Association of BPA and Environmental oestrogen with Diabetes mellitus

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ABSTRACT

BPA and environmental oestrogen are associated with insulin resistance and other metabolic syndromes. The study investigated the relationship between diabetes mellitus and BPA as well as environmental oestrogen. One hundred and thirty six (136) subjects aged 40 years and above were recruited for the study. This comprised of ninety seven (97) non insulin dependent diabetic patients (42 males and 55 females) and thirty nine (39) age and sex matched apparently healthy individuals (16 males and 23 females) who served as the control. With the aid of a structured questionnaire, subjects' exposure to BPA and environmental oestrogen were checked. The test subjects were grouped into different groups by age and duration of sickness. All subjects were assayed for BPA and environmental oestrogen. The results obtained showed that the mean±S.D of BPA (ng/L) and environmental oestrogen (ρmol/L) levels were not statistically different (p>0.05) when the results of the diabetics were compared with the control subjects, and also when the levels of the parameters were compared within the different age groups. There were no significant statistical relationship (p>0.05) between BPA, oestrogen and diabetes mellitus respectively as both the diabetics and control subjects show similar pattern of exposure to the parameters studied. However, there is significantly higher levels of BPA (p<0.05) in male diabetics when compared to female diabetics which could be attributed to gender factor and occupational exposure. The study established no association between non insulin dependent diabetes mellitus with either environmental oestrogen or BPA.

Keywords: Association, BPA, Environmental oestrogen and Diabetes mellitus
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INTRODUCTION

Diabetes mellitus is a group of metabolic diseases in which a person has high blood sugar either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced [1]. Long term complications of diabetes mellitus include the development of retinopathy, nephropathy and neuropathy [2]. Diabetic patients are at risk of cardiac, peripheral arterial and cerebrovascular diseases [3]. Diabetes mellitus and lesser forms of glucose intolerance; impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), can now be found in almost every population in the world and epidemiological evidence suggests that without effective prevention and control programmes, the burden of diabetes mellitus is likely to continue to increase globally [4]. As at 2010, an estimated 285million people had diabetes mellitus globally with type 2 diabetes mellitus making up about 90% of the cases. The prevalence in Nigeria was calculated to be 6.8% [5]. Because diabetes mellitus is now affecting many in the work force, it has a major and deleterious impact on both individual and national productivity. The socioeconomic consequences of diabetes mellitus and its complications could have a serious negative impact on the economies of developed and developing countries [6]. The development of type 2 diabetes mellitus is caused by a combination of factors which includes poor diet, obesity, urbanization, and female gender [7].

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Bisphenol A (BPA) is a widely used high volume production chemical used in the manufacture of polycarbonate plastics (which are used extensively in drinks containers and food packing), and epoxy resins (used in the lining of canned foods) [8]. In developed and developing countries, exposure to BPA is significant and continuous. It is found in plastics such as baby and water bottles, sports equipment, medical tubings, CDs and DVDs, household electronics, eyeglass lenses, foundry castings, and the lining of water pipes, metal can linings, dental sealants, toys and other products and can leach out of these products especially when exposed to heat or acidity [9]. Hence, widespread and continuous human exposure to BPA is believed to be mainly through dietary intake, with additional exposure through drinking water, dental sealants, dermal exposure and inhalation of household dusts [10]. Significant amount of BPA has been found in rainwater stored in plastic containers in Nigeria [11]. Worldwide, over 6billion pounds of BPA are produced each year, and over 100tons are released into the air annually [10].

Bisphenol A (BPA) is a contaminant which, increasing exposure to, exerts both toxic and estrogenic effects on mammalian cells. Exposure to endocrine disrupting chemicals (EDCs) such as BPA is of concern because they interfere with many metabolic processes and cause widespread damage to body tissues and cardiovascular disease [12]. It is said to have oestrogenic activity which disrupts pancreatic β-cell function by activating oestrogen receptors and induces insulin resistance leading to diabetes mellitus [13]. Alonso-Magdalena *et al* (2006) showed that mice exposed to BPA levels as low as 10μg/kg developed hyperinsulinaemia, insulin resistance and glucose intolerance [13].

Environmental oestrogens (Xenoestrogens) are a type of xenohormone that imitates oestrogen. They can be either synthetic or natural chemical compounds. Natural xenoestrogens include phytoestrogens which are plant-derived xenoestrogens. However, xenoestrogens can be obtained from the following: exhaust fumes, pesticides & herbicides on all inorganically grown foods, cling wrap, polystyrene, plastics, synthetic clothes, vaseline and aqueous hand and body creams, shampoos and other personal care products, household detergents, insect repellants, insecticides used in the home, wax floor polish, P.C.B.'s and other industrial chemicals, paint, solvents, glues, pharmaceutical drugs and hormones (e.g pills, fertility drugs, hormone replacement therapy (H.R.T.), hormones fed to beef and chickens to fatten them, hormones given to cows to prolong lactation [14].

