Review of Contemporary Philosophy
ISSN: 1841-5261, e-ISSN: 2471-089X
Vol 22 (1), 2023
Pp 2050 - 2069

Endocrine System Disruptions and Diabetes Mellitus Connections: An Updated Review and The Role of Family Medicine.

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Abstract:

Background: Diabetes mellitus (DM) is a global metabolic disorder characterized by chronic hyperglycemia and its associated health burdens. While traditional factors such as diet and inactivity are well-established contributors, recent attention has shifted to endocrine-disrupting chemicals (EDCs) as potential drivers of DM. Persistent and non-persistent EDCs disrupt hormonal pathways, contributing to insulin resistance and glucose intolerance.

Aim: This review examines the role of EDCs, particularly persistent organic pollutants (POPs) and bisphenol A (BPA), in the pathogenesis of DM, emphasizing their metabolic and environmental interactions. The study aim also to investigate the main role of family medicine in diabetes and endocrinology.

Methods: A comprehensive review of epidemiological studies, clinical trials, and experimental data was conducted, focusing on the associations between EDC exposure and DM. Special attention was given to persistent POPs such as dioxins and polychlorinated biphenyls (PCBs), non-persistent chemicals like BPA, and emerging alternatives.

Results: Evidence suggests strong correlations between exposure to POPs and the prevalence of type 2 diabetes (T2D), with mechanisms including impaired insulin secretion and resistance. Non-persistent EDCs like BPA also exhibit significant associations with DM, even at low exposure levels. Emerging alternatives to BPA, such as bisphenol S (BPS), demonstrate similar risks, raising concerns about their safety. The dose-response relationship is non-linear, with low-dose exposures often more impactful than high doses.

Conclusion: EDCs represent critical environmental risk factors in DM development, compounding traditional contributors like obesity and lifestyle. While regulatory efforts have reduced certain EDCs, their persistent and non-persistent forms continue to pose significant challenges. Addressing these

environmental toxins is imperative for mitigating DM risk globally. The study investigated the important role of family medicine in this condition.

Keywords: Diabetes mellitus, endocrine-disrupting chemicals, persistent organic pollutants, bisphenol A, environmental toxins, insulin resistance, Family Medicine.

Received: 05 october 2023 **Revised:** 19 November 2023 **Accepted:** 02 December 2023

Introduction:

Diabetes mellitus encompasses a range of metabolic illnesses distinguished by persistent hyperglycemia (chronic elevation of blood glucose levels). Diabetes has traditionally been categorized according to its principal etiological mechanisms: insulin secretion deficit, characteristic of type 1 diabetes mellitus (T1D), and/or insulin resistance impacting the liver and peripheral organs, which defines type 2 diabetes mellitus (T2D). The differentiation between T1D and T2D has become progressively unclear, leading to the reclassification of diabetes to encompass other particular subtypes. The incidence of diabetes has attained historic levels. Ten years prior, the World Health Organization (WHO) indicated that 422 million people worldwide were impacted by diabetes, with 95% of these instances being Type 2 Diabetes (T2D) [1]. This statistic exceeded previous forecasts from the 2000s, which anticipated 330 million cases by 2030. The International Diabetes Federation (IDF) reports that the global prevalence of diabetes has increased to 537 million individuals, representing 1 in 10 adults aged 20 to 79 years. Furthermore, around 240 million persons globally demonstrate decreased glucose tolerance, which is a precursor to the onset of diabetes [2]. Unregulated chronic hyperglycemia is linked to serious consequences, resulting in significant economic burdens worldwide. The IDF estimates that 10% of worldwide healthcare costs, surpassing USD 760 billion annually, are designated for diabetes, with the United States alone facing an annual expense of over USD 330 billion.

The factors contributing to the swift increase in diabetes prevalence are not well comprehended, however the simultaneous rise in worldwide obesity indicates potential common underlying mechanisms. Excessive caloric intake and inactivity are identified as key factors in both diseases. Recent data has implicated "non-traditional" risk factors, including exposure to environmental toxins, micronutrient imbalances, and changes in the gut flora, in the etiology of diabetes. The heightened production and environmental discharge of endocrine-disrupting chemicals (EDCs), which disrupt hormonal control, have attracted much attention. Since the early 2010s, significant in vitro and in vivo data has associated EDC exposure with diabetes and metabolic diseases. The US National Institute of Environmental Health Sciences (NIEHS) has recognized differing levels of plausibility, ranging from suggestive to high, regarding the influence of environmental toxins on the diabetes epidemic [4]. This review rigorously analyzes the impact of endocrine-disrupting chemicals (EDCs) on the pathogenesis of diabetes, integrating epidemiological data about type 1 and type 2 diabetes, experimental results on chemical-induced impairments in insulin production and function, and the involvement of EDCs in metabolic programming during fetal development.

