

Assessment of the Health Risks of the Exposure to Environmental Estrogen among Males

Thesis

Submitted for partial fulfillment for Degree of Doctor Philosophy

In

Environmental Science

By

Eman Ahmed Sultan Mohammed

M.B.B.,ch. & M.Sc &MD

Supervised By

Professor Doctor: Mahmoud serry Albokhary

Professor in the Department of Medical Science

Institute of Environmental Studies and research

Professor Doctor: Osama Mohammad Radwan

Professor in the Department of Agricultural Science

Institute of Environmental Studies and research

Professor Doctor: Hala Ibrahim Awad Allah

Professor in the Department of Medical Science

Institute of Environmental Studies and research

Doctor: Nancy Mohammad Sallam

Lecturer in Department of Medical Science

Institute of Environmental Studies and research

Institute of Environmental Studies and research

Department of Medical Science

Ain Shams University

2017

Acknowledgement

I would like to express my deep gratitude and appreciation to Professor ***Mahmoud Serry Albokhary*** Professor of Chest Disease, Department of Environmental Medical Science, Institute of Environmental Studies & research Ain Shams University for suggesting the point of the thesis, supervision of the work and for the invaluable guidance, the longtime and tremendous effort to offer every possible help to finish this thesis. It was a great honor to finish this work under her supervision.

I would like also to thank ***Prof. Osama Mahmmad Radwan*** Prof. of Food Science& Technology, Department of Environmental Agricultural Science Institute of Environmental Studies &research for his close supervision, valuable scientific assistance and undoubted effort he had exerted during his supervision during the preparation of this thesis.

Also I would like to thank ***Prof. Hala Ibrahim Awad Allah*** Prof. of Community Medicine, Department of Environmental Medical Science, Institute of Environmental Studies & research Ain Shams University for her continuous help and reviewing this work. It was a great honor to finish this work under her supervision.

I am greatly honored to express my thanks for Nancy Mohammad Sallam lecturer in Department of Environmental Medical Science, Institute of Environmental Studies &research Ain Shams University.

Abstract

A major challenge for life scientists in the 21st century is to understand how a changing environment impacts all life on earth. Over the past 20 years, a great deal of attention has focused on the impact of endocrine disruptors released in the environment on animal and human health. Generally, endocrine disruptors have estrogenic activity. These products interfere with hormone biosynthesis, metabolism, or action resulting in a deviation from normal homeostatic control or reproduction. **Aim:** Our primary aim was to evaluate the possible role of environmental estrogen on sexual disturbance among males. **SUBJECTS & METHODS:** A cross-sectional cohort community based study that recruited 26 apparently healthy males that agreed to participate in the study after explained details about the study and investigation that will be done and signed the informed consent for the study. We surveyed their characteristics of life style, symptoms covering various systems, general examination including blood pressure measurements, body mass index, waist line, resting blood pressure, Venous blood samples were used for detection of both total testosterone & plasma BuChE activity that is measured with a Test-mate ChE Randox kit from the hydrolysis of butyrylcholine iodide, and data were expressed as micromoles per minute per milliliter of plasma (U/ml). Evaluation of Test-mate ChE results was based on AChE and BuChE inhibition associated with different degrees. **RESULTS:** the mean age was (36.54 ± 6.04) years with mean BMI of (28.98 ± 5.16) kg/m². , mean waist (102.78 ± 11.18) cm. 66.7% of the cases were married and 13.3% have fertility problem & 20% with sexual problem. 66.7% of the studied group use pesticide at home. The mean serving intake of fruit & vegetables /week were (2.65 ± 2.90) serving.

CONCLUSION: Nearly all studied group had hormonal values and AChE within the reference range. There is a negative association between OP pesticides exposure assessed by the AChE as indicator and serum total testosterone levels as well as with fruit & vegetables consumption/week; whereas there is a positive association with age. Taken together, the epidemiologic data on the environmental EDCs suggest that there may be associations between exposure and adverse health outcomes in men. However, the limited human data, and in many instances inconsistent data across studies, highlight the need for further research on these chemicals. Future longitudinal molecular epidemiology studies with appropriately designed exposure assessments are needed to determine potential causal relationships, to identify the most important time windows/life stages of exposure, and to define individual susceptibility factors for adverse effects on men's health in response to exposure.

Exposure to environmental chemicals which have major risks for human by targeting different organs in the body has significant impacts on biological systems. For several years there have been a great amount of interest on the environmental endocrine disruptors (EEDs) and their relation with human health. A wide range of substances, both natural and man-made, are thought to cause endocrine disruption. They arise from many different sources, including pesticides among them organophosphates (OPs). Exposure to OPs may occur in four different ways: occupational exposure, residential use, environmental exposure for communities living in areas with intensive agricultural production or community pest control programs, and dietary exposure of the general population. OP inhibit acetylcholinesterase (AChE), an enzyme located in the post synaptic membrane that degrades acetylcholine (ACh) into choline and acetic acid .

