 **Shi J**, Cai Y. Environmental chemistry and toxicology of heavy metals. *Ecotoxicol Environ Saf* 2020; **202**: 110926 [PMID: 32800213 DOI: 10.1016/j.ecoenv.2020.110926]

147 **Li Y**, Zhang Y, Wang W, Wu Y. Association of urinary cadmium with risk of diabetes: a meta-analysis. *Environ Sci Pollut Res Int* 2017; **24**: 10083-10090 [PMID: 28233200 DOI: 10.1007/s11356-017-8610-8]

148 **Guo FF**, Hu ZY, Li BY, Qin LQ, Fu C, Yu H, Zhang ZL. Evaluation of the association between urinary cadmium levels below threshold limits and the risk of diabetes mellitus: a dose-response meta-analysis. *Environ Sci Pollut Res Int* 2019; **26**: 19272-19281 [PMID: 31069655 DOI: 10.1007/s11356-019-04943-3]

149 **Little BB**, Reilly R, Walsh B, Vu GT. Cadmium Is Associated with Type 2 Diabetes in a Superfund Site Lead Smelter Community in Dallas, Texas. *Int J Environ Res Public Health* 2020; **17** [PMID: 32599884 DOI: 10.3390/ijerph17124558]

150 **Tinkov AA**, Filippini T, Ajsuvakova OP, Aaseth J, Gluhcheva YG, Ivanova JM, Bjørklund G, Skalnaya MG, Gatiatulina ER, Popova EV, Nemereshina ON, Vinceti M, Skalny AV. The role of cadmium in obesity and diabetes. *Sci Total Environ* 2017; **601-602**: 741-755 [PMID: 28577409 DOI: 10.1016/j.scitotenv.2017.05.224]

151 **Li XT**, Yu PF, Gao Y, Guo WH, Wang J, Liu X, Gu AH, Ji GX, Dong Q, Wang BS, Cao Y, Zhu BL, Xiao H. Association between Plasma Metal Levels and Diabetes Risk: a Case-control Study in China. *Biomed Environ Sci* 2017; **30**: 482-491 [PMID: 28756807 DOI: 10.3967/bes2017.064]

152 **Haswell-Elkins M**, Satarug S, O'Rourke P, Moore M, Ng J, McGrath V, Walmby M. Striking association between urinary cadmium level and albuminuria among Torres Strait Islander people with diabetes. *Environ Res* 2008; **106**: 379-383 [PMID: 18045586 DOI: 10.1016/j.envres.2007.10.004]

153 **Son HS**, Kim SG, Suh BS, Park DU, Kim DS, Yu SD, Hong YS, Park JD, Lee BK, Moon JD, Sakong J. Association of cadmium with diabetes in middle-aged residents of abandoned metal mines: the first health effect surveillance for residents in abandoned metal mines. *Ann Occup Environ Med* 2015; **27**: 20 [PMID: 26306202 DOI: 10.1186/s40557-015-0071-2]

154 **Buha A**, Đukić-Ćosić D, Ćurčić M, Bulat Z, Antonijević B, Moulis JM, Goumenou M, Wallace D. Emerging Links between Cadmium Exposure and Insulin Resistance: Human, Animal, and Cell Study Data. *Toxics* 2020; **8** [PMID: 32867022 DOI: 10.3390/toxics8030063]

155 **Qiao W**, Peng Z, Wang Z, Wei J, Zhou A. Chromium improves glucose uptake and metabolism through upregulating the mRNA levels of IR, GLUT4, GS, and UCP3 in skeletal muscle cells. *Biol Trace Elem Res* 2009; **131**: 133-142 [PMID: 19283340 DOI: 10.1007/s12011-009-8357-2]

156 **Wiernsperger N**, Rapin J. Trace elements in glucometabolic disorders: an update. *Diabetol Metab Syndr* 2010; **2**: 70 [PMID: 21167072 DOI: 10.1186/1758-5996-2-70]

157 **Khodavirdipour A**, Haddadi F, Keshavarzi S. Chromium Supplementation; Negotiation with Diabetes Mellitus, Hyperlipidemia and Depression. *J Diabetes Metab Disord* 2020; **19**: 585-595 [PMID: 32550211 DOI: 10.1007/s40200-020-00501-8]

158 **Talab AT**, Abdollahzad H, Nachvak SM, Pasdar Y, Eghtesadi S, Izadi A, Aghdashi MA, Mohammad Hossseini Azar MR, Moradi S, Mehaki B, Moradi S. Effects of Chromium Picolinate Supplementation on Cardiometabolic Biomarkers in Patients with Type 2 Diabetes Mellitus: a Randomized Clinical Trial. *Clin Nutr Res* 2020; **9**: 97-106 [PMID: 32395440 DOI: 10.7762/cnr.2020.9.2.97]

159 **Asbaghi O**, Fatemeh N, Mahnaz RK, Ehsan G, Elham E, Behzad N, Damoon AL, Amirmansour AN. Effects of chromium supplementation on glycemic control in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res* 2020; **161**: 105098 [PMID: 32730903 DOI: 10.1016/j.phrs.2020.105098]

160 **Ganz T**, Nemeth E. Iron imports. IV. Hepcidin and regulation of body iron metabolism. *Am J Physiol Gastrointest Liver Physiol* 2006; **290**: G199-G203 [PMID: 16407589 DOI: 10.1152/ajpgi.00412.2005]

161 **Kundu D**, Roy A, Mandal T, Bandyopadhyay U, Ghosh E, Ray D. Relation of iron stores to oxidative stress in type 2 diabetes. *Niger J Clin Pract* 2013; **16**: 100-103 [PMID: 23377481 DOI: 10.4103/1119-3077.106776]