Persistent Endocrine-Disrupting Chemicals (EDCs) and Type 2 Diabetes

Persistent organic pollutants (POPs), a significant class of endocrine-disrupting chemicals (EDCs), are extensively recognized for their correlation with obesity and diabetes. These compounds predominantly comprise synthetic chemicals, such as polycyclic aromatic hydrocarbons and halogenated hydrocarbons, all of which are enumerated under the Stockholm Convention (available at http://chm.pops.int/TheConvention/ThePOPs/AllPOPs/tabid/2509/Default.aspx). Prominent persistent organic pollutants (POPs) encompass organochlorine (OC) pesticides, including dichloro-diphenyl-trichloroethane (DDT) and its metabolites, chlordane, as well as industrial chemicals such as polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), dioxins (e.g., TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin), and per- and polyfluoroalkyl substances (PFAS). These compounds demonstrate resistance to environmental degradation, possess low water solubility, high lipid solubility, and tend to bioaccumulate in human adipose tissue at considerable amounts. Their prolonged half-lives—

lasting decades—and inadequate metabolic and excretory clearance processes explain their accumulated existence, even with minimal daily consumption levels [5]. These compounds are associated with many health issues, including carcinogenesis and impairments of the brain and reproductive systems. Nonetheless, their metabolic effects became acknowledged after extensive poisoning events. The 1976 chemical factory explosion in Seveso, Italy, which resulted in a significant dioxin emission, was associated with an increased risk of type 2 diabetes (T2D), especially among women. Among exposed individuals, the youngest women (aged 12 years or younger at the time of exposure) exhibited a markedly elevated risk of metabolic syndrome (adjusted odds ratio [OR] = 2.03, 95% CI 1.25–3.30) in contrast to those older than 12 years (adjusted OR = 0.96, 95% CI 0.68–1.35, p-interaction = 0.01) [8][9]. Comparable results were noted among military soldiers exposed to dioxins in the "Agent Orange" herbicide during the Vietnam War, with a relative risk (RR) of 1.5 (95% CI 1.2–2.0) for the onset of type 2 diabetes (T2D) [10].

The "Yu-cheng" incident in Taiwan, which involved the intake of rice bran oil polluted with PCBs and dioxins, was linked to an increased incidence of Type 2 Diabetes, especially among women (OR = 2.1, 95% CI 1.1–4.5). [11]. Epidemiological studies indicate associations between exposure to persistent organic pollutants (POPs) and metabolic problems in non-incident populations. Taiwanese inhabitants in areas with significant dioxin contamination demonstrated elevated abdominal obesity and insulin resistance (HOMA index) at peak serum dioxin concentrations (OR = 5.23, 95% CI 3.53–7.77 for males; OR = 4.57, 95% CI 2.70–7.64 for women) [12]. Interpreting these data is difficult due to the constraints of retrospective occupational cohort studies, where exposure frequently precedes analysis by many years, and estimations depend on questionnaires or biomarker reconstructions [13]. Moreover, these investigations frequently examine individual EDC doses, overlooking the cumulative effects of pollutant mixtures [14]. For instance, PCBs were linked to elevated fasting glucose levels and an increased incidence of T2D in Chinese populations (PCB52 OR = 1.558, 95% CI 1.109–2.189, p = 0.025; PCB153 OR = 1.841, 95% CI 1.275–2.656, p = 0.001) [15]. In adolescent populations, PCB118 and PBDE153 were associated with increased glucose levels in oral glucose tolerance assessments [16]. The dose-response correlations further confound the assessment of the hazards of type 2 diabetes associated with endocrine-disrupting chemicals. Low to extremely low doses of endocrine-disrupting chemicals (EDCs), considerably beneath regulatory limits, have been linked to the onset of type 2 diabetes (T2D), especially concerning PFAS exposure; conversely, elevated dosages frequently exhibit no detrimental metabolic consequences. This indicates non-monotonic dose-response relationships, exemplified by inverted U-shaped curves, as seen with bisphenol A [20]. Furthermore, the interplay between persistent organic pollutants (POPs) and obesity complicates risk evaluation. Due to their tendency to accumulate in adipose tissue, persistent organic pollutants (POPs) may synergistically elevate the risk of Type 2 Diabetes (T2D) in conjunction with increased fat mass. Notably, certain studies indicate a distinct correlation between persistent organic pollutants (POPs) and type 2 diabetes (T2D) in adults of normal weight, implying processes that are independent of obesity, maybe related to modified insulin production or secretion pathways [25][26]. Consequently, whereas epidemiological statistics indicate substantial connections, meticulous interpretation is necessary to clarify the actual effect of POPs on the general population.