Human male fertility is a complex process and therefore a great variety of sites may be affected by exogenous harmful mediators. Lifestyle factors as well as various environmental and occupational agents may impair male fertility. In the past years, there has been increased interest in assessing the relationship between impaired male fertility and environmental factors. Many studies have been published reporting on reproductive dysfunctions in male animals and humans. However, relevant epidemiology studies in men are limited.

In the present study, we examined the potential association between serum AchE biomarkers of OP insecticide exposure and serum reproductive hormones on 26 apparently healthy males in reproductive age.

As regard male sex hormones we found no association between total testosterone and anthropometric or clinical variables. When evaluating AchE as indicator of OPs exposure there were negative association with Total testosterone & with fruit & vegetables consumption/week ,while no association with LH .

Content

	Page
List of Tables	2
List of Figures	3
List of Abbreviations	4
Introduction	5
Aim of the work	7
Review of Literature	
I-Endocrine-disrupting chemicals	8
1. Polycyclic aromatic hydrocarbons (PAHs)	10
2. Bisphenol A (BPA)	10
3. Phthalic acid esters (PAEs)	11
4. Other chemicals	11
5. Contemporary use pesticides	12
II-Organophosphorus (OPs) Pesticides	17
1. Procedure of action for Ops	21
2. Sources of Exposure	21
3. Human health hazards and environmental impact	25
III-The male reproductive system	28
1. Spermatogenesis	30
2. Hormone Regulation	34
IV- Estrogen and male reproductive tract	36
1. Estrogen hormone in the adult male reproductive tract	36
2. Estrogen receptors in the male tract	37
3. Estrogen function in testis	38
4. Role of aromatase in male reproduction	39
Effects of environmental pollution on male reproduction	42
Subjects and Methods	47
Results	51
Discussion	64
Summary & conclusion	73
References	76
Arabic Abstract	
Arabic Summary	

List of tables

1	Body mass index classification	49
2	Demographic clinical character of the studied sample	51
3	Anthropometric measure of the studied sample	52
4	Laboratory parameters of the studied sample	53
5	Androgenic Manifestation of the studied sample	54
6	Use of pesticides in the studied sample	55
7	Fruit & vegetable consumption /week	55
8	Correlations between AchE and other variables	56
9	Correlations between AchE and androgenic hormones	56
10	Correlation between testosterone and anthropometric parameters	57
11	Correlation between testosterone and clinical parameters	58
12	Correlation between testosterone and lab parameters	59
13	Correlation between Fruit & vegetables consumption/week and clinical variables	60
14	Correlation between Fruit & vegetables consumption/week and anthropometric variables	61
15	Correlation between Fruit & vegetables consumption/week and lab variables	62

	List of figures	page
Figure 1	Organophosphorus chemical structure	17
Figure 2	Acetylcholine chemical structure	18
Figure 3	Acetylcholine esterase effect	18
Figure 4	Organophosphates mechanism of action	18
Figure 5-A	Male reproductive system	29
Figure 5-B	Detailed structure of the testis and epididymis	29
Figure 6-A	Spermatogonia	30
Figure 6-B	Spermatogenesis	30
Figure 7	Steps of Spermatogenesis	31
Figure 8	Meiosis	32
Figure 9	Structure of the human spermatozoon	33
Figure 10	Correlation between Total Testosterone (ng/dl) and AchE (U/ml)	63

List of Abbreviations

AChE	Acetylcholinesterase
BMI	Body Mass Index
BPA	Bisphenol A
BuChE	butyrylcholinesterase
ChE	Cholinesterase
DBP	di-n-butyl phthalate
E2	Estradiol
EDC	Endocrine-disrupting chemical
EEDs	Environmental endocrine disruptors
EPA	Environmental Protection Agency
ER	Estrogen receptor
ER alpha (α)	Estrogen receptor alpha
ER beta	Estrogen receptor Beta
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
kDa	Kilo Dalton
LH	Luteinizing Hormone
NHL	Non-Hodkin's lymphoma
OCPs	Organochlorine pesticides
OPs	Organophosphorus pesticides
PAEs	Phthalic acid esters
PAHs	Polycyclic aromatic hydrocarbons
PON	Paraoxonase
TDS	Testicular dysgenesis syndrome TDS
α ERKO	Estrogen α -receptor knockout