162 **Soliman AT**, De Sanctis V, Yassin M, Soliman N. Iron deficiency anemia and glucose metabolism. *Acta Biomed* 2017; **88**: 112-118 [PMID: 28467345 DOI: 10.23750/abm.v88i1.6049]

163 **Feng Y**, Feng Q, Lv Y, Song X, Qu H, Chen Y. The relationship between iron metabolism, stress hormones, and insulin resistance in gestational diabetes mellitus. *Nutr Diabetes* 2020; **10**: 17 [PMID: 32513913 DOI: 10.1038/s41387-020-0122-9]

164 **Momeni A**, Behradmanesh MS, Kheiri S, Abasi F. Serum ferritin has correlation with HbA1c in type 2 diabetic patients. *Adv Biomed Res* 2015; **4**: 74 [PMID: 25878999 DOI: 10.4103/2277-9175.153900]

165 **Forouhi NG**, Harding AH, Allison M, Sandhu MS, Welch A, Luben R, Bingham S, Khaw KT, Wareham NJ. Elevated serum ferritin levels predict new-onset type 2 diabetes: results from the EPIC-Norfolk prospective study. *Diabetologia* 2007; **50**: 949-956 [PMID: 17333112 DOI: 10.1007/s00125-007-0604-5]

166 **Rajpathak SN**, Wylie-Rosett J, Gunter MJ, Negassa A, Kabat GC, Rohan TE, Crandall J; Diabetes Prevention Program (DPP) Research Group. Biomarkers of body iron stores and risk of developing type 2 diabetes. *Diabetes Obes Metab* 2009; **11**: 472-479 [PMID: 19207293 DOI: 10.1111/j.1463-1326.2008.00985.x]

167 **Shang XJ**, Du XM, Fang T, Zhang R, Tian FS. [Effect of iron overload on the level of carbohydrate antigen 199 in type 2 diabetes mellitus]. *Zhonghua Yi Xue Za Zhi* 2019; **99**: 1722-1726 [PMID: 31216819 DOI: 10.3760/cma.j.issn.0376-2491.2019.22.008]

168 **Thielen V**, Paquot N, Scheen AJ. [Hematochromatosis and diabetes]. *Rev Med Liege* 2004; **59**: 29-31 [PMID: 15035540]

169 **Acton RT**, Barton JC, Passmore LV, Adams PC, Speechley MR, Dawkins FW, Sholinsky P, Reboussin DM, McLaren GD, Harris EL, Bent TC, Vogt TM, Castro O. Relationships of serum ferritin, transferrin saturation, and HFE mutations and self-reported diabetes in the Hemochromatosis and Iron Overload Screening (HEIRS) study. *Diabetes Care* 2006; **29**: 2084-2089 [PMID: 16936157 DOI: 10.2337/dc05-1592]

170 **Worwood M**. Serum transferrin receptor assays and their application. *Ann Clin Biochem* 2002; **39**: 221-230 [PMID: 12038596 DOI: 10.1258/0004563021902152]

171 **Liu J**, Li Q, Yang Y, Ma L. Iron metabolism and type 2 diabetes mellitus: A meta-analysis and systematic review. *J Diabetes Investig* 2020; **11**: 946-955 [PMID: 31975563 DOI: 10.1111/jdi.13216]

172 **Mokgalaboni K**, Mabusela MS, Moraba MM. Haematological Indices and Anaemia in Patients with Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis. *SN Compr Clin Med* 2020; **2**: 899-908 [DOI: 10.1007/s42399-020-00314-z]

173 **Samadi A**, Isikhan SY, Tinkov AA, Lay I, Doşa MD, Skalny AV, Skalnaya MG, Chirumbolo S, Bjørklund G. Zinc, copper, and oxysterol levels in patients with type 1 and type 2 diabetes mellitus. *Clin Nutr* 2020; **39**: 1849-1856 [PMID: 31427180 DOI: 10.1016/j.clnu.2019.07.026]

174 **Matter RM**, Elbarbary NS, Ismail EAR, Darwish YW, Nada AS, Banoub VP. Zinc supplementation improves glucose homeostasis in patients with β-thalassemia major complicated with diabetes mellitus: A randomized controlled trial. *Nutrition* 2020; **73**: 110702 [PMID: 32007694 DOI: 10.1016/j.nut.2019.110702]

175 **Fernández-Cao JC**, Warthon-Medina M, H Moran V, Arija V, Doepking C, Serra-Majem L, Lowe NM. Zinc Intake and Status and Risk of Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Nutrients* 2019; **11** [PMID: 31071930 DOI: 10.3390/nu11051027]

176 **Yang A**, Liu S, Cheng Z, Pu H, Cheng N, Ding J, Li J, Li H, Hu X, Ren X, Yang K, Zheng T, Bai Y. Dose-response analysis of environmental exposure to multiple metals and their joint effects with fasting plasma glucose among occupational workers. *Chemosphere* 2017; **186**: 314-321 [PMID: 28787687 DOI: 10.1016/j.chemosphere.2017.08.002]

177 **Forte G**, Bocca B, Peruzzu A, Tolu F, Asara Y, Farace C, Oggiano R, Madeddu R. Blood metals concentration in type 1 and type 2 diabetics. *Biol Trace Elem Res* 2013; **156**: 79-90 [PMID: 24222606 DOI: 10.1007/s12011-013-9858-6]

178 **Brender JR**, Hartman K, Nanga RP, Popovych N, de la Salud Bea R, Vivekanandan S, Marsh EN, Ramamoorthy A. Role of zinc in human islet amyloid polypeptide aggregation. *J Am Chem Soc* 2010; **132**: 8973-8983 [PMID: 20536124 DOI: 10.1021/ja1007867]

