

# Endocrine disruptors: Can it be the missing link explaining the diabetes epidemic in India?

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## ABSTRACT

India is the diabetes capital of the world with an exponential increase in diabetes prevalence in the last few decades. It may not be just a simple co-occurrence that the global increase in diabetes is associated with an exponential increase in industrial chemical output. Literature searches through PubMed, Medline and Embase for articles published until July 2014 evaluating link between endocrine disrupting chemicals (EDCs) and diabetes was done. This review observed that a large volume of data is available from preclinical studies implicating commonly used synthetic compounds in the pathogenesis of diabetes. EDCs have been demonstrated to interact with almost all the steps of insulin homeostasis starting from its synthesis to its signaling and action. Bisphenol-A, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)/dioxin, polychlorinated biphenyls (PCBs), persistent organic pollutants, diethylhexylphthalate, cadmium and arsenic are some of the important EDCs which interfere with a maximal number of pathways of insulin homeostasis. However data from humans establishing the causality lacks from across the globe, with maximal data available from bisphenol-A and TCDD from USA. Their evaluation among Indians, especially with regards to dysglycemia, insulin resistance and beta cell function is non-existent, thus warranting urgent research in this area.

**Key words:** Beta cell function, diabetes, endocrine disruptors, insulin resistance, prediabetes

## INTRODUCTION

India is the diabetes capital of the world. As per 2010 estimates, it is believed that India has around 5.8 crore individuals suffering from diabetes, which is believed to surge to 8.7 crores by 2030, unless some drastic interventions are undertaken.<sup>[1]</sup> China, in spite of having a much larger population than India, is a distant second in the list with 4.3 crores individuals with diabetes (2010) which is expected to increase at a slower rate to 6.26 crore individuals by 2030.<sup>[1]</sup> Nearly 8-10% of our population is believed to be suffering from diabetes.<sup>[2]</sup> To aggravate

the problem, there is even a larger proportion of the population in India suffering from prediabetes (10-14%), a transient state, with a high annual risk of progression to diabetes.<sup>[2]</sup> Prediabetes is defined as any individual having a fasting blood glucose between 100 and 125 mg/dl and/or a 2 h post meal/75 g glucose blood glucose between 140 and 199 mg/dl.<sup>[2,3]</sup> India prediabetics have one of the highest annual rates of progression to diabetes in the world. The annual risk of progression in USA is 2.5%,<sup>[3]</sup> 11.5% in China,<sup>[4]</sup> when compared to 14-18% in India.<sup>[5,6]</sup> Diabetes is the leading cause of blindness, chronic renal failure, and non-traumatic amputations. Hence, the cost of morbidity and mortality associated with diabetes is staggering, even more so for a developing country like ours. Sadly, we have limited interventions available as of now to prevent this progression of prediabetes to diabetes.<sup>[5,7,9]</sup>

Although genetic factors,<sup>[10]</sup> sedentary lifestyles, abundance of food, especially processed food, unhealthy food habits, thrifty phenotype, nutritional deficiencies<sup>[8,9]</sup> are believed to have some role, they fail to fully account for both the

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10.4103/2321-0656.140878

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rapidity and magnitude with which diabetes rates have increased across the globe, and even more so in India. Epidemiologic studies have suggested a link between the exponential rise in output of industrial chemicals with the parallel epidemiological rise in metabolic syndrome and diabetes.<sup>[11]</sup> This has been beautifully recapitulated by Grun, “We may have been born in a “primeval soup,” but today, we are swimming in a “synthetic soup” of toxins, carcinogens, and endocrine disrupting chemicals (EDCs).”<sup>[12]</sup>

Endocrine disrupting chemicals are a diverse group of molecules such as organochlorinated pesticides and industrial chemicals, plastics and plasticizers, fuels, and many other chemicals that are present in the environment or are in widespread use.<sup>[13]</sup> They usually have molecular weight <1000 Dalton, most commonly polyhalogenated derivatives, or have phenyl group or are heavy metals, usually having high lipid solubility.<sup>[13]</sup> A large proportion of EDCs have estrogen mimetic properties, generating a pregnancy like metabolic state characterized by insulin resistance and hyperinsulinemia.<sup>[14]</sup> Lipophilic EDCs are highly resistant to degradation and are stored in adipose tissue for years to decades, hence known as persistent organic pollutants (POPs), which include dioxins, organochlorine pesticides, polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE), the primary degradation product of dichlorodiphenyltrichloroethane (DDT).<sup>[14]</sup>

