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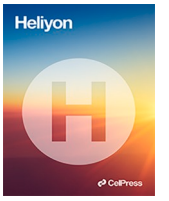

Review article

Potential effects of bisphenol A on diabetes mellitus and its chronic complications: A narrative review

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ABSTRACT

Diabetes mellitus (DM) is a metabolic disease caused by multiple factors such as genetics, environment, and lifestyle. Bisphenol A (BPA), as one of the most common endocrine-disrupting chemicals (EDCs), has been strongly implicated in the development of type 2 diabetes mellitus (T2DM). BPA exposure is associated with target organ damage in DM and may exacerbate the progression of some chronic complications of DM. This paper reviews relevant epidemiological, in vivo, and in vitro studies to better understand BPA's potential risk associations and pathological mechanisms in several chronic diabetic complications.

1. Introduction

Diabetes mellitus (DM) is a chronic disease severely threatening human health. According to the International Diabetes Federation's latest Global Diabetes Map, in 2021, the global number of adults with diabetes was estimated at 537 million (aged 20–79 years). This number will increase to about 643 million by 2030 and 783 million by 2045 [1]. DM is divided into three types based on its etiology: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and other specific types. T2DM is the most common type of clinical DM, accounting for 90–95% of diabetic patients [2]. Long-term, uncontrolled blood glucose levels can damage various organ tissues, including the heart, kidneys, brain, feet, and eyes, leading to chronic diabetic complications [3]. The most critical chronic diabetic complications are coronary heart disease, peripheral vascular disease, end-stage renal disease, retinopathy and neuropathy. These chronic diabetic complications are all major burdens for people with DM [4]. Traditionally, obesity, physical inactivity, advanced age, and an unhealthy diet have been considered significant risk factors for DM [5–7]. In recent years, there has been increasing evidence that endocrine-disrupting chemicals (EDCs) are emerging as additional risk factors for the development of diabetes, including T1DM and T2DM [8].

Bisphenol A (BPA) is an organic compound found in a variety of consumer products, including polycarbonate plastics, epoxy resins and thermal receipt paper [9]. Due to its widespread use, BPA has been found in soil and surface water [10]. External BPA can enter the body through the gastrointestinal, respiratory and dermal tracts. Due to its endocrine-disrupting effects, it can cause damage to the reproductive, immune and neuroendocrine systems (Fig. 1) [11]. Recently, increasing evidence suggests that BPA exposure is an

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independent environmental risk factor for DM that is separate from traditional risk factors [12]. BPA promotes the key pathogenesis of T2DM, including insulin resistance, impaired insulin and glucagon secretion, and pancreatic β-cell dysfunction and injury [13–16]. BPA increases the metabolic stress of high glucose, accelerating cellular senescence and apoptosis, which in turn promotes the progression of DM [17]. BPA exposure is positively associated with obesity, another significant risk factor for the progression of diabetes [18]. By promoting obesity-related disturbances in lipid metabolism and insulin resistance, BPA indirectly exacerbates the progression of DM [19,20]. Furthermore, several studies have identified a possible link between the mechanisms of BPA-induced organ damage and the pathogenesis of diabetic complications in these organs [21,22]. BPA exposure may promote the development and progression of some chronic diabetic complications. However, to our knowledge, no comprehensive review summarises the potential effects and mechanisms of BPA on some common chronic diabetic complications. Therefore, after a brief overview of the sources and hazards of BPA, we review the risk associations and potential mechanisms of action of BPA on diabetic nephropathy, diabetic cognitive dysfunction, diabetic retinopathy, and diabetic cardiopathy (Fig. 2).

