Assessment of Bisphenol A as a hormonal and lipid metabolism disruptor

A thesis

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BY

Asmaa Mohamed Ahmed Elfiky

Under the supervision of

Prof. Dr. Magdy Mahmoud Mohamed
Professor of Biochemistry
Faculty of Science
Ain shams University

Prof. Dr. Fateheya Mohamed Metwally
Professor of environmental and occupational medicine
Division of Environmental Research
National Research Center

Prof .Dr. Mohamed Abel-Hady Ghazy
Professor of Biochemistry
Faculty of Science
Ain Shams University

Prof .Dr. Nevin Ezzeldin Sharaf
Professor of environmental and occupational medicine
Division of Environmental Research
National Research Center

Biochemistry department

Faculty of science

Ain shams university

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CONTENTS

Abstract

Bisphenol A (BPA), is one of the highest volume chemicals produced and used to manufacture polymeric materials used in many products. Human can be exposed to it through its migration from polymers to food or water by heating. It is considered as an environmental obesogenic through promoting adipogenesis, lipid accumulation and endocrinal disrupting chemicals (EDCs) altering adipokine hormone release. The aim of this study was to assess the impact of BPA on lipid profile and metabolism. This work included 85 females aging from 16 to 58 years, after application of exclusion criteria. Among them 48 females with BMI $\geq$ 25 kg/m^2 group A (Gr-A) and 37 females with BMI< 25 kg/m^2 group B (Gr-B). All participants were subjected to detailed questionnaire and a clinical examination, sBPA, adiponectin, leptin hormones and lipid profile were assessed for all subjects. Results showed that a significantly high levels of leptin, cholesterol and LDL-c (p < 0.001) were recorded with significantly low levels of adiponectin (p < 0.001) & HDL-c (p<0.05) in (Gr-A) compared with those of (Gr-B). When the studied population was divided according to their BPA concentration, the adiponectin was significantly lower with high BPA concentration group. For most of these results non-monotonic dose–response relationships were observed. On the other hand, we observed no mutation at PPARG2 across the three percentiles of BPA. In conclusion, BPA generated a clear response in which the general obesity (BMI) and the central obesity (WC) showed significant increase at the low and high percentiles. Moreover, BPA had a disturbed action on lipid profile and suppressive effect on adiponectin release which support the claim that BPA is an endocrine disruptor increasing the risk of developing obesity associated disorders such

as glucose intolerance, hyperinsulimia, hypertension and increasing the risk of diabetes and cardiovascular disease.

Keywords: BPA, obesogen, adipogenesis, non-monotonic dose–response relationships, adiponectin**.**

List of abbreviation

BF%	**Body Fat percentage.**
8-OHdG	**8-Hydoxydeoxyguanosine**
ADP	**Adiponectin**
AMPK	**Adenosine Monophosphate-Activated Protein Kinase**
APCs	**Antigen-Presenting Cells**
BADGE	**Bisphenol A Diglycidyl Ether**
BIA	**Bioelectrical Impedance Analysis**
BMI	**Body Mass Index**
BPA	**Bisphenol A**
CVD	**Cardiovascular Disease**
DBP	**Diastolic Blood Pressure**
DXA	**Dual-energy X-ray absorptiometry**
E2	**17β-Estradiol**
EDCs	**Endocrine Disruptor chemicals**
ELISA	**Enzyme-Linked Immunosorbent Assay**
ER	**Estrogen Receptor**
ERK	**Extracellular signal-Regulated Kinases**
ERR-γ	**Estrogen-Related Receptor Gamma**

FBG	**Fasting Blood Glucose**
FBI	**Fasting Blood Insulin**
FFA	**Free Fatty Acid**
GLUT4	**Glucose Transporter-4**
HDL-c	**High Density Lipoprotein cholesterol**
HRP	**Horseradish Peroxidase**
HR	**Heart Rate**
IGF-1	**Insulin-Like Growth Factor 1**
INS-1	**insulinoma**
IR	**Insulin resistance**
IVF	**In Vitro Fertilization**
LDL-c	**Low Density Lipoprotein cholesterol**
LOAEL	**Lowest Observed Adverse Effect Level**
LPL	**Lipoprotein Lipase**
MAPKs	**Mitogen-Activated Protein Kinases**
MDA	**Malondialdehyde**
MS	**Metabolic Syndrome**
NHANES	**National Health and Nutrition Examination Survey**
NMDRCs	**Non-Monotonic Dose–Response Curves**

PCR	**Polymerase Chain Reaction**
PDI	**Protein Disulfide Isomerase**
PET	**Polyethylene Terephthalate**
PPARγ	**Peroxisome Proliferator-Activated Receptor Gamma**
Pro12Ala	**Prolin 12 Alanine**
PCOs	**Polycystic Ovarian Syndrome**
RFLP	**PCR–Restriction Fragment Length Polymorphism**
RXRs	**Retinoid X Receptors**
SBP	**Systolic Blood Pressure**
SP	**Streptavidin- Peroxidase**
SPSS	**Statistical Package For Social Science**
STAT	**Signal Transducers And Activator Of Transcription**
TDI	**Tolerable daily intake**
TMB	**Tetramethylbenzidine**
TNF-α	**Tumor necrosis factor alpha**
UGT2B1	**UDP-glucuronosyltransferase 2B1**
WB	**Wash Buffer**
WC	**Waist Circumference**

LIST OF FIGURES

List of tables

Introduction

Bisphenol A (BPA) is a monomer of polycarbonate plastics. It is amongst the highest volume of chemicals in commerce. Polycarbonates are found in numerous consumer products, including water and food bowls, baby bottles, linings of metal food and drink cans, medical tubing, epoxy resins, and dental fillings. Small quantities of BPA can be transferred from polymers to food or water, especially while heated **(Le *et al.*, 2008).**

BPA is an environmental endocrine-disrupting chemical (EDC) detected in ninety-five percent of human urine samples **(Calafat *et al*., 2008**) as well as in serum, breast milk, and fat **(Rubin, 2011; Taylor *et al.*, 2011).** BPA was declared to change several metabolic functions at environmentally appropriate concentrations in the low nanomolar range **(Sakurai *et al.*, 2004; Masuno *et al.*, 2005; Alonso-Magdalena *et al.*, 2006).** Moreover, BPA often shows a lack of linear dose-dependent relationship, but U-shaped or inverted U-shaped curves instead. Consequently, extrapolation from an action or lack of the action of BPA at high doses to the assumed bioactivity at low doses is unwarranted.

Mechanistically, BPA binds to estrogen receptors (ER) α and ER β and results in competition with estrogen **(Kurosawa *et al*., 2002)** and disrupting the folding, assembly, and shedding of several cellular proteins by targeting protein disulfide isomerase **(Hiroi *et al.*, 2006).** Experimental data demonstrated that exposure to BPA alters normal lipid metabolism and adipogenesis **(Grün and Blumberg, 2009)**, by binding to Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) receptors, an important regulatory component of lipid metabolism and adipogenesis., BPA exposure has the possibility to promote weight gain **(Newbold *et al.*, 2007; Grün and Blumberg, 2009)** and displays its effects on metabolic function by inducing