179 **Sisnande T**, Lima CK, da Silva DC, Beninatto TM, Alves NL, Amaral MJ, Miranda-Alves L, Lima LMTR. Dietary zinc restriction promotes degeneration of the endocrine pancreas in mice. *Biochim Biophys Acta Mol Basis Dis* 2020; **1866**: 165675 [PMID: 31927001 DOI: 10.1016/j.bbadis.2020.165675]

180 **Ohta S**, Ikemoto T, Wada Y, Saito Y, Yamada S, Imura S, Morine Y, Shimada M. A change in the zinc ion concentration reflects the maturation of insulin-producing cells generated from adipose-derived mesenchymal stem cells. *Sci Rep* 2019; **9**: 18731 [PMID: 31822724 DOI: 10.1038/s41598-019-55172-0]

181 **Wijesekara N**, Dai FF, Hardy AB, Giglou PR, Bhattacharjee A, Koshkin V, Chimienti F, Gaisano HY, Rutter GA, Wheeler MB. Beta cell-specific Znt8 deletion in mice causes marked defects in insulin processing, crystallisation and secretion. *Diabetologia* 2010; **53**: 1656-1668 [PMID: 20424817 DOI: 10.1007/s00125-010-1733-9]

182 **Barman S**, Srinivasan K. Diabetes and zinc dyshomeostasis: Can zinc supplementation mitigate diabetic complications? *Crit Rev Food Sci Nutr* 2020: 1-16 [PMID: 33938330 DOI: 10.1080/10408398.2020.1833178]

183 **Pompano LM**, Boy E. Effects of Dose and Duration of Zinc Interventions on Risk Factors for Type 2 Diabetes and Cardiovascular Disease: A Systematic Review and Meta-Analysis. *Adv Nutr* 2021; **12**: 141-160 [PMID: 32722790 DOI: 10.1093/advances/nmaa087]

184 **Farooq DM**, Alamri AF, Alwhahabi BK, Metwally AM, Kareem KA. The status of zinc in type 2 diabetic patients and its association with glycemic control. *J Family Community Med* 2020; **27**: 29-36 [PMID: 32030076]

185 **Hamedifard Z**, Farrokhian A, Reiner Ž, Bahmani F, Asemi Z, Ghotbi M, Taghizadeh M. The effects of combined magnesium and zinc supplementation on metabolic status in patients with type 2 diabetes mellitus and coronary heart disease. *Lipids Health Dis* 2020; **19**: 112 [PMID: 32466773 DOI: 10.1186/s12944-020-01298-4]

186 **Fung EB**, Ahmad T, Killilea DW, Hussain R, Lal A. Zinc supplementation improves markers of glucose homeostasis in thalassaemia. *Br J Haematol* 2020; **190**: e162-e166 [PMID: 32488893 DOI: 10.1111/bjh.16771]

187 **Das KK**, Das SN, Dhundasi SA. Nickel, its adverse health effects & oxidative stress. *Indian J Med Res* 2008; **128**: 412-425 [PMID: 19106437]

188 **Nestle FO**, Speidel H, Speidel MO. Metallurgy: high nickel release from 1- and 2-euro coins. *Nature* 2002; **419**: 132 [PMID: 12226655 DOI: 10.1038/419132a]

189 **Liu G**, Sun L, Pan A, Zhu M, Li Z, ZhenzhenWang Z, Liu X, Ye X, Li H, Zheng H, Ong CN, Yin H, Lin X, Chen Y. Nickel exposure is associated with the prevalence of type 2 diabetes in Chinese adults. *Int J Epidemiol* 2015; **44**: 240-248 [PMID: 25324152 DOI: 10.1093/ije/dyu200]

190 **Wang X**, Gao D, Zhang G, Zhang X, Li Q, Gao Q, Chen R, Xu S, Huang L, Zhang Y, Lin L, Zhong C, Chen X, Sun G, Song Y, Yang X, Hao L, Yang H, Yang L, Yang N. Exposure to multiple metals in early pregnancy and gestational diabetes mellitus: A prospective cohort study. *Environ Int* 2020; **135**: 105370 [PMID: 31864020 DOI: 10.1016/j.envint.2019.105370]

191 **Hong YS**, Ye BJ, Kim YM, Kim BG, Kang GH, Kim JJ, Song KH, Kim YH, Seo JW. Investigation of Health Effects According to the Exposure of Low Concentration Arsenic Contaminated Ground Water. *Int J Environ Res Public Health* 2017; **14** [PMID: 29186890 DOI: 10.3390/ijerph14121461]

192 **Tsai ML**, Yen CC, Lu FJ, Ting HC, Chang HR. Environmentally relevant concentration of arsenic trioxide and humic acid promoted tumor progression of human cervical cancer cells: In vivo and *in vitro* studies. *Environ Toxicol* 2016; **31**: 1121-1132 [PMID: 25728215 DOI: 10.1002/tox.22121]

193 **Rehman K**, Fatima F, Waheed I, Akash MSH. Prevalence of exposure of heavy metals and their impact on health consequences. *J Cell Biochem* 2018; **119**: 157-184 [PMID: 28643849 DOI: 10.1002/jcb.26234]

194 **Jablonska E**, Socha K, Reszka E, Wieczorek E, Skokowski J, Kalinowski L, Fendler W, Seroczynska B, Wozniak M, Borawska MH, Wasowicz W. Cadmium, arsenic, selenium and iron- Implications for tumor progression in breast cancer. *Environ Toxicol Pharmacol* 2017; **53**: 151-157 [PMID: 28586725 DOI: 10.1016/j.etap.2017.05.014]