2. BPA: sources and hazards

BPA ($C_{15}H_{16}O_2$) is an organic compound that can dissolve in fats and oils. It has a symmetrical chemical structure of two phenolic rings linked by a methyl bridge. BPA is one of the world's most commonly manufactured and used chemicals. It is commonly used to make epoxy resins and polycarbonate (PC) plastics. These materials can be found in everyday products such as water pipes, electronic devices, thermal paper and toys [23]. Due to the high volume of BPA production and use, BPA has been found in air, soil and surface water [10]. In particular, a meta-analysis of 15 studies involving 28,353 participants found BPA in the urine of more than 90% of participants. Despite their differences, the studies highlight the widespread exposure of the population to BPA [24]. People are more likely to get BPA from food and water stored in plastic containers than from BPA in the environment. BPA is found in cups, bottles, packaging, can coatings and other items used as raw materials for food contact materials [25]. Canned food contains higher levels of BPA. The main routes of BPA into the environment and food include migration from PCs, cans and coatings [26]. PC material is

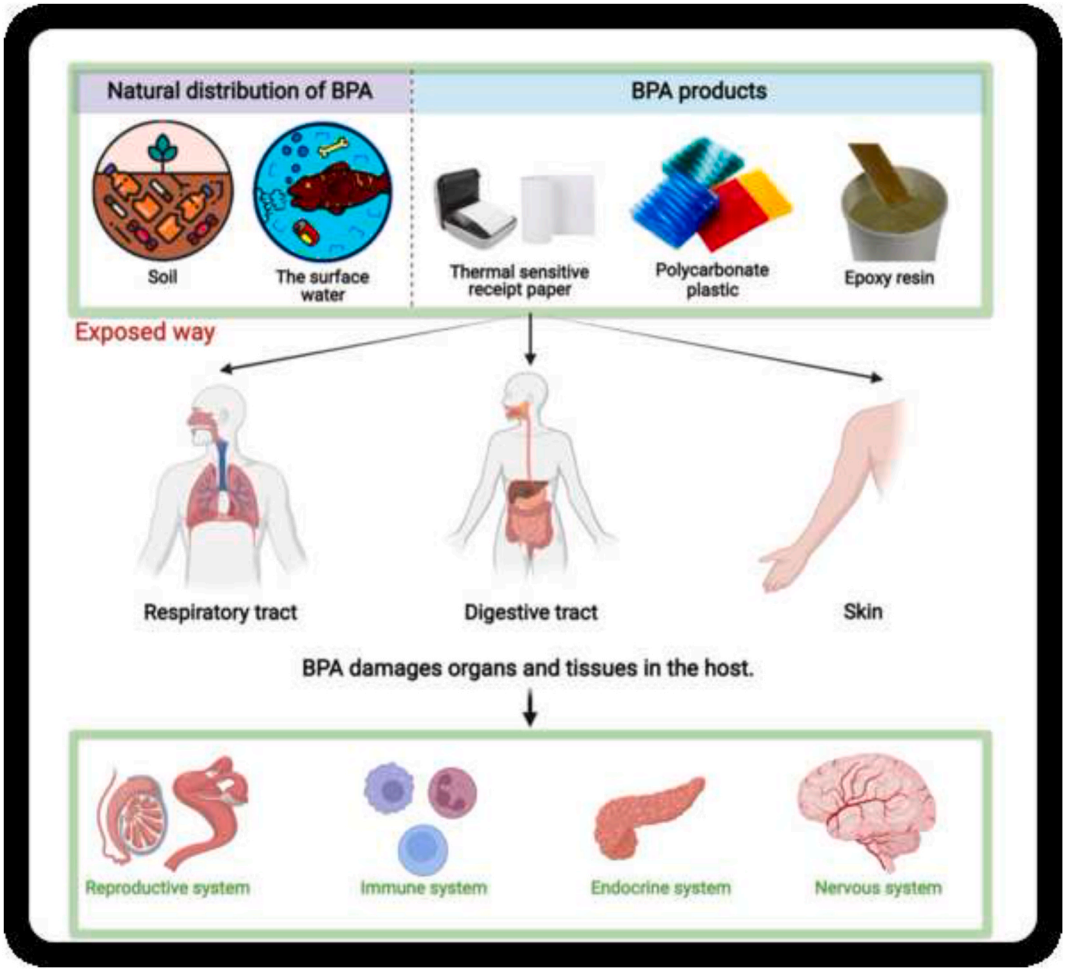

Fig. 1. Major sources of BPA, routes of human exposure and health effects.

