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DETECTION OF INSULIN RESISTANCE AND RISK OF TYPE 2 DIABETES MELLITUS AMONG BISPHENOL A EXPOSED WORKERS.

By

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Abstract

Introduction: Many previous studies suggested that bisphenol A (BPA) exposure could trigger insulin resistance (IR) and elevate the risk to develop type 2 diabetes mellitus (T2DM). **Aim of work:** This research was done to detect IR prevalence and risk to develop T2DM among non-diabetic BPA exposed workers involved in the plastic industry. **Materials and Methods:** This work was conducted in a factory for manufacturing polyvinyl chloride (PVC) pipes present in the 10th of Ramadan City, Egypt. The study population involved an exposed group of 44 non-diabetic workers occupationally-exposed to the plastics manufacturing process and a control group of 46 non-diabetic matching administrative subjects. Full medical and occupational histories in addition to clinical examination, were done. Fasting serum samples were used to measure adiponectin, insulin, lipid profile parameters: Total cholesterol (TC), Triglycerides (TG), Low-density lipoproteins (LDL), and High-density lipoproteins (HDL) and BPA levels. Insulin resistance was evaluated using homeostasis model assessment of insulin resistance (HOMA-IR). **Results:** The study showed a statistically significant increase in the levels of BPA, insulin, TC, TG and LDL, in addition to HOMA-IR indices, and a statistically significant decrease in the levels of adiponectin and HDL among BPA exposed workers compared to the control group. All measured parameters of IR were significantly correlated with each other, with the BPA levels, and with the duration of occupational exposure among the exposed workers. **Conclusion:**

Long-term occupational exposure to BPA in the plastic industry is accompanied by an elevated risk of developing IR and hence T2DM.

Key words: Insulin resistance, Risk of Type 2 Diabetes Mellitus, Adiponectin, Lipid profile Bisphenol A and Plastic Industry.

Introduction

Bisphenol A (BPA) is widely used in the polyvinyl chloride (PVC) plastic industry to form epoxy resins and polycarbonate plastic which are further utilized to manufacture different products. It is also used as an antioxidant and inhibitor of end polymerization. Human exposure to BPA may occur as a result of occupational or environmental sources through various routes that include inhalation, ingestion, and transdermal absorption (Wang et al., 2012).

Bisphenol A could be considered as an endocrine-disrupting chemical (EDC) (xenoestrogen) that mimics the effects of endogenous oestrogen through interaction with oestrogen receptors and thus disturbing oestrogen signalling pathways. This could potentially induce a chronic hormonal disturbance that resembles endocrinal disruption status which occurs with pregnancy due to the effect of oestrogen, known as gestational insulin resistance (GIR) (Pjanic, 2017 and Akash et al., 2020).

Insulin resistance (IR) is defined as an impaired biologic response to insulin stimulation of the target tissues, mainly the liver, muscle, and adipose tissue. This leads to inability of insulin to induce peripheral glucose disposal and inhibit hepatic glucose uptake. To maintain glucose homeostasis, a compensatory rise in β-cell insulin production and normoglycemia is maintained leading to a state of chronic hyperinsulinemia. Hyperinsulinemia aims to unlock the cell for the utilization of glucose. The persistence of this mechanism could end in apoptosis of islet cells and thus stoppage of insulin production which could subsequently progress to type 2 diabetes mellitus (T2DM) (Deacon, 2019).

Evolution of prediabetes status involves various factors including genetic causes, peripheral insulin resistance, defective insulin secretion, glucotoxicity, lipotoxicity, inflammatory reactions, oxidative conditions, and diminished beta cell mass that leads to its dysfunction. Recent researches emphasized the involvement of