195 **Xu L**, Mondal D, Polya DA. Corrections: Xu, L.; Mondal, D.; Polya, D.A. Positive Association of Cardiovascular Disease (CVD) with Chronic Exposure to Drinking Water Arsenic (As) at Concentrations below the WHO Provisional Guideline Value: A Systematic Review and Meta-Analysis. *Int. J. Environ. Res. Public Health* 2020, *17*, 2536. *Int J Environ Res Public Health* 2020; **17** [PMID: 33276700 DOI: 10.3390/ijerph17238947]

196 **Xu L**, Mondal D, Polya DA. Positive Association of Cardiovascular Disease (CVD) with Chronic Exposure to Drinking Water Arsenic (As) at Concentrations below the WHO Provisional Guideline Value: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* 2020; **17** [PMID: 32272785 DOI: 10.3390/ijerph17072536]

197 **Tyler CR**, Allan AM. The Effects of Arsenic Exposure on Neurological and Cognitive Dysfunction in Human and Rodent Studies: A Review. *Curr Environ Health Rep* 2014; **1**: 132-147 [PMID: 24860722 DOI: 10.1007/s40572-014-0012-1]

198 **Liu S**, Guo X, Wu B, Yu H, Zhang X, Li M. Arsenic induces diabetic effects through beta-cell dysfunction and increased gluconeogenesis in mice. *Sci Rep* 2014; **4**: 6894 [PMID: 25367288 DOI: 10.1038/srep06894]

199 **Maull EA**, Ahsan H, Edwards J, Longnecker MP, Navas-Acien A, Pi J, Silbergeld EK, Styblo M, Tseng CH, Thayer KA, Loomis D. Evaluation of the association between arsenic and diabetes: a National Toxicology Program workshop review. *Environ Health Perspect* 2012; **120**: 1658-1670 [PMID: 22889723 DOI: 10.1289/ehp.1104579]

200 **Ramdas M**, Sharma S, Kaul D, Bhatia A. Possible role of miR-2909 RNomics in arsenic mediated pancreatic β-cell dysfunction. *J Trace Elem Med Biol* 2018; **50**: 263-267 [PMID: 30262289 DOI: 10.1016/j.jtemb.2018.07.006]

201 **Wei H**, Hu Q, Wu J, Yao C, Xu L, Xing F, Zhao X, Yu S, Wang X, Chen G. Molecular mechanism of the increased tissue uptake of trivalent inorganic arsenic in mice with type 1 diabetes mellitus. *Biochem Biophys Res Commun* 2018; **504**: 393-399 [PMID: 29890131 DOI: 10.1016/j.bbrc.2018.06.029]

202 **Ludvigsson J**, Andersson-White P, Guerrero-Bosagna C. Toxic metals in cord blood and later development of Type 1 diabetes. *Pediatr Dimens* 2019; **4** [PMID: 31396560 DOI: 10.15761/PD.1000186]

203 **Grau-Pérez M**, Kuo CC, Spratlen M, Thayer KA, Mendez MA, Hamman RF, Dabelea D, Adgate JL, Knowler WC, Bell RA, Miller FW, Liese AD, Zhang C, Douillet C, Drobná Z, Mayer-Davis EJ, Styblo M, Navas-Acien A. The Association of Arsenic Exposure and Metabolism With Type 1 and Type 2 Diabetes in Youth: The SEARCH Case-Control Study. *Diabetes Care* 2017; **40**: 46-53 [PMID: 27810988 DOI: 10.2337/dc16-0810]

204 **Chafe R**, Aslanov R, Sarkar A, Gregory P, Comeau A, Newhook LA. Association of type 1 diabetes and concentrations of drinking water components in Newfoundland and Labrador, Canada. *BMJ Open Diabetes Res Care* 2018; **6**: e000466 [PMID: 29527309 DOI: 10.1136/bmjdrc-2017-000466]

205 **Swaminathan R**. Magnesium metabolism and its disorders. *Clin Biochem Rev* 2003; **24**: 47-66 [PMID: 18568054]

206 **Volpe SL**. Magnesium in disease prevention and overall health. *Adv Nutr* 2013; **4**: 378S-383S [PMID: 23674807 DOI: 10.3945/an.112.003483]

207 **Romani AM**. Magnesium in health and disease. *Met Ions Life Sci* 2013; **13**: 49-79 [PMID: 24470089 DOI: 10.1007/978-94-007-7500-8\_3]

208 **Musso CG**. Magnesium metabolism in health and disease. *Int Urol Nephrol* 2009; **41**: 357-362 [PMID: 19274487 DOI: 10.1007/s11255-009-9548-7]

209 **de Baaij JH**, Hoenderop JG, Bindels RJ. Magnesium in man: implications for health and disease. *Physiol Rev* 2015; **95**: 1-46 [PMID: 25540137 DOI: 10.1152/physrev.00012.2014]

210 **Afridi HI**, Kazi TG, Kazi N, Jamali MK, Arain MB, Jalbani N, Sarfaraz RA, Shah A, Kandhro GA, Shah AQ, Baig JA. Potassium, calcium, magnesium, and sodium levels in biological samples of hypertensive and nonhypertensive diabetes mellitus patients. *Biol Trace Elem Res* 2008; **124**: 206-224 [PMID: 18488152 DOI: 10.1007/s12011-008-8142-7]

211 **Zhao B**, Zeng L, Zhao J, Wu Q, Dong Y, Zou F, Gan L, Wei Y, Zhang W. Association of magnesium intake with type 2 diabetes and total stroke: an updated systematic review and meta-analysis. *BMJ Open* 2020; **10**: e032240 [PMID: 32198298 DOI: 10.1136/bmjopen-2019-032240]