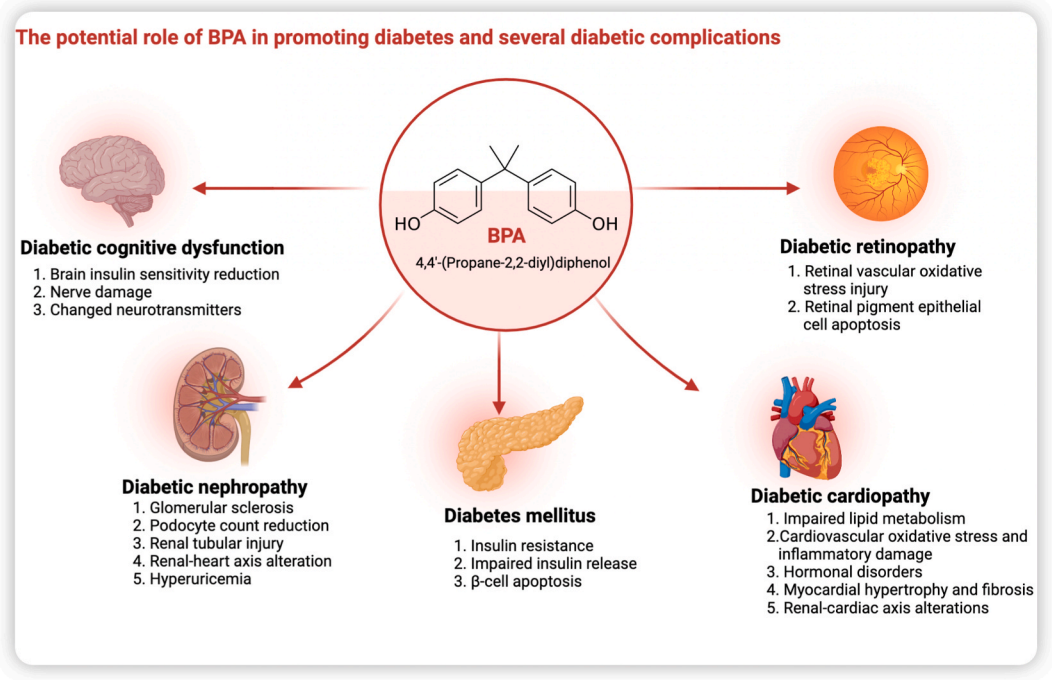

Fig. 2. Potential harmful effects of BPA on DM and various diabetic complications.

commonly used to make cups. Studies have shown that BPA can migrate from PC into water. Increased temperature increases the hydrolysis of the polymer, which accelerates the migration of BPA [27]. As mentioned above, the coatings and paints on canned foods release BPA, so canned foods contain more than fresh foods. When canned foods are exposed to 100 °C, BPA is released up to 18 times faster [28].

As an EDC, BPA could disrupt hormone levels by binding to hormone receptors such as the estrogen receptor, androgen receptor, thyroid hormone receptor, glucocorticoid receptor and peroxisome proliferator-activated receptors, resulting in neuroendocrine disruption. These disruptive neuroendocrine effects cause damage to the reproductive, nervous, immune and metabolic systems [29]. Studies have shown that BPA affects hormones such as oestradiol, progesterone, testosterone, luteinising hormone and cortisol [30–33]. These hormone-altering effects play a role in developing conditions such as polycystic ovary syndrome, recurrent miscarriage and male infertility [34,35]. Moreover, there is increasing epidemiological evidence that BPA exposure is associated with several other human diseases. A longitudinal study found that BPA exposure was independently associated with prediabetes and impaired glucose homeostasis in middle-aged and older women [36]. A cross-sectional study of the National Health and Nutrition Examination Survey (NHANES) found that higher urinary BPA concentrations in the general adult population in the United States were associated with coronary heart disease [37]. BPA exposure was significantly associated with obesity in children and adolescents [38]. BPA may also affect immune function, linked to asthma, T1DM and other autoimmune diseases [39–41].

3. BPA and diabetic nephropathy

Diabetic nephropathy is a significant complication of DM. It is a major cause of chronic and end-stage renal disease worldwide [42]. Diabetic nephropathy accelerates the decline in glomerular filtration rate, shortens the time to start late dialysis treatment, and increases patient mortality [43].

