

**EFFECTS OF IONIZING RADIATION IN ATOPIC
PATIENTS EXPOSED TO RADIATION**

Submitted By

Nashwa Kamal El Din Abd El Hamid Radwan

M.B.B.Ch., Faculty of Medicine, Cairo University, 1997

Master of (Dermatology), Faculty of Medicine, Cairo University, 2003

A thesis submitted in Partial Fulfillment
Of
The Requirement for the Doctor of Philosophy Degree
In
Environmental Science

Department of Environmental Medical Science
Institute of Environmental Studies and Research
Ain Shams University

2014

APPROVAL SHEET
**EFFECTS OF IONIZING RADIATION IN ATOPIC
PATIENTS EXPOSED TO RADIATION**

Submitted By

Nashwa Kamal El Din Abd El Hamid Radwan

M.B.B.Ch., Faculty of Medicine, Cairo University, 1997

Master of (Dermatology), Faculty of Medicine, Cairo University, 2003

This thesis Towards a Doctor of Philosophy Degree in
Environmental Science Has been Approved by:

Name

Signature

1-Prof. Dr. Mahmoud Serry El Bokhary

Prof. of Chest Disease& Head of Department of Environmental
Medical Science
Institute of Environmental Studies & Research
Ain Shams University

2-Prof. Dr. Ahmed Fathi El Bedewi

Prof. of Dermatology
National Center for Research and Radiation Technology
Atomic Energy Authority

3-Prof. Dr. Mohamed Salah Gabil

Prof. of Community and Environment Medicine
Faculty of Medicine
Ain Shams University

4-Prof. Dr. Hisham Aly Shokeir

Prof. of Dermatology
National Institute of Laser Enhanced Sciences
Cairo University

2014

EFFECTS OF IONIZING RADIATION IN ATOPIC PATIENTS EXPOSED TO RADIATION

Submitted By

Nashwa Kamal El Din Abd El Hamid Radwan

M.B.B.Ch., Faculty of Medicine, Cairo University, 1997

Master of (Dermatology), Faculty of Medicine, Cairo University, 2003

A thesis submitted in Partial Fulfillment
Of
The Requirement for the Doctor of Philosophy Degree
In
Environmental Science
Department of Environmental Medical Science

Under The Supervision of:

1-Prof. Dr. Mahmoud Serry El Bokhary

Prof. of Chest Disease& Head of Department of Environmental
Medical Science
Institute of Environmental Studies & Research
Ain Shams University

2-Prof. Dr. Abd El – Monem Sayed Bashandy

Prof. of Microbiology
National Center for Research and Radiation Technology
Atomic Energy Authority

3-Dr. Ahmed Fathi El Bedewi

Assistant Prof. of Dermatology
National Center for Research and Radiation Technology
Atomic Energy Authority

2014

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢



Acknowledgement

*First and foremost, thanks are due to **GOD**, the most merciful and benevolent for his gifts to all of us.*

*I am deeply indebted to **Dr. Mahmoud Seri AL Bokhari**, Professor of Medical Science, Institute of Environmental Studies and Research, Ain Shams University, for his idea of this work, keen supervision, precious time, continuous encouragement and his Co-operation throughout this work.*

*I feel much honored to express my indebtedness to **Dr. Abd El Monem Bashandy**, Professor of microbiology, National Center for Radiation Research and Technology (NCRRT), Atomic Energy Authority. No words can truly express my deep feeling of gratitude for **Dr. Abd El Monem** who spared no time, effort and knowledge to help and guide me through each step required to accomplish this study, and his helping hands will never be forgotten.*

*I wish to express my thanks and gratitude to **Dr. Ahmed Fathi EL Bedewi**, Professor of dermatology, NCRRT, Atomic Energy Authority, for his valuable suggestions, discussions, great efforts in reviewing this thesis and follow up which was a real encouragement to accomplish this work.*

*A special thank for **Dr. Noha Fawzy Ibrahim** Assistant Professor of Dermatology, NCRRT, Atomic Energy Authority for her assistance and I believe that without her help this work could not be completed.*

I would like to thank everyone who helped me during the preparation of this work, specially Dr. Dina Fathi El Essawi and all the members of the laboratory in the NCRRT.

Last but not least, my deepest gratitude goes to my beloved husband & also to my lovely children for their endless love, prayers & encouragement. Thank you very much.

Finally, I Dedicate this work to my family especially my great mother whom without their sincere emotional support, pushing me forward, understanding and everything we share in our life; this work would not have ever been completed.

Nashwa Kamal

To

*The person I love
most, and to who I
owe everything, to
soul of my father.*



List of Contents

Title	Page No.
List of Tables	i
List of Figures.....	ii
List of Abbreviations	iv
Abstract	
Introduction	1
Aim of the Work	3
Review of Literature	
Chapter (1): Atopy	4
Chapter (2): Low Ionizing Radiations	40
Chapter (3): Biological Effects of Low Radiation	49
Patients and Methods.....	66
Results	85
Discussion.....	117
Summary	132
Conclusion	135
Recommendation.....	136
References	137
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table (1):	(A) Clinical Data of AD Patients (Group 1).	86
Table (2):	(A) Grading of Disease Severity in AD Patients (Group 1).	88
Table (3):	Statistical analysis of severity grades in AD patients (group 1&2).	90
Table (4):	Statistical analysis of bacterial distribution in patients with AD (group 1&2).	92
Table (5):	Identification of different <i>Malassezia</i> species.....	102
Table (6):	Statistical analysis of different types of <i>Malassezia</i> species in patients with AD (group 1&2).	105
Table (7):	The amount of total IgE among atopic dermatitis in group 1&2	111
Table (8):	Level and detection frequency of specific IgE antibody and colonization frequency of <i>Malassezia</i> species.....	113
Table (9):	Relationship between the numbers of species detected and total IgE antibody levels against <i>Malassezia</i> species.	114
Table (10):	Level and detection frequency of specific IgE antibody of <i>S. aureus</i>	115
Table (11):	The Eosinophil differential count among group 1&2.	116