212 **Zhao B**, Deng H, Li B, Chen L, Zou F, Hu L, Wei Y, Zhang W. Association of magnesium consumption with type 2 diabetes and glucose metabolism: A systematic review and pooled study with trial sequential analysis. *Diabetes Metab Res Rev* 2020; **36**: e3243 [PMID: 31758631 DOI: 10.1002/dmrr.3243]

213 **Esmeralda CAC**, David PE, Maldonado IC, Ibrahim SNA, David AS, Escorza MAQ, Dealmy DG. Deranged Fractional Excretion of Magnesium and Serum Magnesium Levels in Relation to Retrograde Glycaemic Regulation in Patients with Type 2 Diabetes Mellitus. *Curr Diabetes Rev* 2021; **17**: 91-100 [PMID: 32664840 DOI: 10.2174/1573399816666200714150434]

214 **Asbaghi O**, Hosseini R, Boozari B, Ghaedi E, Kashkooli S, Moradi S. The Effects of Magnesium Supplementation on Blood Pressure and Obesity Measure Among Type 2 Diabetes Patient: a Systematic Review and Meta-analysis of Randomized Controlled Trials. *Biol Trace Elem Res* 2021; **199**: 413-424 [PMID: 32385715 DOI: 10.1007/s12011-020-02157-0]

215 **Fang X**, Han H, Li M, Liang C, Fan Z, Aaseth J, He J, Montgomery S, Cao Y. Dose-Response Relationship between Dietary Magnesium Intake and Risk of Type 2 Diabetes Mellitus: A Systematic Review and Meta-Regression Analysis of Prospective Cohort Studies. *Nutrients* 2016; **8** [PMID: 27869762 DOI: 10.3390/nu8110739]

216 **Rodríguez-Morán M**, Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. *Diabetes Care* 2003; **26**: 1147-1152 [PMID: 12663588 DOI: 10.2337/diacare.26.4.1147]

217 **Zhang K**. Case report: Magnesium-A new therapeutic target in gestational diabetes mellitus? *Clin Case Rep* 2020; **8**: 2857-2859 [PMID: 33363837 DOI: 10.1002/ccr3.3309]

218 **Pfalzer AC**, Bowman AB. Relationships Between Essential Manganese Biology and Manganese Toxicity in Neurological Disease. *Curr Environ Health Rep* 2017; **4**: 223-228 [PMID: 28417441 DOI: 10.1007/s40572-017-0136-1]

219 **Christianson DW**. Structural chemistry and biology of manganese metalloenzymes. *Prog Biophys Mol Biol* 1997; **67**: 217-252 [PMID: 9446936 DOI: 10.1016/S0079-6107(97)88477-5]

220 **Serdar MA**, Bakir F, Haşimi A, Celik T, Akin O, Kenar L, Aykut O, Yildirimkaya M. Trace and toxic element patterns in nonsmoker patients with noninsulin-dependent diabetes mellitus, impaired glucose tolerance, and fasting glucose. *Int J Diabetes Dev Ctries* 2009; **29**: 35-40 [PMID: 20062562 DOI: 10.4103/0973-3930.50713]

221 **Gong JH**, Lo K, Liu Q, Li J, Lai S, Shadyab AH, Arcan C, Snetselaar L, Liu S. Dietary Manganese, Plasma Markers of Inflammation, and the Development of Type 2 Diabetes in Postmenopausal Women: Findings From the Women's Health Initiative. *Diabetes Care* 2020; **43**: 1344-1351 [PMID: 32295807 DOI: 10.2337/dc20-0243]

222 **Eshak ES**, Muraki I, Imano H, Yamagishi K, Tamakoshi A, Iso H. Manganese intake from foods and beverages is associated with a reduced risk of type 2 diabetes. *Maturitas* 2021; **143**: 127-131 [PMID: 33308618 DOI: 10.1016/j.maturitas.2020.10.009]

223 **Du S**, Wu X, Han T, Duan W, Liu L, Qi J, Niu Y, Na L, Sun C. Dietary manganese and type 2 diabetes mellitus: two prospective cohort studies in China. *Diabetologia* 2018; **61**: 1985-1995 [PMID: 29971528 DOI: 10.1007/s00125-018-4674-3]

224 **Olivares M**, Araya M, Uauy R. Copper homeostasis in infant nutrition: deficit and excess. *J Pediatr Gastroenterol Nutr* 2000; **31**: 102-111 [PMID: 10941959 DOI: 10.1097/00005176-200008000-00004]

225 **Bjørklund G**, Dadar M, Pivina L, Doşa MD, Semenova Y, Aaseth J. The Role of Zinc and Copper in Insulin Resistance and Diabetes Mellitus. *Curr Med Chem* 2020; **27**: 6643-6657 [PMID: 31475889 DOI: 10.2174/0929867326666190902122155]

226 **Kako K**, Takehara A, Arai H, Onodera T, Takahashi Y, Hanagata H, Ogra Y, Takagi H, Kodama H, Suzuki KT, Munekata E, Fukamizu A. A selective requirement for copper-dependent activation of cytochrome c oxidase by Cox17p. *Biochem Biophys Res Commun* 2004; **324**: 1379-1385 [PMID: 15504366 DOI: 10.1016/j.bbrc.2004.09.211]

227 **Hill G**, Edes TE. Diabetes and carbohydrates: the copper connection. *JAMA* 1987; **257**: 2593 [PMID: 3573253 DOI: 10.1001/jama.257.19.2593b]