4. Epidemiological evidence linking BPA to diabetic nephropathy

BPA is excreted from the body in the urine. It accumulates in the blood of patients with chronic kidney disease as renal excretion decreases [44]. In a 10-year prospective cohort study of older Chinese women, serum BPA levels were strongly associated with the risk of CKD in all subgroups of women except those with baseline glomerular filtration rates of 60–70 ml/min. The negative association with chronic kidney disease was stronger in women with high serum BPA levels than those with low serum BPA levels [45]. These findings suggest that BPA accumulation is a risk factor for chronic kidney disease in women and that as renal excretion of BPA decreases, more accumulated BPA could worsen chronic kidney disease. In addition, a cross-sectional survey of Chinese adults found that BPA exposure was associated with an increased risk of low-grade albuminuria [46]. Subsequently, a cross-sectional study of US children showed consistent results for an association between BPA exposure and low-grade albuminuria [47]. The association of creatinine excretion and low-grade proteinuria with BPA indirectly suggests a potential renal adverse effect of BPA. Researchers have

begun investigating the link between BPA and diabetic nephropathy (Table 1). A 6-year prospective cohort study by Hu et al. found that fasting glucose and serum BPA levels in T2DM patients were significantly and negatively associated with annual and percentage changes in estimated glomerular filtration rate [48]. In addition, people with T2DM who had higher serum BPA levels were about seven times more likely to develop chronic kidney disease than people with T2DM who had lower serum BPA levels [48]. BPA is associated with low-grade albuminuria, and low-grade albuminuria is a feature of early diabetic nephropathy. Therefore, BPA appears to be a risk indicator for the early stages of diabetic nephropathy. However, the relationship between low-grade proteinuria and BPA in DM patients has not been established. There is also a need to clarify the role of BPA in developing diabetic nephropathy.

5. Potential pathological mechanisms of BPA-promoted diabetic nephropathy

Diabetes-related glomerular pathology includes 1) diffuse glomerular thylakoid expansion and sclerosis, 2) changes in the endothelial glycocalyx, 3) thickening of the glomerular basement membrane and 4) a decrease in the number of podocytes [49]. In an in vivo test, the offspring of T2DM-prone mouse models exposed to BPA before birth had abnormal glomerular morphology and fewer glomeruli which were more pronounced in female offspring [50]. BPA exposure increased the cell cycle protein-dependent kinase inhibitors p27kip1, TGF-β and collagen IV, which are involved in glomerulosclerosis. In parallel, thylakoid expansion and reduced podocyte numbers were observed in mouse kidneys [51]. Interestingly, although BPA did not cause hyperglycemia in the animals, the renal changes were similar to the structural changes that occur in the early stages of diabetic nephropathy [51]. BPA exposure reduced podocyte density, size and function in mouse glomeruli by inducing downregulation of E-calmodulin, podocin and waveform proteins, resulting in residual podocyte stress hypertrophy and glomerular collapse [52]. The negative correlation between BPA and urinary protein may be explained by BPA-induced podocyte injury. In addition, podocyte injury in diabetic nephropathy has been associated with proteinuria in another study [53]. Based on these two lines of evidence, we hypothesize that BPA-induced podocyte injury may cause diabetic nephropathy. In addition, renal tubular interstitial lesions play a role in the progression of diabetic nephropathy [54]. BPA induces renal tubular injury by promoting autophagy dysregulation and oxidative stress, which may be another potential mechanism by which BPA exacerbates diabetic nephropathy [54]. BPA induces hyperuricemia via the xanthine oxidase pathway [55]. This alteration may also promote the progression of diabetic nephropathy. Furthermore, BPA accelerates renal-cardiac axis alterations in diabetic mouse models by over activating metabolic reconstitution, neuroendocrine disruption, and immune-inflammatory responses via the MAPK pathway [56].

6. BPA and diabetic cognitive dysfunction

Diabetic cognitive dysfunction is an essential complication of DM that progresses insidiously and severely affects the quality of life of older people with DM [57]. Epidemiological evidence suggests that up to 20% of T2DM patients over 60 will develop dementia [58]. As the population ages and the burden of DM increases, the global prevalence of diabetic cognitive dysfunction will continue to rise.