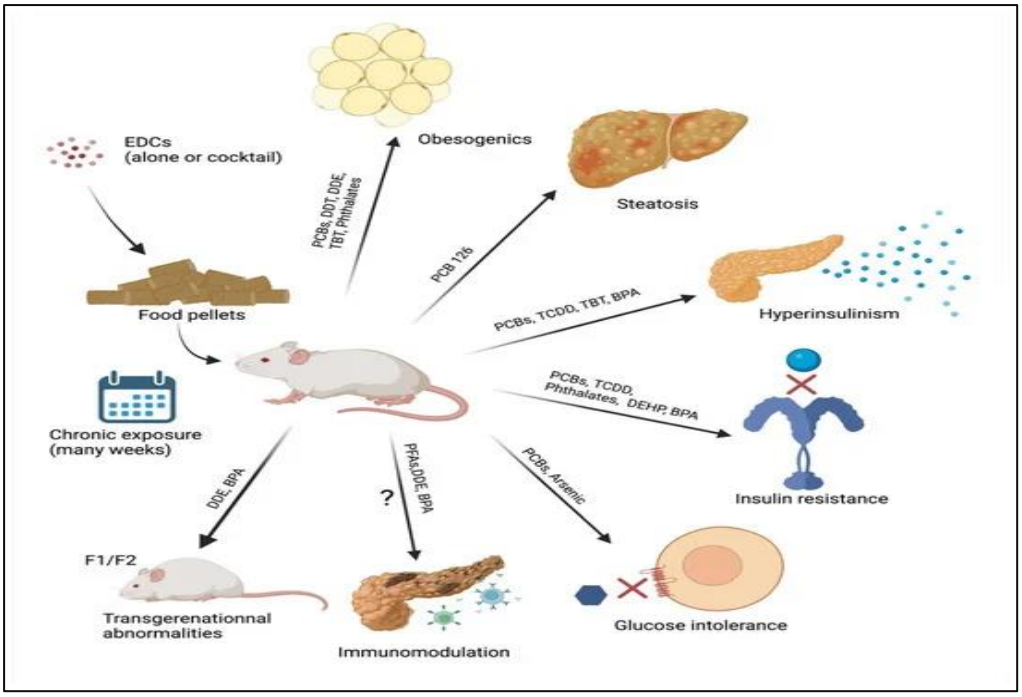

Figure 1: Schematic representation of the main EDC in vivo effects related to diabetes.

Non-Persistent EDCs and Type 2 Diabetes

Since the early 2000s, various longitudinal studies have investigated the impact of persistent and non-persistent endocrine-disrupting chemicals (EDCs), focusing specifically on phthalates and bisphenol A (BPA). Significantly, more than 95% of individuals worldwide possess BPA in their systems [27]. BPA, created in 1891, is one of the most well researched endocrine-disrupting chemicals (EDCs) due to its estrogenic properties, raising concerns over its potential effects on human health, especially in developmental and reproductive contexts, as well as hormone-dependent malignancies [28,29].

The U.S. National Health and Nutrition Examination Survey (NHANES), established in 1960, offers the most extensive data among population-based research. It conducts an annual assessment of 5,000 to 10,000 representative Americans and has incorporated chemical exposure testing since 1999. Research has consistently demonstrated substantial correlations between diabetes (either diagnosed or self-reported) and exposure to both persistent organic pollutants (POPs), including polychlorinated biphenyls (PCBs), dioxins, and p,p'-DDE, as well as non-persistent endocrine-disrupting chemicals (EDCs) such as phthalates and BPA (adjusted odds ratio [OR] = 2.74; 95% CI 1.44–5.23) [30,31]. Supplementary cross-sectional investigations validate this trend, especially for BPA exposure, with several indicating robust correlations with diabetes and prediabetes [32,33,34]. Sun et al. established a positive association between urine BPA and butyl-phthalate levels (assessed 5–10 years earlier) and the risk of type 2 diabetes (T2D) in the Nurses' Health Study II cohort, although this was not observed in older NHS participants [35]. A meta-analysis of clinical research on BPA conducted till mid-2014 identified a correlation between elevated urine BPA levels and heightened risk of Type 2 Diabetes (OR = 1.47) [36]. Additionally, the BPA CLARITY project, launched by the National Institute of Environmental Health Sciences (NIEHS), National Toxicology Program (NTP), and the FDA, validated metabolic adverse effects at the lowest tested dose (2.5 μg/kg/day), which is substantially lower than the maximum safe daily oral BPA intake (50 μg/kg/day) established by the EPA and FDA [CLARITY-BPA Program, accessed on 10 January 2023].