228 **Laouali** **N**, MacDonald CJ, El Fatouhi D, Mancini FR, Fagherazzi G, Boutron-Ruault MC. Dietary Copper-Zinc Ratio and Type 2 Diabetes Risk in Women: The E3N Cohort Study. *Curr Dev Nutr* 2020; **4**: 1431-1431 [DOI: 10.1093/cdn/nzaa061\_059]

229 **Saker F**, Ybarra J, Leahy P, Hanson RW, Kalhan SC, Ismail-Beigi F. Glycemia-lowering effect of cobalt chloride in the diabetic rat: role of decreased gluconeogenesis. *Am J Physiol* 1998; **274**: E984-E991 [PMID: 9611146 DOI: 10.1152/ajpendo.1998.274.6.E984]

230 **Winship KA**. Toxicity of antimony and its compounds. *Adverse Drug React Acute Poisoning Rev* 1987; **6**: 67-90 [PMID: 3307336]

231 **Choe SY**, Kim SJ, Kim HG, Lee JH, Choi Y, Lee H, Kim Y. Evaluation of estrogenicity of major heavy metals. *Sci Total Environ* 2003; **312**: 15-21 [PMID: 12873394 DOI: 10.1016/S0048-9697(03)00190-6]

232 **Black RE**, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, Ezzati M, Grantham-McGregor S, Katz J, Martorell R, Uauy R; Maternal and Child Nutrition Study Group. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* 2013; **382**: 427-451 [PMID: 23746772 DOI: 10.1016/S0140-6736(13)60937-X]

233 **Feng W**, Cui X, Liu B, Liu C, Xiao Y, Lu W, Guo H, He M, Zhang X, Yuan J, Chen W, Wu T. Association of urinary metal profiles with altered glucose levels and diabetes risk: a population-based study in China. *PLoS One* 2015; **10**: e0123742 [PMID: 25874871 DOI: 10.1371/journal.pone.0123742]

234 **Sharma B**, Singh S, Siddiqi NJ. Biomedical implications of heavy metals induced imbalances in redox systems. *Biomed Res Int* 2014; **2014**: 640754 [PMID: 25184144 DOI: 10.1155/2014/640754]

235 **Valko M**, Morris H, Cronin MT. Metals, toxicity and oxidative stress. *Curr Med Chem* 2005; **12**: 1161-1208 [PMID: 15892631 DOI: 10.2174/0929867053764635]

236 **Beyersmann D**, Hartwig A. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. *Arch Toxicol* 2008; **82**: 493-512 [PMID: 18496671 DOI: 10.1007/s00204-008-0313-y]

237 **Kaneto H**, Katakami N, Kawamori D, Miyatsuka T, Sakamoto K, Matsuoka TA, Matsuhisa M, Yamasaki Y. Involvement of oxidative stress in the pathogenesis of diabetes. *Antioxid Redox Signal* 2007; **9**: 355-366 [PMID: 17184181 DOI: 10.1089/ars.2006.1465]

238 **Han JC**, Park SY, Hah BG, Choi GH, Kim YK, Kwon TH, Kim EK, Lachaal M, Jung CY, Lee W. Cadmium induces impaired glucose tolerance in rat by down-regulating GLUT4 expression in adipocytes. *Arch Biochem Biophys* 2003; **413**: 213-220 [PMID: 12729619 DOI: 10.1016/S0003-9861(03)00120-6]

239 **Henson MC**, Chedrese PJ. Endocrine disruption by cadmium, a common environmental toxicant with paradoxical effects on reproduction. *Exp Biol Med (Maywood)* 2004; **229**: 383-392 [PMID: 15096650 DOI: 10.1177/153537020422900506]

240 **Roden M**, Prskavec M, Fürnsinn C, Elmadfa I, König J, Schneider B, Wagner O, Waldhäusl W. Metabolic effect of sodium selenite: insulin-like inhibition of glucagon-stimulated glycogenolysis in the isolated perfused rat liver. *Hepatology* 1995; **22**: 169-174 [PMID: 7601409 DOI: 10.1016/0270-9139(95)90370-4]

241 **Zheng T**, Liu S, Bai Y, Cheng N, Buka S, Yang A, Shi K, Zhang X, Li Y, Xu S, Zhang B, Wise J. Current Understanding of the Relationship between Metal Exposures and Risk of Type 2 Diabetes. *Curr Res Diabetes Obes J* 2018; **7**: 1-9 [DOI: 10.19080/CRDOJ.2018.07.555710]

242 **Zhu X**, Hua R. Serum essential trace elements and toxic metals in Chinese diabetic retinopathy patients. *Medicine (Baltimore)* 2020; **99**: e23141 [PMID: 33217819 DOI: 10.1097/MD.0000000000023141]

243 **Afridi HI**, Kazi TG, Kazi N, Baig JA, Jamali MK, Arain MB, Sarfraz RA, Sheikh HU, Kandhro GA, Shah AQ. Status of essential trace metals in biological samples of diabetic mother and their neonates. *Arch Gynecol Obstet* 2009; **280**: 415-423 [PMID: 19169697 DOI: 10.1007/s00404-009-0955-x]

244 **Cai L**, Chen S, Evans T, Cherian MG, Chakrabarti S. Endothelin-1-mediated alteration of metallothionein and trace metals in the liver and kidneys of chronically diabetic rats. *Int J Exp Diabetes Res* 2002; **3**: 193-198 [PMID: 12458661 DOI: 10.1080/15604280214281]

245 **Chen ML**, Failla ML. Metallothionein metabolism in the liver and kidney of the streptozotocin-diabetic rat. *Comp Biochem Physiol B* 1988; **90**: 439-445 [PMID: 3409670 DOI: 10.1016/0305-0491(88)90101-0]