Table 1
Summary of epidemiological studies on renal damage caused by BPA exposure.

Year	Title	Study design, study, country	Number of participants	Follow-up period	Main findings	Reference
2007	Accumulation of bisphenol A in hemodialysis patients	A cross-sectional study of BPA before and during dialysis in nephropathy, Japan.	37	Not available	In patients with nephropathy without hemodialysis, serum BPA concentration increased with worsening renal function, and there was a significant inverse correlation.	[44]
2021	Associations of serum bisphenol A levels with incident chronic kidney disease risk	A prospective study aimed to evaluate the association between serum BPA levels and CKD in middle-aged and elderly Chinese population, China.	1370	10 years	Serum BPA level is negatively correlated with the risk of CKD.	[45]
2012	Exposure to bisphenol A is associated with low-grade albuminuria in Chinese adults	A cross-sectional study examined the association between urinary protein and BPA in Shanghai adults over 40 years of age, China.	3055	Not available	There is an association between BPA exposure and low-grade albuminuria.	[46]
2013	Bisphenol A exposure is associated with low-grade urinary albumin excretion in children of the United States	A cross-sectional study examined the association between urinary BPA and low protein levels in children from the 2009–10 NHANES, USA.	710	Not available	There is an association between BPA exposure and low-grade albuminuria.	[47]
2015	Serum bisphenol A and progression of type 2 diabetic nephropathy: a 6-year prospective study	A prospective study investigated whether serum BPA concentration is a predictor of the progression of DN, China.	121	6 years	Serum BPA may be a predictor of CKD in T2D patients.	[48]

Annotation: BPA: Bisphenol A; CKD: Chronic Kidney Disease; DN: Diabetic Nephropathy; NHANES: National Health And Nutrition Examination Survey; T2D: Type 2 diabetes.

Table 2
Summary of epidemiological and animal evidence on the potential damage of BPA to diabetic coronary heart disease.

First author, Year	study design	study object	Main findings	Reference
Avinash Soundararajan,	cross-sectional study	human	In patients with T2DM, elevated BPA levels are associated with cellular senescence, proinflammation, poor glycemic control, insulin resistance, and telomere shortening.	[13]
Ziwei Chen, 2022	cross-sectional study	human	BPA was associated with CVD risk in a J-curve relationship.	[72]
Fanny Rancière, 2015	meta-analysis	human	Individuals with higher urinary BPA concentrations are more likely to develop diabetes, general/abdominal obesity, and hypertension than those with lower urinary BPA concentrations.	[73]
P Monica Lind, 2011	cross-sectional study	human	Phthalates and BPA have been linked to plaque echo.	[74]
Pei-Lun Chu, 2021	cross-sectional study	human	In the presence of elevated BPA levels, there is a higher risk of thicker CIMT associated with altered MPs. BPA exposure is associated with endothelial dysfunction and subclinical atherosclerosis in younger populations.	[75]
David Melzer, 2012	prospective study	human	The association between higher BPA exposure, as reflected by higher urinary concentrations, and CHD events over a follow-up period of more than ten years showed a similar trend to the cross-sectional findings reported previously for higher exposure NHANES respondents.	[76]
Chunyun Hu, 2019	nested case-control study	human	BPA exposure is positively associated with diabetes and coronary heart disease.	[77]
Alice Marmugi, 2014	animal experiment	mice	Chronic BPA exposure overexpresses genes critical for cholesterol biosynthesis, resulting in hypercholesterolemia in mice.	[78]
Yipeng Sui, 2014	animal experiment	mice	BPA exposure did not affect plasma lipid levels but increased CD36 expression and lipid accumulation in mouse macrophages.	[79]

Annotation: BPA: Bisphenol A; CHD: Coronary Heart Disease; CIMT: Carotid artery Intima-Media Thickness; CVD: Cardiovascular Disease; MPs: Microparticles; NHANES: National Health And Nutrition Examination Survey; PXR: Pregnane X Receptor; T2DM: Type 2 diabetes mellitus.