adiponectin (a beneficial adipokine that is released exclusively from the adipose tissue) in regulating the metabolism of lipids and glucose. Adiponectin shows insulin-sensitization activity as it suppresses hepatic gluconeogenesis and could promote fatty acid oxidation thus lowering blood glucose levels. Adiponectin also confers protective properties against inflammation and atherosclerosis. It is a novel biomarker for IR in addition of being a significant independent predictor of diabetes. Decreased adiponectin levels are usually accompanied by impaired glucose tolerance, increased IR and body-weight in addition to dyslipidemia, while elevated levels were detected among subjects attempting prevention of T2DM development through diet and physical activity modulation (Iwabu et al., 2019). The relationship between adiponectin level and T2DM risk seems to be clear during an early time before reaching the manifest diabetes state; thus, minimal adiponectin levels could be noticed about ten years before established T2DM, especially among males (Dorcely et al., 2017). Recent studies concluded that measuring the total adiponectin level could be associated with a sensitivity of 88%, a specificity of 65.9% for the diagnosis of IR and T2DM. Additionally, the area under the curve (AUC) or the area under adiponectin ROC (Receiver Operating Characteristics) Curve for diagnosis of DM could reach 0.74 (Almeda-Valdes et al., 2010; Abdella and Mojiminiyi, 2018).

Moreover, T2DM is usually associated with dyslipidemia that could be considered an evident predisposing factor for diabetes development. Previous studies have demonstrated the role of dyslipidemia in impairing pancreatic β-cells function, and inducing insulin resistance in an early stage that precedes the manifestations of T2DM among non-diabetic subjects. Furthermore, the dyslipidemic pattern is usually noticed in diabetic patients as well as in subjects with normal glucose tolerance (NGT). A recent Chinese study showed that the sensitivity and specificity of blood lipid indicators in screening IR were 70.1% and 66.1% respectively. Thus, assessment of the serum levels of different lipid indices and analysing their association with IR and beta cell functional condition could provide an efficient tool for discriminating non-diabetic individuals with high risk to develop T2DM (Zhou et al., 2016 and Zheng et al., 2017).

Aim of work

To detect insulin resistance prevalence and risk to develop T2 Diabetes Mellitus among non-diabetic bisphenol A exposed workers involved in the plastic industry.

Materials and methods

Study design: This current study presents the results of a comparative cross-sectional study.

Place and duration of the study: This research was conducted in a factory for manufacturing polyvinyl chloride (PVC) pipes present in the 10th of Ramadan City, industrial area A3, Egypt. It was done over three month's duration from February to May 2019.

Study sample: The studied population involved an exposed group of 44 non-diabetic male workers occupationally-exposed to the plastics manufacturing process which involves the use of BPA. The control group represented 46 non-diabetic male administrative subjects from Kasr Al-Aini hospital. The exposed group included the factory workers whose duration of exposure to the industrial process exceeded 5 years. Twenty-six workers were ruled out prior the beginning of the research based upon some specific exclusion criteria (NB: the whole number of exposed workers in the studied factory was 70).

The exclusion criteria comprised the following:

∑ Subjects who have a medical history of diabetes mellitus, liver and/or kidney diseases, and past or present diseases causing dyslipidemia such as thyroid diseases.

∑ Subjects who gave a family history of diabetes mellitus and/or dyslipidemia.

∑ Previous or concomitant use of known diabetogenic drugs as corticosteroids or drugs affecting the lipid profile parameters such as statins.

The control group represented 46 matching administrative subjects from Kasr Al-Ainy hospital without exposure history to the plastics industrial process that uses BPA. The selected individuals were comparable to the exposed group as regards their sex, age, body mass indices (BMI), socioeconomic standards, and certain habits or lifestyle of medical significance. The same exclusion conditions were also applied to them.

Study methods:

A- Personal, occupational and medical histories were taken from the studied groups including their age, residence, smoking habits and any

specific habits of medical significance. Detailed occupational history was taken as regards the description and duration of the present job in addition to the extent of dependence on the personal protective equipment (PPE). Also, all of the studied individuals were asked to give information about the nature of any previous or currently associated occupations if present. Additionally, they were checked for the absence of any recent medical symptoms suggesting the development of diabetes mellitus in the form of frequent micturition, repeated sensation of severe thirst and/or hunger, remarkable weight loss, excessive fatigue, irritability, and blurred vision.