246 **Gu Y**, Lian X, Sun W, Gao B, Fu Y. Diabetes Mellitus induces alterations in metallothionein protein expression and metal levels in the testis and liver. *J Int Med Res* 2018; **46**: 185-194 [PMID: 28760087 DOI: 10.1177/0300060517708923]

247 **Mahmoud HM**, Ali AF, Al-Timimi DJ. Relationship Between Zinc Status and DNA Oxidative Damage in Patients with Type 2 Diabetes Mellitus. *Biol Trace Elem Res* 2021; **199**: 1276-1279 [PMID: 32666431 DOI: 10.1007/s12011-020-02267-9]

248 **Lemaire K**, Chimienti F, Schuit F. Zinc transporters and their role in the pancreatic β-cell. *J Diabetes Investig* 2012; **3**: 202-211 [PMID: 24843567 DOI: 10.1111/j.2040-1124.2012.00199.x]

249 **Wijesekara N**, Chimienti F, Wheeler MB. Zinc, a regulator of islet function and glucose homeostasis. *Diabetes Obes Metab* 2009; **11 Suppl 4**: 202-214 [PMID: 19817803 DOI: 10.1111/j.1463-1326.2009.01110.x]

250 **Quilliot D**, Dousset B, Guerci B, Dubois F, Drouin P, Ziegler O. Evidence that diabetes mellitus favors impaired metabolism of zinc, copper, and selenium in chronic pancreatitis. *Pancreas* 2001; **22**: 299-306 [PMID: 11291933 DOI: 10.1097/00006676-200104000-00012]

251 **Satyanarayana S**, Sekhar JR, Kumar KE, Shannika LB, Rajanna B, Rajanna S. Influence of selenium (antioxidant) on gliclazide induced hypoglycaemia/anti hyperglycaemia in normal/alloxan-induced diabetic rats. *Mol Cell Biochem* 2006; **283**: 123-127 [PMID: 16444594 DOI: 10.1007/s11010-006-2387-2]

252 **Vinceti M**, Grioni S, Alber D, Consonni D, Malagoli C, Agnoli C, Malavolti M, Pala V, Krogh V, Sieri S. Toenail selenium and risk of type 2 diabetes: the ORDET cohort study. *J Trace Elem Med Biol* 2015; **29**: 145-150 [PMID: 25169979 DOI: 10.1016/j.jtemb.2014.07.017]

253 **Zhang Y**, Li H, Zhang J, Cao Y, Zhao X, Yu N, Gao Y, Ma J, Zhang H, Zhang J, Guo X, Liu X. The clinical characteristics and outcomes of patients with diabetes and secondary hyperglycaemia with coronavirus disease 2019: A single-centre, retrospective, observational study in Wuhan. *Diabetes Obes Metab* 2020; **22**: 1443-1454 [PMID: 32406594 DOI: 10.1111/dom.14086]

254 **Letko M**, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol* 2020; **5**: 562-569 [PMID: 32094589 DOI: 10.1038/s41564-020-0688-y]

255 **Rutenberg D**, Zhang Y. A Mini-review of the 2019 Novel Coronavirus, SARS-CoV-2. *Am J Biomed Sci Res* 2020; **8**: 15-17 [DOI: 10.34297/AJBSR.2020.08.001226]

256 **Zheng HY**, Zhang M, Yang CX, Zhang N, Wang XC, Yang XP, Dong XQ, Zheng YT. Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. *Cell Mol Immunol* 2020; **17**: 541-543 [PMID: 32203186 DOI: 10.1038/s41423-020-0401-3]

257 **Jiang S**, Hillyer C, Du L. Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses: (Trends in Immunology 41, 355-359; 2020). *Trends Immunol* 2020; **41**: 545 [PMID: 32362491 DOI: 10.1016/j.it.2020.04.008]

258 **Li H**, Liu L, Zhang D, Xu J, Dai H, Tang N, Su X, Cao B. SARS-CoV-2 and viral sepsis: observations and hypotheses. *Lancet* 2020; **395**: 1517-1520 [PMID: 32311318 DOI: 10.1016/S0140-6736(20)30920-X]

259 **Feldman EL**, Savelieff MG, Hayek SS, Pennathur S, Kretzler M, Pop-Busui R. COVID-19 and Diabetes: A Collision and Collusion of Two Diseases. *Diabetes* 2020; **69**: 2549-2565 [PMID: 32938731 DOI: 10.2337/dbi20-0032]

260 **Yaribeygi H**, Sathyapalan T, Jamialahmadi T, Sahebkar A. The Impact of Diabetes Mellitus in COVID-19: A Mechanistic Review of Molecular Interactions. *J Diabetes Res* 2020; **2020**: 5436832 [PMID: 33294461 DOI: 10.1155/2020/5436832]

261 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

262 **Cariou B**, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, Amadou C, Arnault G, Baudoux F, Bauduceau B, Borot S, Bourgeon-Ghittori M, Bourron O, Boutoille D, Cazenave-Roblot F, Chaumeil C, Cosson E, Coudol S, Darmon P, Disse E, Ducet-Boiffard A, Gaborit B, Joubert M, Kerlan V, Laviolle B, Marchand L, Meyer L, Potier L, Prevost G, Riveline JP, Robert R, Saulnier PJ, Sultan A, Thébaut JF, Thivolet C, Tramunt B, Vatier C, Roussel R, Gautier JF, Gourdy P; CORONADO investigators. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. *Diabetologia* 2020; **63**: 1500-1515 [PMID: 32472191 DOI: 10.1007/s00125-020-05180-x]