The aim of this article is to review the current literature available on the relation between EDCs and diabetes pathogenesis. English language literature searches were done through PubMed, Medline and Embase for articles published until July 2014, by use of the terms “endocrine disruptor” [MeSH Terms] OR “EDC” [All Fields] AND “diabetes” [All Fields]. The reference lists of the articles thus identified were also searched for relevant information.

## ENDOCRINE DISRUPTING CHEMICALS AND INSULIN HOMEOSTASIS

There is a large volume of data available from basic studies involving cell culture models and animal models of diabetes, suggestive of a large number of EDCs to be obesogenic, to worsen insulin resistance and/or accelerate beta cell loss.<sup>[15]</sup> Beta cells are exquisitely sensitive to oxidative stress, in the absence of robust anti-oxidant defense systems, when compared to several other tissues.<sup>[15]</sup> These studies have suggested that EDCs interact with almost all the steps of insulin homeostasis starting from its synthesis to its signaling and action. EDCs targeting

different aspects of insulin signaling such as insulin synthesis, release, and cellular action have been elaborated in Table 1.<sup>[15]</sup> While these studies are highly suggestive of connections between various exposures and diabetes risk, they fall short of establishing causality. Studies evaluating the relation between these EDCs and diabetes pathogenesis in humans are scant across the globe. Data on some of the more common EDCs and their relation with dysglycemia has been elaborated below.

### Bisphenol-A

Bisphenol-A (BPA), the main component of polycarbonate plastic, epoxy resins, a nonpolymer additive to other plastics, has become a ubiquitous EDC found in the blood and urine of 92.6% of Americans.<sup>[16]</sup> Blood levels of BPA range in Americans range from 1 to 7 nmol/l.<sup>[16-18]</sup> Levels in Indians are, unfortunately, not known. BPA has been reported to impair insulin sensitivity and cause compensatory hyperinsulinism.<sup>[19]</sup> Interestingly, BPA in some studies has also been reported to improve glucose tolerance and cause hypoglycemia.<sup>[20]</sup> Augmenting beta cell insulin production may explain this occurrence of hypoglycemia.<sup>[21]</sup> However, this improvement in glucose tolerance does not necessarily imply an improvement in insulin homeostasis, and it may be a sign of metabolic toxicity and beta cell destruction. Augmentation of

**Table 1: Endocrine disruptors acting at different levels of insulin signaling pathway**

Step of insulin signalling pathway	Endocrine disruptor
Insulin	TCDD
	BPA
	PCBs
	Triphenyltin
	Cadmium
	Arsenic
	Mercury
Insulin receptor	TCDD
	BPA
	DEHP
Insulin receptor substrates	TCDD
	DEHP
	Tolyfluaniid
	BPA
PI3 kinase	Arsenic
	PCBs
	Arsenic
Akt	TCDD
	BPA
	DEHP
	Cadmium
GLUT4	TCDD
	BPA
	DEHP
	Cadmium
	Arsenic
Glucose uptake in muscle and adipocytes	TCDD
	BPA
	DEHP
	Cadmium
	Arsenic

TCDD: 2,3,7,8-tetrachlorodibenzo-dioxin; BPA: Bisphenol-A; PCBs: Polychlorinated biphenyls; DEHP: Diethylhexylphthalate; PI3: Phosphoinositide-3; GLUT4: Glucose transporter 4