In reaction to health apprehensions, BPA alternatives (e.g., bisphenol S, F, M, B, AP, AF, BADGE) have been progressively utilized over the previous decade, resulting in elevated urine and blood concentrations of these substances worldwide. Nonetheless, there is a paucity of data concerning their safety. Bisphenol S (BPS) is among the most extensively researched alternatives; yet, studies connecting BPS exposure to

diabetes, fasting glucose levels, or insulin resistance are few. Two investigations revealed substantial correlations between BPS exposure and the development of diabetes (OR = 3.83; 95% CI 2.37–6.20, and adjusted hazard ratio [aHR] at year 3: 2.81; 95% CI 1.74–4.53) [36,37]. Analogous to BPA, this heightened risk was independent of obesity, with urine BPS levels significantly related with greater insulin resistance in non-overweight women (BMI < 25 kg/m^2; p = 0.017) [41]. Phthalates, commonly utilized as plasticizers, also demonstrate endocrine-disrupting chemical (EDC) characteristics and are associated with the onset of obesity and diabetes. Recent investigations have presented inconclusive results concerning their influence on insulin resistance, as assessed by the homeostatic model assessment (HOMA) index [42]. A meta-analysis of seven studies with more than 12,000 participants demonstrated that exposure to low and high molecular weight phthalate metabolites and di-2-ethylhexyl phthalate (DEHP) markedly elevated the risk of Type 2 Diabetes (OR = 1.69, 1.71, and 2.15, respectively) [43].

Other endocrine-disrupting chemicals, such as triclosan and triclocarban—despite the FDA's prohibition in 2016—persist in circulation, notably within personal care items. Data from NHANES (2013–2014) demonstrated a notable correlation between triclocarban exposure and diabetes prevalence in women (OR = 1.79; 95% CI 1.05–2.05), although no significant connection was found in males (OR = 1.29; 95% CI 0.73–2.27; p = 0.032) [44]. Moreover, heavy metals (cadmium, lead, mercury), trace elements (zinc), arsenic, and air pollutants (e.g., ozone, nitrogen dioxide, PM2.5) have been associated with metabolic syndromes and diabetes, although the results are inconsistent [45–54]. Notably, the effects of air pollution are intensified in warm, humid climates, heightening concerns regarding the influence of climate change on diabetes risk [54]. Notwithstanding these connections, the limitations of these epidemiological research must be recognized. Observational methods are incapable of establishing causality, and present EDC levels may not accurately represent exposures during disease progression. Moreover, endocrine-disrupting chemicals frequently coexist, complicating the differentiation of the effects of particular compounds. Genetic polymorphisms affecting EDC metabolism may also play a role in variability of susceptibility, especially during crucial exposure times such as pregnancy and early childhood [55]. Finally, confounding variables may obscure the observed relationships [13,56,57].

EDCs and Type 1 Diabetes

The association between environmental toxicants and type 1 diabetes (T1D) is less investigated than that of type 2 diabetes (T2D). Nonetheless, the frequency of Type 1 Diabetes is increasing, especially in industrializing areas such as China. Cross-sectional studies present contradictory results, with some indicating increased EDC levels at T1D diagnosis in children, whereas others propose that specific EDCs (e.g., perfluoroalkyls) may confer protective effects [58,59]. Due to the autoimmune nature of T1D, it is postulated that EDCs may affect disease initiation by triggering beta-cell death or impairing immunological function, especially with BPA and its alternatives [58]. Epidemiological data also associates air pollution with the development of Type 1 Diabetes (T1D). Exposure to pollutants, including ozone, during prenatal development has been associated with a heightened risk of early-onset Type 1 Diabetes in children (Hazard Ratio per interquartile increase = 2.00; 95% Confidence Interval 1.04–3.86) [60,61]. Recent corroboration of these findings emerged from a comprehensive environmental association research in the UK, encompassing 14,000 children, which underscored regional variation in Type 1 Diabetes incidence attributable to 15 environmental risk variables, such as air pollutants, lead, radon, and nocturnal outdoor light. In conclusion, additional study is crucial to clarify the involvement of EDCs and environmental exposures in the etiology of T1D.