7. Potential pathological mechanisms of BPA-promoted diabetic cognitive dysfunction

There are no evidence-based or mechanistic studies on the relationship between BPA exposure and diabetic cognitive dysfunction in human adults. However, several studies in rodents and non-human primates suggest that BPA exposure impairs learning and memory [59]. BPA, through its effects on brain insulin signaling pathways, neurotoxicity, and neurotransmitter induction, may influence the progression of diabetic cognitive dysfunction. Li and colleagues found that administering a low dose of BPA to adult male mice decreased insulin sensitivity, decreased expression of GLUT1 and GLUT3 in the brain, and hyperactivation of the IR/IRS/AKT/GSK3 axis [60]. Another in vitro study found that the neurotoxic effects of BPA were similar to those of Alzheimer's disease (AD) when tested on SH-SY5Y cells (a tri-clonal subline of the neuroblastoma cell lines SK-N-SH) [61]. This BPA-induced neurotoxicity was associated with disruption of IR, IRS-1, and Akt signaling and activation of downstream GSK3β [61]. In addition, BPA exposure increased the expression of pathological proteins associated with neurotoxicity, such as amyloid precursor protein, beta-site amyloid precursor protein cleavage-1 (BACE1), β-amyloid (Aβ) 1–42 and hyperphosphorylated microtubule-associated protein (p-tau) [58]. Notably, BPA-induced AD-like neurotoxicity implicates pathways consistent with those that induce T2DM [61]. Ni et al. found that BPA-mediated neuroinflammation and blood-brain barrier impairment impaired learning and memory function in male mice. Mechanistically, BPA affects cognitive function in mice by inducing changes in neurotransmitters such as tryptophan, 5-hydroxytryptamine, and 5-hydroxy indole acetic acid via the gut-brain axis [62]. The mechanism of diabetic cognitive dysfunction is not well understood. However, the above studies have shown that brain insulin resistance and impaired insulin signaling pathways are essential in diabetic cognitive dysfunction [63]. Based on the above evidence, BPA-induced brain insulin resistance and disruption of the insulin signaling pathway in the brain may be underlying causes of diabetic cognitive dysfunction.

8. BPA and diabetic retinopathy

Diabetic retinopathy is the most common microvascular complication of DM. It is the leading cause of blindness in adults worldwide. There were reportedly 96 million people with diabetic retinopathy worldwide in 2012 [64]. BPA can cause abnormal retinal development and visual impairment [65]. A cross-sectional study of 100 children with T1DM found an association between BPA and diabetic retinopathy [66]. However, evidence from retrospective studies is limited, and a causal relationship between BPA and diabetic retinopathy has not yet been established.

9. Potential pathological mechanisms of BPA-promoted diabetic retinopathy

The retina is more susceptible to reactive oxygen species (ROS) due to its high concentration of polyunsaturated fatty acids [67]. The reactive oxygen species (ROS) produced by hyperglycemia cause changes in the retinal vasculature, resulting in cellular damage. In an animal study, Ola found that hyperglycemia-induced non-mitochondrial sources may be the primary source of ROS production in diabetic retinopathy rather than hyperglycemia itself [68]. BPA exposure may increase oxidative stress. In vitro, BPA exposure increased ROS, decreased glutathione (GSH) levels, caused lipid peroxidation, and altered the enzymatic activities of superoxide dismutase and catalase [69]. Chronic BPA exposure may be an additional source of oxidative stress in diabetic retinopathy, distinct from hyperglycemia-mediated oxidative stress. In addition, another study found that BPA degrades the antioxidants superoxide dismutase and catalase downstream of nuclear factor erythroid 2-related factor 2 by inhibiting the expression of heme oxygenase-1 and nuclear factor erythroid 2-related factor 2 [70]. Increased oxidative stress via BPA can induce apoptosis of the retinal pigment epithelium (ARPE-19 cell) [70]. Unfortunately, no studies have directly investigated the effects and mechanisms of BPA-induced additional oxidative stress on ex vivo models of diabetic retinopathy. Future research should focus on the potential role of the nuclear factor erythroid 2-related factor 2/oxygenase-1 pathway and downstream components of the oxidative and antioxidant systems in BPA-induced diabetic retinopathy.