insulin release secondary to BPA has been shown to down-regulate insulin receptor and consequently increased insulin resistance.<sup>[21]</sup> BPA is believed to increase intracellular  $Ca^{2+}$  oscillations through decreased activity of  $K_{ATP}$  channel, through modulation of estrogen receptor-beta.<sup>[22]</sup> BPA interferes with insulin signaling by augmenting phosphorylation of the transcription factor cyclic adenosine monophosphate-response element binding protein.<sup>[23]</sup> BPA, 2,3,7,8-tetrachlorodibenzo-dioxin (TCDD) and PCBs have been demonstrated to promote adipocyte development from preadipocytes and mesenchymal stem cells, thus worsening obesity and metabolic syndrome.<sup>[24,25]</sup> Adiponectin, an adipokine with insulin sensitizing and anti-inflammatory properties has beneficial effects on beta-cell function. Increased BPA and cadmium have been associated with decreased adiponectin.<sup>[26,27]</sup> BPA, diethylhexylphthalate (DEHP) and cadmium have also been shown to antagonize insulin action through their effects on GLUT4, resulting in increased insulin resistance by hampering insulin-mediated glucose disposal.<sup>[28-30]</sup> BPA has been demonstrated to increase the activity of 11 $\beta$ -hydroxysteroiddehydrogenase (HSD)-1.<sup>[31]</sup> Up-regulation of 11 $\beta$ -HSD-1 leads to increased endogenous cortisol production, especially in visceral fat, which can worsen insulin resistance.

The reference dose for BPA established by the Environmental Protection Agency of the USA and the tolerable daily intake recommended by the European Food and Safety Authority (EFSA) as being safe during a lifetime is 50  $\mu$ g/kg/day.<sup>[32,33]</sup> This safety cut-off is a level 1000 times lower than the lowest dose documented to produce adverse effects in laboratory animals, assuming a linear relationship.<sup>[16]</sup> Hence, these cut-offs are approximate as most of the EDC host interactions are not linear and follow a “U” or “inverted U” dose-response relationship.<sup>[16]</sup> Similar cut-offs are not available for India.

### 2,3,7,8-tetrachlorodibenzo-dioxin/dioxin

2,3,7,8-tetrachlorodibenzo-dioxin/dioxins are produced as unwanted by-products of industrial processes, such as the manufacture of certain pesticides, waste incineration and pulp and paper bleaching.<sup>[14]</sup> TCDD is believed to precipitate diabetes primarily through decreased insulin secretion and destruction of beta cells.<sup>[34-37]</sup> In addition, it also worsens obesity by enhancing adipocyte differentiation.<sup>[22]</sup> TCDD and PCBs like PCB-77 have been associated with increased circulating inflammatory cytokines like tumor necrosis factor-alpha.<sup>[26,38]</sup> Increased systemic inflammation is a well-known risk factor for insulin resistance. TCDD through increased JNK and mitogen-activated protein kinase (MAPK) modulate insulin-signaling pathways.<sup>[38]</sup>

TCDD decrease glucose uptake by adipose tissues and pancreas.<sup>[39]</sup> TCDD also increases insulin resistance, by impairing insulin mediated glucose disposal through inhibition of GLUT4.<sup>[38]</sup> TCDD was shown to reduce expression of phosphoenolpyruvate carboxykinase (PEPCK), a central regulator of gluconeogenesis.<sup>[40]</sup>

### Polychlorinated biphenyls and persistent organic pollutants

POPs like DDT, DDE, several PCBs, hexachlorobenzene (HCB) and  $\beta$ -HCB have been documented in >85% population in the Catalonia state of Spain with levels ranging from 92 ng/g to 399 ng/g in adipose tissue.<sup>[41]</sup> Since 1930, PCBs have been used in industry (mainly as dielectric fluids in capacitors and transformers, but also as flame retardants, ink solvents, plasticizers, etc.) because of their chemical stability.<sup>[14]</sup> PCBs have been demonstrated to cause beta cell loss.<sup>[42]</sup> Some studies have demonstrated PCBs to augment beta cell insulin production through activation of  $Ca^{2+}$ /calmodulin-dependent kinase II, resulting in increased intracellular calcium.<sup>[43,44]</sup> Intracellular  $Ca^{2+}$  is a key second messenger responsible for insulin secretion. PCB treatment of beta-cells was observed to increase the activity of MAPK 1 and 2.<sup>[44]</sup> Dioxin-like PCBs have been reported to reduce primary hepatocyte glycogen levels and impair gluconeogenesis due to a specific downregulation of PEPCK expression.<sup>[45]</sup>