Maternal Exposure to EDCs and Diabetes

The influence of maternal exposure to endocrine-disrupting chemicals (EDCs) during gestation offers substantial study opportunities, especially on the emergence of diabetes in pregnancy and its possible repercussions on the progeny [63]. The fetal stage is a crucial developmental phase that affects the origins of health and disease (DOHaD) by adjustments in gene expression and metabolic changes, as proposed by David Barker [64]. Gestational diabetes, potentially induced by endocrine-disrupting

chemicals (EDCs) or exposure during this critical period, may predispose offspring to diabetes. Human research investigating prenatal exposure to endocrine-disrupting chemicals (EDCs) and maternal metabolic dysfunction produce contradictory findings; nonetheless, some evidence associates phthalates and BPA with increased plasma glucose levels and reduced glucose tolerance in pregnant women [65]. BPS has been associated with impaired glucose tolerance during pregnancy, however no clear link to gestational diabetes has been established [40]. A meta-analysis conducted by Yan et al., which included 25 research, found PCBs, PBDEs, PFAs, and phthalates as significant risk factors for gestational diabetes [66]. Further epidemiological studies have linked gestational diabetes with heavy metals, PFASs, persistent organic pollutants, and specific bisphenol analogs, particularly bisphenol AF. While these findings indicate a potential association between EDCs and gestational diabetes, additional research is required to enhance the understanding of this risk. Moreover, maternal exposure to endocrine-disrupting chemicals (EDCs) such bisphenol A (BPA) can be directly transmitted to progeny through the placenta or breastfeeding [71,72]. Research has indicated correlations between prenatal exposure to DDE and PFAs and heightened vulnerability to diabetes in progeny [73]. Moreover, exposure to pollutants during gestation is associated with an increased incidence of being overweight and obesity in childhood and adolescence, aligning with the early catch-up growth phenomenon outlined in the DOHaD hypothesis [64]. The CHAMACOS study indicated that prenatal exposure to phthalate and phenol combinations, as well as DDT and its metabolites (e.g., DDE), increased the incidence of obesity in children at ages 5 and 12. This cohort has not yet assessed the risk of type 2 diabetes (T2D) in kids, but early metabolic abnormalities may reasonably lead to a heightened prevalence of T2D.

In Vivo Evidence of Diabetogenic Pollutants

Epidemiological studies are essential for comprehending the possible effects of EDCs on human health. Nevertheless, these investigations frequently produce correlational, not causal, evidence, requiring in vivo and in vitro experiments to clarify the doses, mechanisms, and kinetics of endocrine system disturbances, despite their constraints in duplicating human variability [77,78,79,80]. Animal studies have investigated pathophysiological characteristics from preconception to maturity by phenotypic and functional analysis in conjunction with omics techniques. Studies have shown the obesogenic impact of endocrine-disrupting chemicals (EDCs), particularly their effects on adipose tissue hypertrophy and hyperplasia [23,78,82,83]. Obesity, while a risk factor for type 2 diabetes, is not a universal cause nor intrinsically associated with the condition. Endocrine-disrupting chemicals (EDCs) have been identified as diabetogenic pollutants, as evidenced by previous reviews [56,82,84,85,86,87,88]. In vivo investigations often assess alterations in glucose metabolism and insulin production linked to insulin resistance. Recent studies has investigated the impact of endocrine-disrupting chemicals (EDCs) on gut microbial ecology, establishing a connection between alterations in microbiota and diabetes [89].

Persistent EDCs and T2D

Chronic exposure to endocrine-disrupting chemicals, particularly through the consumption of fat-rich diets, has been examined in animal models. Ruzzin et al. revealed that rats consuming a high-fat diet with EDCs from salmon oil exhibited insulin resistance, aggravated obesity, and hepatic steatosis [90,91]. Prolonged exposure to endocrine-disrupting chemical mixtures (e.g., TCDD, PCB153, DEHP, and BPA) from the periconception period forward caused sex-specific metabolic disturbances in progeny [92]. Exposure to PCBs, whether via mixtures or specific chemicals such as PCB126, has consistently compromised glucose tolerance and elicited insulin resistance in diet-controlled murine models [95,96]. Moreover, acute exposure to TCDD has been demonstrated to impair insulin production through the Aryl hydrocarbon Receptor (AhR) pathway [99,100].