B- Clinical examination

Thorough general and systemic examinations were performed in addition to anthropometric measures in the form of height and weight to calculate BMI according to the following formula:

BMI = weight (kg) / height (m^2) kg/ m^2**.**

C- Laboratory investigations

a- All participants were instructed to test the levels of their fasting, 2-hours postprandial blood glucose and glycosylated haemoglobin (Hb A1c) within one week before the day of the study. The results of the included individuals were checked and confirmed to be within normal levels.

b- Ten to twelve hours of overnight fasting was instructed for both exposed and control groups. After overnight fasting, 6 ml of venous blood was drawn from the studied individuals and was transferred in plain tubes (without anticoagulant) for estimation of serum fasting insulin, serum adiponectin, total cholesterol (TC), triglycerides (TG), LDL, HDL, and serum BPA. The fasting insulin level was determined by radioimmunoassay while the serum level of adiponectin was measured by using enzyme-linked immunosorbent assay (ELISA). The other biochemical indicators (TC, TG, LDL, and HDL) were estimated by the automatic biochemical analysis produced by Hitachi (Tokyo, Japan) (Xu et al., 2018). Serum BPA was evaluated through usage of human BPA ELISA kit (G-SCIENCE Kit / USA) following the method of Kodaira et al. (2000).

c- Insulin resistance (IR) was estimated using the Homeostasis Model Assessment of Insulin

Resistance (HOMA-IR). It could be calculated through this equation:

HOMA-IR = (FINS × FPG) / 22.5 where:

FINS: fasting insulin concentration (μU/ml)

FPG: fasting plasma glucose (mmol/L) (Gutch et al., 2015 and Zheng et al., 2017).

The recommended healthy range of HOMA-IR is < 1 which denotes optimal tissue sensitivity to insulin. More than 1.9 denotes early IR while ≥ 3 indicates significant insulin resistance

(Esteghamati et al., 2010 and Shashaj et al., 2016).

Consent

Each participant voluntarily signed the written informed consent to be included in the research after a clear explanation of the purposes of the present work. Perfect clinical practices (GMC, 2013) and high confidentiality (GMC, 2017) were followed through the whole study.

Ethical Approval

An approval had been obtained from the Main Executive Officer of the studied factory. The research was revised and accepted by the Ethical Committee of Occupational and Environmental Medicine Department, Faculty of Medicine, Cairo University, Egypt.

Data Management

The obtained data were analysed using the statistical package for social sciences (SPSS-25). The quantitative continuous data were presented as means, standard deviations (SD), medians, and interquartile ranges (IQR). The quantitative variables were compared between both studied groups through the Mann-Whitney U test for the obtained non-parametric data. Further analysis by correlation and linear regressions (univariate) was done to detect the significant predictors for the insulin resistance among the exposed group. P-values > 0.05 were regarded as statistically non-significant, while those < 0.001 were evaluated as highly-significant.

Results

Table (1) : Comparison between the BPA exposed and control groups as regards their general characteristics and the measured parameters of insulin resistance (IR).

	Exposed (No=44)			Controls (No=46)		
	Mean ± SD	**Median**	**IQR**	**Mean ± SD**	**Median**	**IQR**
Age *(years)*	38.25 ±11.07	40.5	17.75	37.43 ±12.17	39	22
Smoking Index *(pack. yrs)*	12.23 ±3.12	7.5	6.75	10.06 ±9.97	6.5	18.25
Duration of work *(years)*	10.61 ±4.1	10	7	11.87 ±7.45	8	9.25
Body mass index *(kg/m^2)*	29.08 ±6.17	27.7	7.13	27.1 ±6.88	26.05	9.44
Adiponectin *(µg/mL)*	**7.11±4.33***	6.9	4.92	18.41±3.2	19	2.82
Insulin *(µIU/ml)*	**11.42±2.43***	11.2	3.88	5.78±2.31	5.15	3.18
TC *(mmol/l)*	**6.9±1.46***	6.9	2.35	4.4±1.11	4.1	1.32
TG *(mmol/l)*	**6.39±1.23***	6.52	1.09	2.52±1.56	1.9	1.17
LDL *(mmol/l)*	**5.86 ±1.22***	5.99	1.53	3.46 ±0.92	3.39	1.54
HDL *(mmol/l)*	**0.73±0.21***	0.76	0.27	1.16±0.17	1.21	0.3
BPA *(ng/ml)*	**12.92 ±7.83***	14.66	3.01	4.04±2.83	3.99	0.6
HOMA-IR	**2.63±0.51***	2.55	0.79	1.14±0.56	0.93	0.84

TC: Total Cholesterol. **TG:** Triglycerides. **LDL:** Low-density lipoproteins.
HDL: High-density lipoproteins. **BPA:** Bisphenol A. **IQR:** Interquartile ranges
HOMA-IR: Homeostasis Model Assessment of insulin Resistance. ***:** Highly significant p-value (<0.001).