Xenoestrogens mimic oestrogen and can alter the functions of the endocrine system and cause various health defects by interfering with synthesis, metabolism, binding or cellular responses of natural estrogens. Hence, the overall mechanism of action is binding of the exogenous compounds that mimic oestrogen to the oestrogen binding receptors and causing the determined action in the target organs while blocking the action of natural hormones [15]. Significantly high or low levels of oestrogen could both be involved in the development of insulin resistance and other effects of metabolic syndrome [16]. Loss of oestrogen receptors has been shown to cause insulin resistance and type 2 diabetes in a male patient [17].

Moreover, oestrogen acts directly on pancreatic β-cells to make them resistant to apoptosis and prevent insulin-deficient diabetes mellitus in mice [18]. This mechanism is thought to assist the pancreatic cells to adapt to higher insulin demands like in obesity and pregnancy. It has also been reported that oestrogen function deficiency results in impaired glucose metabolism to such an extent that one developed type 2 diabetes mellitus [19]. In animal studies, ovariectomy is associated with decreased insulin secretion and increased risk of diabetes, whereas oestrogen administration protects against diabetes and increases the insulin response to glucose. The mechanism is uncertain but direct effects on the pancreas via steroid receptors or indirect effects via oestrogen-induced glucagon antagonism and subclinical increases in glucocorticoids and growth hormone could all contribute [20]. Again, abnormal increase in oestrogen or stimulation with oestrogen-mimics like BPA can provoke insulin resistance by exhausting β-cells through over stimulation and subsequent hyperinsulinaemia [21]. Furthermore, ablation of oestrogen by removal of ovaries in animal models impairs insulin sensitivity. Moderate or severe decrease in serum oestrogen levels enhances the prevalence of insulin resistant states in both men and women [16].

EXPERIMENTAL SECTION

Design: One hundred and thirty six (136) subjects aged 40 years and above were randomly selected and recruited for the study. This comprised of ninety seven (97) non insulin dependent diabetic patients (42 males and 55 females) who were atttending Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi and thirty nine (39) age and sex matched apparently healthy individuals (16 males and 23 females) who served as the control. A questionnaire was administered to all subjects to check their pattern of exposure to the studied parameters. The participants'

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informed consents and the hospital's ethical consent were sought and obtained before recruitment and before the commencement of the study respectively.

Sample collection: 2ml of venous fasting blood sample was aseptically collected from room temperature, and then centrifuged for 5minutes at 5,000r.p.m for prompt separation.

All serum samples were separated immediately after centrifugation into clean, sterile and dry glass tubes. The samples were taken to the laboratory where they were stored frozen at -20ºC and analyzed within 1month.

Sample analysis: BPA and Environmental oestrogen were analysed by ELISA method using Human BPA and Human environmental oestrogen ELISA Kits by Wkea Med Supplies Corp, China respectively. Samples and standards were analysed in duplicates and the average used for the calculation. Internal quality control serum was used for each batch of the assay.

Result analysis: Results were expressed as mean±SD. Statistical differences between means were determined by students't-test and comparisms made with ANOVA using Statistical Package for Social Sciences (SPSS).

RESULTS

TABLE 1: MEAN AND SD OF BPA AND ENVIRONMENTAL OESTROGEN IN DIABETICS AND CONTROL SUBJECTS

Parameter	Diabetic n = 97	Control n = 39	P-value
BPA (ng/L)	60.45±22.20	62.64±16.41	0.579
Environmental oestrogen (pmol/L)	3.17±2.20	2.77±1.72	0.267

* - Significant at P<0.05

TABLE 2: MEAN AND SD OF BPA AND ENVIRONMENTAL OESTROGEN IN MALE AND FEMALE DIABETICS

Parameter	Male diabetic n = 42	Female diabetic n = 55	P-value
BPA (ng/L)	65.99±21.31	56.22±22.11	0.031*
Environmental oestrogen (pmol/L)	2.72±2.15	3.50±2.19	0.083

TABLE 3: MEAN AND SD OF BPA AND ENVIRONMENTAL OESTROGEN IN MALE DIABETICS AND MALE CONTROL SUBJECTS

Parameter	Male Diabetic n = 42	Male Control n = 16	P-value
BPA (ng/L)	65.99±21.31	72.66±4.27	0.060
Environmental oestrogen (pmol/L)	2.72±2.15	2.92±1.74	0.724

TABLE 4: MEAN AND SD OF BPA AND ENVIRONMENTAL OESTROGEN IN FEMALE DIABETICS AND FEMALE CONTROL SUBJECTS

Parameter	Female diabetic n = 55	Female control n = 23	P-value
BPA (ng/L)	56.2±22.11	55.67±22.11	0.915
Environmental oestrogen (pmol/L)	3.50±2.19	2.67±1.74	0.107