Non-Persistent EDCs and T2D

Research on non-persistent endocrine-disrupting chemicals, such as BPA, underscores its potential to induce diabetes, although discrepancies in experimental methodologies and results. BPA has been

demonstrated to interfere with insulin production, cause β-cell dysfunction, and facilitate adipogenesis and insulin resistance [55,71,82,104,105,106]. Comparable negative effects have been noted for BPA analogs, including BPS, affecting pathways such as PPARγ signaling [107,108,109]. In contrast, the data connecting phthalates/DEHP to diabetes is scarce, with research mostly examining their impact on oxidative stress and insulin resistance [110,111]. Wei et al. identified that DEHP induces oxidative stress dysregulation via the miR-17/Keap1-Nrf2/miR-200a axis, which contributes to insulin resistance [112]. Chronic arsenic exposure in rodents results in compromised glucose sensing, glucose intolerance, and modified insulin secretion. These findings underscore the complex impacts of EDCs on metabolic health and the necessity for additional research to clarify their unique contributions to diabetes etiology.

EDCs and Type 1 Diabetes (T1D):

The association between endocrine-disrupting chemicals (EDCs) and type 1 diabetes (T1D) has been predominantly studied utilizing non-obese diabetic (NOD) mice as experimental models [118]. Nonetheless, the results are unclear owing to the restricted quantity of studies and the conflicting evidence regarding both immunosuppressive and immunoproliferative effects. Kuiper et al. revealed that polychlorinated biphenyls (PCBs), delivered in both high and low levels during acute or chronic exposure, were linked to a reduced incidence of T1D in NOD mice, due to diminished T cell populations [119]. These results, however, arose amidst contradictory epidemiological data [120–122], and following confirmatory research are absent. Likewise, whereas one study associated perfluoroalkyl compounds (PFAs) with expedited insulitis in NOD mice [123], epidemiological evidence continues to be incongruous [118]. Exposure to dichlorodiphenyldichloroethylene (DDE) was associated with a heightened incidence of type 1 diabetes (T1D) in NOD mice [124], but prior research on immune response changes following exposure to dichlorodiphenyltrichloroethane (DDT) produced inconsistent results [125]. The facts regarding dioxins, including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), are equally inconsistent: While TCDD treatment in wild-type mice hindered second-phase glucose-stimulated secretion [99], in NOD mice, it diminished insulitis through the proliferation of Foxp3 T cells [126]. The effects of TCDD seem to be mediated via aryl hydrocarbon receptor (AhR) pathways. Research on non-persistent endocrine-disrupting chemicals (EDCs) is similarly constrained. Exposure to bisphenol A (BPA) was associated with expedited onset of type 1 diabetes in NOD mice, unlike phthalates or a combination of BPA and phthalates [127]. Exposure to developmental phthalates compromised pancreatic beta-cell functionality and glucose tolerance in rats [58,110]. The effects of BPA seem to be contingent upon the timing of exposure, dietary influences, and sex, however these conclusions are still debated. Moreover, research on arsenic and air pollution exposure in NOD and streptozotocin (STZ) mice is limited [118], underscoring the necessity for additional investigations to elucidate the pathways via which endocrine-disrupting chemicals affect autoimmunity and type 1 diabetes (T1D). In addition to immunomodulation, certain studies indicate that endocrine-disrupting chemicals (EDCs) may influence gut microbiota or vitamin D metabolism as possible factors in Type 1 Diabetes (T1D) [89,118]. Comprehensive in vitro studies are crucial to clarify the molecular mechanisms of action of EDCs.

Maternal-Fetal Exposure to EDCs and Diabetes:

Animal studies investigating EDC exposure during pregnancy often focus on diabetes development in offspring. Notably, DDE exposure in rat dams from gestational days 8 to 15 induced transgenerational glucose intolerance and pancreatic dysfunction in F1 and F2 generations, linked to altered genomic imprinting on the *igf2/H19* locus and transmitted via the male germline to F3 progeny [130,131]. Conversely, data on BPA's developmental effects remain inconsistent [65,105,132]. Some studies report transgenerational phenotypic abnormalities after BPA exposure, though these vary regarding T1D or type 2 diabetes (T2D) risk [105,129,133,134]. Other EDCs demonstrate similarly mixed results, with opposing effects observed in combination studies.