263 **Galloway JB**, Norton S, Barker RD, Brookes A, Carey I, Clarke BD, Jina R, Reid C, Russell MD, Sneep R, Sugarman L, Williams S, Yates M, Teo J, Shah AM, Cantle F. A clinical risk score to identify patients with COVID-19 at high risk of critical care admission or death: An observational cohort study. *J Infect* 2020; **81**: 282-288 [PMID: 32479771 DOI: 10.1016/j.jinf.2020.05.064]

264 **Li Y**, Han X, Alwalid O, Cui Y, Cao Y, Liu J, Gu J, Wang L, Fan Y, Shi H. Baseline characteristics and risk factors for short-term outcomes in 132 COVID-19 patients with diabetes in Wuhan China: A retrospective study. *Diabetes Res Clin Pract* 2020; **166**: 108299 [PMID: 32623030 DOI: 10.1016/j.diabres.2020.108299]

265 **Chao WC**, Tseng CH, Wu CL, Shih SJ, Yi CY, Chan MC. Higher glycemic variability within the first day of ICU admission is associated with increased 30-day mortality in ICU patients with sepsis. *Ann Intensive Care* 2020; **10**: 17 [PMID: 32034567 DOI: 10.1186/s13613-020-0635-3]

266 **Wang S**, Ma P, Zhang S, Song S, Wang Z, Ma Y, Xu J, Wu F, Duan L, Yin Z, Luo H, Xiong N, Xu M, Zeng T, Jin Y. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study. *Diabetologia* 2020; **63**: 2102-2111 [PMID: 32647915 DOI: 10.1007/s00125-020-05209-1]

267 **Callaghan BC**, Reynolds EL, Banerjee M, Chant E, Villegas-Umana E, Gardner TW, Votruba K, Giordani B, Pop-Busui R, Pennathur S, Feldman EL. The Prevalence and Determinants of Cognitive Deficits and Traditional Diabetic Complications in the Severely Obese. *Diabetes Care* 2020; **43**: 683-690 [PMID: 31932459 DOI: 10.2337/dc19-1642]

268 **Kayem G**, Lecarpentier E, Deruelle P, Bretelle F, Azria E, Blanc J, Bohec C, Bornes M, Ceccaldi PF, Chalet Y, Chauleur C, Cordier AG, Desbrière R, Doret M, Dreyfus M, Driessen M, Fermaut M, Gallot D, Garabédian C, Huissoud C, Luton D, Morel O, Perrotin F, Picone O, Rozenberg P, Sentilhes L, Sroussi J, Vayssière C, Verspyck E, Vivanti AJ, Winer N, Alessandrini V, Schmitz T. A snapshot of the Covid-19 pandemic among pregnant women in France. *J Gynecol Obstet Hum Reprod* 2020; **49**: 101826 [PMID: 32505805 DOI: 10.1016/j.jogoh.2020.101826]

269 **Sentilhes L**, De Marcillac F, Jouffrieau C, Kuhn P, Thuet V, Hansmann Y, Ruch Y, Fafi-Kremer S, Deruelle P. Coronavirus disease 2019 in pregnancy was associated with maternal morbidity and preterm birth. *Am J Obstet Gynecol* 2020; **223**: 914.e1-914.e15 [PMID: 32553908 DOI: 10.1016/j.ajog.2020.06.022]

270 **Mota M**, Banini BA, Cazanave SC, Sanyal AJ. Molecular mechanisms of lipotoxicity and glucotoxicity in nonalcoholic fatty liver disease. *Metabolism* 2016; **65**: 1049-1061 [PMID: 26997538 DOI: 10.1016/j.metabol.2016.02.014]

271 **Codo AC**, Davanzo GG, Monteiro LB, de Souza GF, Muraro SP, Virgilio-da-Silva JV, Prodonoff JS, Carregari VC, de Biagi Junior CAO, Crunfli F, Jimenez Restrepo JL, Vendramini PH, Reis-de-Oliveira G, Bispo Dos Santos K, Toledo-Teixeira DA, Parise PL, Martini MC, Marques RE, Carmo HR, Borin A, Coimbra LD, Boldrini VO, Brunetti NS, Vieira AS, Mansour E, Ulaf RG, Bernardes AF, Nunes TA, Ribeiro LC, Palma AC, Agrela MV, Moretti ML, Sposito AC, Pereira FB, Velloso LA, Vinolo MAR, Damasio A, Proença-Módena JL, Carvalho RF, Mori MA, Martins-de-Souza D, Nakaya HI, Farias AS, Moraes-Vieira PM. Elevated Glucose Levels Favor SARS-CoV-2 Infection and Monocyte Response through a HIF-1α/Glycolysis-Dependent Axis. *Cell Metab* 2020; **32**: 437-446.e5 [PMID: 32697943 DOI: 10.1016/j.cmet.2020.07.007]

272 **Ugwueze CV**, Ezeokpo BC, Nnolim BI, Agim EA, Anikpo NC, Onyekachi KE. COVID-19 and Diabetes Mellitus: The Link and Clinical Implications. *Dubai Diabetes Endocrinol J* 2020; **26**: 69-77 [DOI: 10.1159/000511354]

273 **Lim S**, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat Rev Endocrinol* 2021; **17**: 11-30 [PMID: 33188364 DOI: 10.1038/s41574-020-00435-4]

274 **Apicella M**, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol* 2020; **8**: 782-792 [PMID: 32687793 DOI: 10.1016/S2213-8587(20)30238-2]

**Footnotes**

**Conflict-of-interest statement:** The authors have no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** January 28, 2021

**First decision:** February 25, 2021

**Article in press:** June 3, 2021

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** Egypt

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): D

Grade E (Poor): E

**P-Reviewer:** Acquaviva R, Moreira TMM, Sun X **S-Editor:** Gao CC **L-Editor:** Filipodia **P-Editor:** Li JH



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**