10. BPA and diabetic cardiopathy

Diabetic cardiopathy is the leading cause of death in people with DM [71]. Diabetic cardiopathy mainly includes coronary artery disease and diabetic cardiomyopathy. We discuss the epidemiological evidence linking BPA exposure to diabetic coronary artery disease and the possible pathological mechanisms (Table 2). We also summarize the possible pathological mechanisms by which BPA exposure promotes diabetic cardiomyopathy.

11. Epidemiological evidence for the association of BPA with diabetic coronary artery disease

A cross-sectional study using NHANES data from 2003 to 2012 found a J-shaped association between BPA and the risk of cardiovascular disease, including congestive heart failure, coronary heart disease, and angina pectoris [72]. A meta-analysis on the risk of cardiometabolic disorders and BPA exposure focused on cross-sectional studies. Rancière et al. found that urinary BPA concentrations were associated with an increased risk of developing diabetes, obesity and hypertension [73]. These metabolic disorders are important risk factors for cardiovascular disease. Atherosclerosis-related metabolites are mainly found in the coronary and carotid arteries [73]. Thus, carotid atherosclerosis may indirectly reflect coronary atherosclerosis. Lind et al. found that high serum BPA levels were associated with carotid atheroma in a cross-sectional study of older adults in Uppsala [74]. In another cross-sectional study of a young population in Taiwan, BPA exposure was associated with endothelial dysfunction and subclinical atherosclerosis. There was also an

increased risk of carotid intima-media thickness associated with altered extracellular microparticles in elevated BPA levels [75]. A 10.8-year prospective cohort study found that increased urinary BPA was associated with incident coronary heart disease in a healthy population (aged 40–74 years without coronary heart disease, stroke, or diabetes) [76]. This study suggests that the risk of coronary heart disease from BPA exposure is independent of the risk from conventional exposure. Hu et al. found that urinary BPA was significantly associated with myocardial infarction in T2DM patients (OR = 1.97; 95% CI = 1.05–3.70, p = 0.04) in a nested case-control study in two European cohorts [77]. This study found, for the first time, an association between BPA exposure and diabetic coronary heart disease. However, the association needs to be validated by further prospective cohort studies with large samples.

12. Potential pathological mechanisms of BPA-promoted diabetic coronary artery disease

The pathology of DM that promotes the development of atherosclerosis includes dyslipidemia with elevated LDL levels, hyperglycemia, oxidative stress and increased inflammation [80]. Chronic exposure to BPA causes overexpression of genes essential for cholesterol biosynthesis, leading to hypercholesterolemia in mice [78]. Another animal study found that BPA increased the atherosclerotic area in the aorta and cephalic brachial artery of pregnane X receptor (PXR) humanized (ApoE) ApoE-deficient mice by activating human PXR [79]. Interestingly, BPA exposure did not affect plasma lipid concentrations but increased lipid accumulation in mouse macrophages [79]. In addition, BPA was associated with poor glycaemic control and insulin resistance in T2DM patients [13].

BPA is a cardiovascular-independent risk factor, suggesting that there may be other mechanisms by which BPA exposure damages the cardiovascular system and alters glucose and lipid metabolism. BPA may increase the risk of cardiovascular disease through increased stimulation of IκB kinase by estrogen receptors, which promotes the expression of pro-inflammatory genes associated with CRP secretion [81]. In addition, BPA may cause cardiovascular damage through the nuclear factor erythroid 2-related factor 2/NF-κB pathway by inducing oxidative stress and inflammation in the cardiovascular system [82].

13. Potential pathological mechanisms of BPA-promoted diabetic cardiomyopathy

The hormone-disrupting effects of BPA may affect the myocardial structure. A cross-sectional study found that serum BPA levels were significantly higher in the dilated cardiomyopathy group than in the healthy group, with increased total testosterone, sex hormone-binding globulin, and free androgen index [83]. It is reasonable to speculate that the hormonal disruption caused by BPA exposure may act as a non-diabetic pathological mechanism for promoting diabetic cardiomyopathy.