Table (1) showed the absence of any significant difference between both studied groups as regards their general characteristics. However, the fasting serum levels of insulin, TC, TG, LDL, BPA, and insulin resistance indices were significantly higher while values of adiponectin and HDL seemed significantly lower for BPA exposed group when compared with their controls (p-value <0.001).

Table (2): Spearman's rank correlation coefficients (r) and their significance between all measured insulin resistance parameters and the general characteristics of the exposed group.

	Adiponectin	Insulin	TC	TG	LDL	HDL	BPA	HOMA-IR
Age	-0.033	0.183	0.051	0.019	0.145	-0.121	0.019	0.188
Smoking index	-0.081	0.057	0.312	0.145	0.053	-0.151	0.146	0.231
Work duration	**-0.870***	**0.832***	**0.671***	**0.609***	**0.736***	**-0.772***	**0.877***	**0.801***
BMI	-0.196	0.166	0.032	0.156	0.315	-0.27	0.278	0.191

TC: Total Cholesterol. **TG:** Triglycerides. **LDL:** Low-density lipoproteins.
HDL: High-density lipoproteins. **BPA:** Bisphenol A. **BMI:** Body Mass Index.
HOMA-IR: Homeostasis Model Assessment of insulin Resistance ***:** Highly significant p-value (<0.001).

Table (2) showed highly statistically significant positive correlations between duration of employment and values of insulin, TC, TG, LDL, BPA and insulin resistance indices (HOMA-IR). Moreover, there were highly statistically significant negative correlations between duration of employment and levels of adiponectin and HDL among the BPA exposed workers. On the other hand, there was non-significant correlation detected between all measured parameters versus the age, smoking indices, and BMI of the exposed subjects.

Table (3): Spearman's rank correlation coefficients (r) and their significance between all measured biomarkers of insulin resistance (IR) among the exposed group.

	Adiponectin	Insulin	TC	TG	LDL	HDL	BPA	HOMA-IR
Adiponectin	-	**-0.812***	**-0.608***	**-0.624***	**-0.745***	**0.728***	**-0.742***	**-0.774***
Insulin	-	-	**0.494***	**0.831***	**0.854***	**-0.848***	**0.778***	**0.966***
TC	-	-	-	**0.482***	**0.408***	**-0.490***	**0.655***	**0.510***
TG	-	-	-	-	**0.774***	**-0.771***	**0.572***	**0.805***
LDL	-	-	-	-	-	**-0.719***	**0.717***	**0.843***
HDL	-	-	-	-	-	-	**-0.747***	**-0.789***
BPA	-	-	-	-	-	-	-	**0.776***

TC: Total Cholesterol. **TG:** Triglycerides. **LDL:** Low-density lipoproteins.
HDL: High-density lipoproteins. **BPA:** Bisphenol A. **BMI:** Body Mass Index.
HOMA-IR: Homeostasis Model Assessment of insulin Resistance * : Highly significant p-value (<0.001).

Table (3) showed highly statistically significant positive and negative correlations among all measured parameters of IR (adiponectin, insulin, TC, TG, LDL, HDL, and HOMA-IR) and also between each of them and BPA levels among the exposed group.

Table (4): Linear regression analysis to detect significant predictors for insulin resistance among exposed group.