### Diethylhexylphthalate

Diethylhexylphthalate is the predominant and the representative molecule of the group of chemicals called plasticizers (phthalates). Global plasticizer consumption (87% phthalates) is estimated to be 6.4 million tons with 52% being consumed in Asia Pacific region. Plasticizers, as the name suggests are extensively used as plastic softening agents, gelling agents, stabilizers, dispersants, lubricants, binders, and as emulsifying agents. DEHP, the most important plasticizer, has been shown to antagonize insulin action through their effects on GLUT4 (vide supra). Improved glucose tolerance and hypoglycemia have also been reported with DEHP, similar to BPA.<sup>[46,47]</sup> The ultimate metabolic effect may be determined by the dose and duration of exposure to the EDC.

### Cadmium

Heavy metals like both cadmium and arsenic has been demonstrated to cause beta cell apoptosis and loss.<sup>[48,49]</sup> Cadmium like BPA is associated with decreased adiponectin levels (vide supra). Cadmium has been demonstrated to modulate the activity of 11 $\beta$ -HSD-2, which interferes with cortisol metabolism, and thus has an indirect effect on insulin resistance.<sup>[50]</sup>

## Arsenic

Impairment of insulin sensitivity along with hyperinsulinism has been documented.<sup>[51]</sup> Arsenic has been demonstrated to inhibit adipocytes and myocyte development, leading to decreased sites for glucose disposal, thus worsening insulin resistance.<sup>[52,53]</sup> Arsenic also modulates insulin signaling via decreased p70-S6-kinase.<sup>[54]</sup> Arsenic is especially relevant for our country, cause of increased prevalence of ground water contamination by arsenic is several eastern states of India.

## Epidemiologic data implicating endocrine disrupting chemicals in the pathogenesis of diabetes

Studies on American soldiers who participated in the Vietnam War and were exposed to TCDD revealed an association between serum TCDD concentration and the prevalence of type 2 diabetes mellitus and insulin resistance.<sup>[55-57]</sup> Exposure to TCDD following an industrial accident in Italy (1976) was associated with increased diabetes several years later, particularly in women.<sup>[58]</sup> In a population study, it has been suggested that obesity is associated with diabetes only in individuals with increased circulating POPs. Adipose tissue in obese individuals acts as a storage site for POPs.<sup>[59]</sup> The US National Health and Nutrition Examination Survey 2003-2004 revealed higher BPA urine concentrations to be associated with diagnosed diabetes mellitus and cardiovascular disease, which persisted for diabetes when pooled analysis of 2003-2004 data with 2005-2006 data was done.<sup>[60,61]</sup> However, no similar data is available from India. Data from Bangladesh has provided conflicting evidence linking arsenic with diabetes with few studies showing association while others are suggesting no relation.<sup>[62]</sup>

## Endocrine disrupting chemicals and the Indian perspective

Data on EDCs is extremely scant from India. Some amount of data is available from preclinical studies. However, epidemiologic and observational data from humans is almost non-existent. Very high levels of phthalates have been detected in Indian toys (16.2% w/w).<sup>[63]</sup> DEHP was detected in 92% of the water samples and sediments taken from different areas of the Cauveri river delta in south India. Levels were higher in the river upstream area where most of the industries were concentrated. DEHP levels in drinking water were observed to be safe with respect to USEPA guideline. However the concentration in the river sediment was well above the recommended cut off (6000 ng/L).<sup>[64]</sup> Analysis of effluents from waste water treatment plants in northern India revealed high levels of aromatic compounds, HCB (gammaxene, an insecticide) and a variety of pharmaceutical chemicals.<sup>[65]</sup>

## CONCLUSION

It may be said that a large volume of data is available from preclinical studies implicating commonly used synthetic compounds in the pathogenesis of diabetes. However, their evaluation among Indians, especially with regards to dysglycemia, insulin resistance and beta cell function is virtually non-existent. Hence, urgent work is warranted to evaluate the link between EDCs and diabetes in our country.

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**How to cite this article:** Dutta D, Khadgawat R. Endocrine disruptors: Can it be the missing link explaining the diabetes epidemic in India?. *J Soc Health Diabetes* 2015;3:16-21.

**Source of Support:** Nil. **Conflict of Interest:** None declared.