In Vitro Evidence of Diabetogenic Pollutants:

In vitro methodologies are essential for elucidating the mechanisms of action of endocrine-disrupting chemicals (EDCs). Screening techniques utilizing 96-well plates and isolated islets for the assessment of reactive oxygen species (ROS) or human embryonic stem cell cultures have elucidated the roots of diabetes [135,136]. Assays of beta-cell function and mechanistic investigations have identified endocrine-disrupting chemicals (EDCs) as involved in multiple pathways, such as nuclear receptor activation (e.g., estrogen receptor, aryl hydrocarbon receptor, peroxisome proliferator-activated receptor), insulin signaling (e.g., phosphoinositide 3-kinase/extracellular signal-regulated kinase/protein kinase B), oxidative stress, control of KATP channels, and disruption of insulin exocytosis. Persistent endocrine-disrupting chemicals (EDCs), including polychlorinated biphenyls (PCBs), per- and polyfluoroalkyl substances (PFAs), and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), have demonstrated an impact on insulin production and beta-cell viability via processes related to calcium signaling, oxidative stress, and receptor-mediated genomic effects [96,138–140]. Simultaneously, non-persistent endocrine-disrupting chemicals (EDCs), such as bisphenol A (BPA) and phthalates, impair beta-cell functionality through reactive oxygen species (ROS)-mediated mechanisms and the activation of apoptosis [55,112,162]. Heavy metals such as arsenic disrupt glucose metabolism by altering critical signaling molecules (e.g., SIRT3, AKT, GLUT4) and stimulating inflammasome activation, hence worsening hepatic insulin resistance [114,163]. Volatile and semi-volatile endocrine-disrupting chemicals in air pollution lead to metabolic dysfunction, as demonstrated by vascular inflammation and insulin resistance following exposure to PM2.5 [166]. These findings highlight the intricacy of the diabetogenic effects of EDCs and the need for additional research to elucidate their molecular and physiological influences.

Role of Family Physicians:

The family physician plays a critical role in managing conditions influenced by environmental endocrine-disrupting chemicals (EDCs), particularly those associated with Type 1 Diabetes (T1D) and Type 2 Diabetes (T2D). Their responsibilities include the following:

1. Early Detection and Screening

- Family physicians are often the first point of contact for patients and can identify early symptoms of diabetes and associated conditions. They may recommend screenings for at-risk populations, especially those with a family history of diabetes or exposure to known EDCs.

2. Patient Education

- Physicians educate patients and families about the potential risks of EDC exposure and its links to diabetes. This includes guidance on avoiding exposure to persistent and non-persistent EDCs such as BPA, phthalates, and PCBs, as well as emphasizing lifestyle modifications.

3. Monitoring and Risk Assessment

- Family physicians monitor patients with known risk factors, including those with gestational diabetes or developmental exposure to EDCs. They assess environmental, dietary, and occupational factors contributing to the risk.

4. Coordinating Multidisciplinary Care

- In complex cases involving T1D or T2D development, family physicians collaborate with endocrinologists, toxicologists, dietitians, and other specialists to ensure comprehensive care.

5. Advocacy and Preventive Measures

- Physicians advocate community-level awareness and policies to reduce environmental EDC exposure. This involves supporting initiatives for cleaner environments, improved food safety, and stricter regulations on harmful chemicals.

6. Research and Awareness

- Engaging in or supporting research to better understand the link between EDCs and diabetes, family physicians contribute to the growing body of evidence. They help translate findings into practical recommendations for patients.

7. Psychosocial Support

- Given the chronic nature of diabetes and its complications, family physicians provide emotional support and counseling, helping families adapt to long-term disease management while addressing concerns about environmental influences.

Conclusion:

Diabetes mellitus (DM) continues to escalate as a public health challenge, fueled by multifaceted contributors, including dietary habits, physical inactivity, and increasing exposure to endocrine-disruption chemicals (EDCs). This review highlights the substantial impact of both persistent and non-persistent EDCs on the development and progression of DM. Persistent organic pollutants (POPs), such as dioxins and PCBs, disrupt glucose metabolism by impairing insulin production and function. Similarly, non-persistent chemicals like BPA, and its alternatives such as bisphenol S (BPS), have been linked to heightened risks of type 2 diabetes (T2D), even at minimal exposure levels. The dose-response relationship of EDCs adds complexity, as low doses often induce more pronounced effects than higher exposures, challenging traditional toxicological paradigms. Furthermore, the interplay between obesity and EDCs intensifies diabetes risk, with some pollutants demonstrating direct metabolic effects independent of body weight. This underscores the necessity of addressing EDC exposure, particularly given their ubiquity and persistence in the environment. Regulatory measures have made strides in curbing the prevalence of some EDCs, but the introduction of poorly studied alternatives raises new concerns. Public health strategies must encompass stricter regulations, enhance monitoring of EDC exposure, and increased awareness about their potential health impacts. Simultaneously, further research is needed to elucidate the mechanisms underlying EDC-induced metabolic disruptions, identify safe alternatives, and inform policy decisions. Ultimately, mitigating the role of EDCs in DM requires a multidisciplinary approach, integrating environmental science, toxicology, public health, and clinical care. By addressing these environmental risk factors, we can complement existing interventions to curb the growing burden of diabetes globally.

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ودور طبيب الاسرة اضطرابات الجهاز الغدد الصماء وعلاقتها بمرض السكري: مراجعة محدثة

الملخص:

الخلفية: يُعد مرض السكري (DM) اضطرابًا استقلابيًا عالميًا يتميز بارتفاع مزمن في نسبة السكر في الدم وما يرتبط به من أعباء صحية. وبينما تُعتبر العوامل التقليدية كعوامل (EDCs) مثل النظام الغذائي وقلة النشاط عوامل مساهمة معروفة، فإن الاهتمام الحديث انصب على المواد الكيميائية المسببة لاضطراب الغدد الصماء محتملة لدفع المرض. تعمل هذه المواد المستدامة وغير المستدامة على تعطيل المسارات الهرمونية، مما يؤدي إلى مقاومة الأنسولين وعدم تحمل الجلوكوز.

الهدف: تهدف هذه المراجعة إلى دراسة دور المواد الكيميائية المسببة لاضطراب الغدد الصماء، خصوصًا الملوثات العضوية الثابتة (POPs) وثنائي الفينول A ودور التفاعلي لطبيب الاسرة في التعامل مع السكر ومشاكل الغدد الصماء. .، في نشوء مرض السكري، مع التركيز على تفاعلاتها الأيضية والبيئية(BPA)

الطرق: تم إجراء مراجعة شاملة للدراسات الوبائية والتجارب السريرية والبيانات التجريبية، مع التركيز على العلاقة بين التعرض للمواد الكيميائية المسببة لاضطراب الغدد الصماء ومرض السكري. وشملت المراجعة الملوثات العضوية الثابتة مثل الديوكسينات وثنائي الفينيل متعدد الكلور (PCBs) ، والمواد الكيميائية غير المستدامة والبدائل الحديثةBPA مثل ..

النتائج: تشير الأدلة إلى وجود ارتباطات قوية بين التعرض للملوثات العضوية الثابتة وانتشار مرض السكري من النوع الثاني (T2D) ، مع آليات تشمل ضعف إفراز الأنسولين ومقاومته. كما أن المواد الكيميائية غير المستدامة مثل BPA تُظهر البدائل تظهر ارتباطات كبيرة مع مرض السكري حتى عند مستويات التعرض المنخفضة. الحديثة لـBPA مثل ثنائي الفينول S (BPS) ، مخاطر مشابهة، مما يثير القلق بشأن سلامتها. العلاقة بين الجرعة والاستجابة غير خطية، حيث تكون التعرضات ذات الجرعات المنخفضة أكثر تأثيرًا من الجرعات العالية في كثير من الأحيان.

الخلاصة: تمثل المواد الكيميائية المسببة لاضطراب الغدد الصماء عوامل خطر بيئية حاسمة في تطور مرض السكري، مما يزيد من تأثير العوامل التقليدية مثل السمنة ونمط الحياة. وعلى الرغم من أن الجهود التنظيمية قد قللت من بعض هذه المواد، إلا أن أشكالها المستدامة وغير المستدامة لا تزال تشكل تحديات كبيرة. التصدي لهذه وجدت الدراسة دور هام لطبيب الاسرة في التعامل مع مشاكل الغدد الصماء والسكري. .السموم البيئية أمر ضروري لتقليل خطر مرض السكري على مستوى العالم

الكلمات المفتاحية: مرض السكري، المواد الكيميائية المسببة لاضطراب الغدد الصماء، الملوثات العضوية الثابتة، ثنائي الفينول A ، السموم البيئية، مقاومة الأنسولين، طبيب الاسرة.