	HOMA-IR	**95% CI of B**	
	B	**Lower**	**Upper**
Age *(years)*	0.001	-0.022	0.019
Smoking Index *(pack. years)*	0.002	-0.032	0.029
Duration of work *(years)*	**0.099***	0.076	0.123
BMI *(kg/m²)*	0.005	-0.040	0.051
Adiponectin	**-0.083***	-0.110	-0.057
Insulin	**0.202***	0.183	0.221
TC	**0.180***	0.086	0.275
TG	**0.308***	0.221	0.396
LDL	**0.345***	0.270	0.420
HDL	**-1.887***	-2.354	-1.421
BPA	**0.049***	0.036	0.063

TC: Total Cholesterol. **TG:** Triglycerides. **LDL:** Low-density lipoproteins.
HDL: High-density lipoproteins. **BPA:** Bisphenol A. **BMI:** Body Mass Index.
HOMA-IR: Homeostasis Model Assessment of insulin Resistance.
***:**Highly significant predictor, p-value < 0.001.

Table (4) showed that age, smoking indices and BMI were statistically non-significant predictors for insulin resistance, while the duration of employment as well as fasting serum values of adiponectin, insulin, TC, TG, LDL, HDL, and BPA were highly statistically significant independent predictors for insulin resistance among BPA exposed group.

Discussion

Several recent researches and reviews discussed the relation between BPA exposure and the risk of metabolic diseases (IR, obesity and T2DM) in adults, with a focus on occupational exposure (Wang et al., 2012; Hussein et al., 2013; Maduka et al., 2014; Caporossi and Papaleo, 2017).

In the current study, both BPA exposed and control groups were matched as regards their demographic characters (Table 1). However, the measured parameters denoted a significant prevalence of insulin resistance and hence a predicted or presumed elevated risk for the occurrence of T2DM among BPA exposed subjects in the future (Table 1).

In 2018, a meta-analytic study detected an association between T2DM risk and BPA exposure (Hwang et al., 2018). Bisphenol A (BPA) might bind to the pancreatic islet of Langerhans cells and initiate impaired insulin and/or glucagon secretion, resulting in an insulin-resistant status. Referring to previous animal studies, when adult mice were subjected to low-dose of BPA, they experienced hyperinsulinemia and IR which are accompanied by pancreatic β-cell malfunction. Also, BPA could affect the peripheral tissues that show insulin sensitivity such as muscular, hepatic, and fatty tissue (Ariemma et al., 2016).

Previous studies declared that mice exposed to BPA showed diminished values of serum adiponectin in addition to derangement of insulin signals in skeletal muscular and hepatic tissues. Moreover, the studied mice exhibited elevated amounts of pro-inflammatory cytokines, like IL-6 and tumor necrosis factors that favour induction of insulin resistance status (Moon et al., 2015).

Additionally, in the present work , the BPA exposed workers showed a relatively elevated mean of body mass indices (mean ±SD: 29.08 ±6.17 kg/m^2) (Table 1) which classified them as overweighed subjects, thus it is worth to mention that BPA has an obesogenic effect that could result in obesity and some metabolic disorders. This was proved when sheep were subjected to BPA during the prenatal period , they gained weight and experienced an augmentation in their adipose tissue mass and in IR status (Veiga-Lopez et al., 2016).

Furthermore, the observed results showed that the fasting serum levels of TC, TG and LDL were significantly higher while HDL values was significantly lower for BPA exposed

group when compared with their controls (Table 1). This could draw the attention to the role of dyslipidemia in impairing pancreatic β-cells function, and inducing insulin resistance even during an early stage that precedes the manifestations of T2DM among non-diabetic subjects. In 2017, Zheng and his colleagues concluded that dyslipidemia could induce insulin resistance through diminishing β cell function. Also, parameters of the lipid profile (TC, TG, LDL, and HDL) were significantly correlated with insulin resistance among non-diabetic individuals. Emphasizing the implication of BPA exposure in inducing dyslipidemia, in 2016, an Egyptian study was done among 85 women to assess the impact of environmental BPA exposure on lipid profile. Results showed that the higher values of serum BPA were correlated with elevated serum levels of TC, TG, and LDL and significantly lower serum levels of adiponectin and HDL among the studied females (Metwally et al., 2016).