TABLE 5: MEAN AND SD OF BPA AND ENVIRONMENTAL OESTROGEN WITHIN DIFFERENT DURATIONS OF DIABETES

Parameter	<1 year n = 34	1-5 years n = 35	>5 years n = 28	P-value
BPA (ng/L)	59.26±25.63	61.15±21.54	61.04±19.03	0.928
Environmental oestrogen (pmol/L)	3.55±2.26	3.45±2.08	2.34±2.12	0.061

Table 1: The results obtained showed that the mean values of BPA (ng/L) and environmental oestrogen (ρmol/L) for diabetic patients (n=97) were 60.45±22.20 and 3.17±2.20 respectively. The mean values of BPA (ng/L) and environmental oestrogen (ρmol/L) for control subjects (n=39) were 62.64±16.41 and 2.77±1.72 respectively. There were no significant statistical difference (p>0.05) in BPA and environmental oestrogen levels between the diabetic and control subjects.

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Table 2: The mean values of BPA (ng/L) and environmental oestrogen (ρmol/L) for male diabetics (n=42) were 65.99 ± 21.31 and 2.72 ± 2.15 respectively, while the values of BPA (ng/L) and environmental oestrogen (ρmol/L) for female diabetics (n=55) were 56.22 ± 22.11 and 3.50 ± 2.19 respectively. There were no significant statistical difference ($p>0.05$) in environmental oestrogen levels between the male diabetics and female diabetics. However, BPA levels were significantly higher ($p<0.05$) in male diabetics when compared to female diabetics.

As shown in **Table 3**, the mean values of BPA (ng/L) and environmental oestrogen (ρmol/L) for male diabetics (n=42) were 65.99 ± 21.31 and 2.72 ± 2.15 respectively, and that of the male control subjects (n=16) were 72.66 ± 4.27 and 2.92 ± 1.74 respectively. There were no significant statistical difference ($p>0.05$) in BPA and environmental oestrogen levels in male diabetics and male controls.

Again, as also shown in **Table 4**, the mean values of BPA (ng/L) and environmental oestrogen (ρmol/L) for female diabetics (n=55) were 56.2 ± 22.11 and 3.50 ± 2.19 respectively, and that of the female control subjects (n=23) were 55.67 ± 22.11 and 2.67 ± 1.74 respectively. There were no significant statistical difference ($p>0.05$) in BPA and environmental oestrogen levels between the female diabetics and female controls.

Table 5 shows the mean values of BPA (ng/L) and environmental oestrogen (ρmol/L) of diabetics for different durations of the disease to be (59.26 ± 25.63 and 3.55 ± 2.26 respectively) for duration of <1year, (61.15 ± 21.54 and 3.45 ± 2.08 respectively) for duration of 1-5years, and (61.04 ± 19.03 and 2.34 ± 2.12 respectively) for duration of >5years. There were no significant statistical difference ($p>0.05$) in BPA and environmental oestrogen levels in diabetics of different duration of illness.

DISCUSSION

Pharmacokinetic and biomonitoring data continue to support our understanding that BPA is quickly and efficiently metabolised once ingested. Once administered orally, BPA is very rapidly metabolized with a biological half-life of approximately six hours and nearly complete elimination within 24 hr [22]. However, molecular studies have revealed a variety of pathways through which BPA can stimulate cellular responses at very low doses [23]. BPA at environmentally relevant doses is considered to pose risks to human health. This study showed that serum BPA level in diabetics is not significantly different from that of the control subjects. This is probably because of the continuous and widespread exposure of both groups to BPA. Hence BPA levels were found not to be statistically different in diabetics when compared to the control groups. Consequently, no association was found between diabetes and BPA. However, mean comparism of BPA levels in male and female diabetics showed BPA levels to be significantly higher in males than in females which is probably due to the gender factor resulting from difference in clearance rate [24] and occupational exposure (workers from BPA-exposed factories are said to be exposed to very high BPA levels in their work place) [25]. On the other hand, environmental oestrogen showed no significant difference between the diabetics and control subjects hence, no association was found between environmental oestrogen and diabetes. This disagrees with the Suba's assertion that significantly high or low levels of oestrogen could both be involved in the development of insulin resistance and other effects of metabolic syndrome [16]. The study found environmental oestrogen levels within the reference range in both diabetics and controls. More so, similar pattern of exposure was found in almost all the subjects.

CONCLUSION

This study found no relationship between diabetes mellitus and BPA as well as between diabetes mellitus and environmental oestrogen since comparison of BPA and environmental oestrogen levels in diabetics and control subjects showed no statistical significant difference. This could be attributed to the fact that both subjects are similarly and frequently exposed with little or no restriction to BPA and environmental oestrogen.

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