BPA may also contribute to the progression of diabetic cardiomyopathy by participating in diabetes-related metabolic pathological mechanisms. BPA and a high-fat diet caused myocardial hypertrophy and aortic intimal thickening in female mice [84]. These exposures also affected their offspring, increasing cardiomyocyte cross-sectional area and blood pressure in second-generation maternal mice [84]. Prenatal exposure to BPA and a high-fat diet predispose mouse offspring to insulin resistance, obesity, impaired glucose tolerance, hypertension, and other metabolic abnormalities. Myocardial fibrosis is the predominant pathological manifestation of diabetic cardiopathy. In an animal study, El-Haleem et al. found a significant increase in the area percentage of collagen fibers in the myocardium of the BPA intervention group, similar to the pathological changes in diabetic cardiopathy [85]. The exact mechanism by which BPA promotes myocardial fibrosis in diabetic cardiopathy is unknown. It could be related to the role of BPA-induced myocardial insulin resistance and the potential activation of fibrotic pathways. Furthermore, as mentioned above, BPA accelerated renal-cardiac axis alterations in the diabetic mouse model via the MAPK pathway, causing structural remodeling of the heart [86].

14. Conclusion and future direction

The above extensive evidence sheds light on the risk and underlying pathogenic mechanisms linking BPA exposure to several common chronic diabetic complications. By affecting the metabolism and directly damaging specific organs, BPA exposure may contribute to the progression of several chronic diabetic complications, including diabetic nephropathy, diabetic cognitive dysfunction, diabetic retinopathy, and diabetic cardiopathy.

Several cross-sectional and prospective cohort studies have found an association between BPA exposure and diabetic nephropathy. Of course, factors such as individual differences in BPA exposure and metabolism limit the generalisability of the findings. Therefore, more studies should provide more conclusive evidence, especially those with large sample sizes and multicentre prospective cohort studies. In addition, epidemiological evidence linking BPA exposure to diabetic cognitive dysfunction and diabetic retinopathy is currently lacking. Future epidemiological studies are needed to investigate this association. Some mechanistic studies have examined the potential mechanisms by which BPA may promote the diabetic complications mentioned above. Notably, these mechanisms are not limited to the effects of BPA exposure on diabetes; they also include direct damage to target organs from BPA exposure. For example, in animal models, BPA causes renal changes similar to the structural changes seen in the early stages of diabetic nephropathy without causing hyperglycemia [51]. However, few studies have focused directly on the pathogenetic effects of BPA on diabetic complications, while other relevant studies have focused on organ-specific damage caused by BPA. In addition, studies on the effects of BPA on diabetic neuropathy are scarce, although the neurotoxicity of BPA is well established. There is evidence that urinary levels of BPA are associated with the development of diabetic peripheral neuropathy [66]. Relevant epidemiologic and pathogenic studies are warranted as human exposure to BPA remains an ongoing concern.

According to the findings of this review, BPA damage to specific organs may contribute to the progression of complications in these organs in DM. In the future, researchers must confirm the adverse effects of BPA in specific in vivo models of diabetic complications. Given that many mechanistic studies have reached their conclusions by studying rodent models, the validity of these mechanisms

needs to be verified in vitro in human cells and tissues using alternative techniques. Researchers should pay close attention to the potential role of BPA exposure in the progression of DM and its complications.

Due to the harmful effects of BPA's endocrine-disrupting properties and reproductive toxicity to humans, many countries and regions have imposed restrictions on the use of BPA. For instance, to prevent human exposure to BPA, the E.U., the U.S., and France, among others, have severely restricted the production and sale of containers, utensils, and food packaging containing BPA [87]. With the limited use of BPA in various applications, some of its alternatives, such as BPF (4,4′-methylene diphenyl), BPS (bis(4-hydroxyphenyl)sulfone), and BPAF (2,2-bis(4-hydroxyphenyl)hexafluoropropane), gradually began to be used on a large scale [87]. However, these substitutes may also risk human health, if not less than BPA. Therefore, we urge researchers to conduct more studies to determine the potential risks of BPA and its substitutes for various human diseases, including DM and its major complications. Accordingly, national regulatory agencies and policymakers should promptly adapt and develop relevant policies to reduce human exposure to these compounds.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

No data was used for the research described in the article.

Additional information

No additional information is available for this paper.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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