The current study also showed that there is a statistically significant difference between BPA exposed group and their controls as regards the calculated insulin resistance indices (HOMA-IR) with means ±SD: 2.63 ± 0.51 and 1.14 ± 0.56 respectively (Table 1). This is similar to the results obtained in 2013 by Hussein and his colleagues who detected a significant statistical difference between the occupationally BPA exposed workers in the fiberglass pipes industry and the non-exposed control group as regards their insulin resistance indices (HOMA-IR) with means ±SD: 3.22 ± 1.15 and 1.93 ± 0.42 respectively.

Aiming to detect the effects of the confounding factors on the relationship between measured parameters and IR, the associations of age, smoking intensity, BMI and duration of employment with the levels of all measured parameters were evaluated among BPA exposed workers (Table 2). The results revealed non-significant correlations for all factors except only for the duration of employment. Further statistical analysis using univariate linear regression revealed the same conclusion (Table 3). In 2017, a review of the literature was performed on occupational BPA exposure and associated health effects. The authors demonstrated that the level of serum BPA increases with the increase in the duration of exposure (Ribeiro et al, 2017). Moreover, in 2018, there was another review article that discussed the timing of exposure

to BPA and its implications for T2DM development. This review mentioned that several studies performed in experimental animals had realised variations in glucose and fat metabolism with BPA exposure. Using different durations and doses of BPA treatment could significantly increase insulin and decrease adiponectin levels. Another analysis using liver samples revealed that prolonged exposure to BPA could elevate the mRNA expression of GLUT2, in addition to essential factors needed for biosynthesis of cholesterol and other lipids. Accordingly, increased levels of plasma TG and cholesterol were observed after administrating BPA during about one month and hypercholesterolemia persisted for more than 8 months after BPA treatment (Tudurí et al., 2018). Besides, the study done by ul Haq et al., 2020 concluded that chronic BPA exposure might accelerate the inflammatory processes and induce oxidative stress status which finally could lead to IR and impaired metabolism of carbohydrates and lipids.

Regarding the other confounding factors, it is important to mention in this current work that the age of the exposed workers wasn't significantly associated with their duration of employment where many relatively young workers gave a history of longer employment duration and vice versa. This accounts for the presence of the statistically significant correlation and regression analysis between the period of exposure and the levels of the measured biomarkers (including also the values of IR indices) despite the absence of such a significant association with the age of the workers (Table 2 and 3). Additionally, the observed relatively low smoking index (mean ±SD: 12.23 ±3.12 pack/ years) (Table 1) could account for the absence of its implication in causing either dyslipidemia or insulin resistance among the exposed group.

Based upon the previously discussed pathogenesis of T2DM development and its link with IR and dyslipidemia which could have resulted from prolonged BPA exposure, the results revealed highly statistically significant correlations between all studied measured parameters (Table 3). Moreover, the results of the univariate linear regression revealed that all measured serum parameters (Adiponectin, insulin, lipids, and BPA) in addition to the duration of exposure are considered as statistically significant independent predictors for the insulin resistance indices (HOMA-IR) among BPA exposed workers (Table 4). Similar

conclusion was obtained by several studies (Hussein et al., 2013; Bhowmik et al., 2018, Xu et al., 2018; Elgawish et al., 2020).

Conclusion and recommendations

This research demonstrated that prolonged occupational BPA exposure is positively correlated with IR occurrence and risk to develop T2DM. This could raise the suspicion of the implication of BPA exposure in elevation of risk for diabetes development. Another factor that might contribute to this implication is that almost all workers didn't show any interest to use the provided PPE as many workers usually feel uncomfortable upon its use. However, further wide scale studies with meticulous data collection considering the occupational and environmental sources of BPA exposure and various confounding factors are mandatory to elucidate the full and comprehensive relationship between BPA exposure, IR induction and diabetes mellitus risk.

Also, usage of both serum adiponectin and lipid profile for assessment of T2DM risk based on IR prevalence seems to present a simple and time-saving screening test for BPA exposed workers to recognise subjects with a relatively elevated risk for diabetes development.

Consequently, major awareness should be conferred as regards the different control measures which aim to protect many at-risk individuals simultaneously. Eliminative or substitutive methods of control beside engineering and administrative solutions should be applied at the workplace. Ultimately, proper usage of personal protective equipment could also be beneficial.

Conflict of interest

The author declared that there is no conflict of interest regarding authorship, and/or publication of this article.

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