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Grades of severity in group 1.	91
Figure (2):	Grades of severity in group 2.	91
Figure (3):	Distribution of bacteria in group 1&2.....	92
Figure (4):	Gram stain of <i>S. aureus</i> Gram positive cocci in grape-like clusters.....	94
Figure (5):	Colonies of <i>S. aureus</i> on Blood agar.	94
Figure (6):	Gram stain of <i>S. epidermidis</i> Gram positive cocci in grape-like clusters, diplococci, cocci.	95
Figure (7):	Colonies of <i>S. epidermidis</i> on Blood agar.	95
Figure (8):	Tween assimilation pattern of <i>Malassezia</i>	96
Figure (9):	Colonies of <i>Malassezia globosa</i> on m Dixon's agar.....	97
Figure (10):	Precipitate test of <i>M. globosa</i> on m Dixon's agar after 3 days of incubation.....	98
Figure (11):	Colonies of <i>Malassezia furfur</i> on m Dixon's agar.....	98
Figure (12):	Colonies of <i>Malassezia sympodialis</i> on m Dixon's agar.....	100
Figure (13):	Precipitate test of <i>M. sympodialis</i> on m Dixon's agar after 1 day of incubation.....	100
Figure (14):	Colonies of <i>Malassezia obtusa</i> on m Dixon's agar.....	101
Figure (15):	Esculin test of <i>Malassezia</i> species (blacknes of the medium is an indication of β - glucosidase activity. Esculin (+).	101
Figure (16):	<i>Malassezia globosa</i> with stable spherical cells with a broad base (Gram stain \times 1000).....	102
Figure (17):	<i>Malassezia furfur</i> with small friable texture colonies (Gram stain \times 1000).....	103
Figure (18):	<i>Malassezia sympodialis</i> with small ovoid characteristic sympodial budding (Gram stain \times 1000).....	103

List of Figures (Cont...)

Fig. No.	Title	Page No.
Figure (19):	<i>Malassezia obtusa</i> with small smooth flat cells (Gram stain×1000).	104
Figure (20):	Total number of different types of <i>Malassezia</i> in patients with Group 1&2.	106
Figure (21):	The primers successfully amplified the target part of 26S rDNA from all <i>Malassezia</i> strains.....	108
Figure (22):	Illustrates the products of restriction digestion separately, the bands generated were of the predicted sizes. Using <i>Cfo</i> 1, four different species could be distinguished including, <i>M. sympodialis</i> , <i>M. furfur</i> , <i>M. globosa</i> and <i>M. obtusa</i>	109
Figure (23):	Illustrates the Agarose gel electrophoresis of PCR-amplified coagulase genes from representatives of <i>S. aureus</i>	110
Figure (24):	The amount of total IgE among AD patients in group 1&2.	111
Figure (25):	The Eosinophil differential count among group 1&2.	116

List of Abbreviations

Abb.	Meaning
AD	Atopic Dermatitis
ALARA	As Low As Reasonably Achievable
BEIR	Biological Effects of Ionizing Radiation
CDLQI	Children's Dermatology Life Quality Index
DFI	Dermatitis Family Impact
DLQ	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EDTA	Ethylene Diamine Tetraacetic Acid
FLG	Filaggrin
ICRP	International Commission on Radiological Protection
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
ITS	Intergenic Transcribed Spacer
LET	Low-Linear Energy Transfer
LNT	Linear No-threshold
m Dixon's Agar	modified Dixon's Agar
M	Malassezia
MDC	Macrophage-Derived Chemoattractant
NCRP	National Council on Radiation Protection
PCR	Polymerase Chain Reaction
POEM	Patient-Oriented Eczema Measure
PRRs	Pattern Recognition Receptors
RBE	Relative Biological Effectiveness
RFLP	Restriction fragment Length polymorphis
ROS	Reactive Oxygen Species

List of Abbreviations (cont...)

Abb.	Meaning
<i>S.aureus</i>	<i>Staphylococcus aureus</i>
SASSAD	Six Area, Six Sign Atopic Dermatitis
SCORAD	Scoring Atopic Dermatitis index and other severity scales
SEA	Staphylococcal enterotoxin A
SEB	Staphylococcal enterotoxin B
SEC	Staphylococcal enterotoxin C
SGA	Sabouraud Glucose Agar
TAR	Cthymus and activation-regulated chemokine
Th 1	T helper 1
Th 2	T helper 2
TISS	Three Item Severity Scale
TNF	Tumor Necrosis Factor
TSST-1	Toxic shock syndrome toxin-1

ABSTRACT

Atopic dermatitis is a chronic relapsing inflammatory skin disease that arises most commonly during early infancy, and is characterized by severe pruritus, age-dependant skin manifestations, and a fluctuating clinical course.

Hereditary, environmental and immunological factors are involved in the aetiopathogenesis of AD. Also the differentiation of helper T- cells, local cytokine profile, IgE, infectious agents and superantigens are factors identified as being involved in the pathogenesis of AD.

One hundred patients with AD were selected from the outpatient clinic of the National Center for Radiation Research and Technology in Cairo, Egypt. They were divided into 2 groups; group 1 included radiation workers in the Hall of gamma irradiation unit and group 2 included workers outside controlled area and not exposed to radiation with comparable age and sex.

The severity of the disease was evaluated according to the grade of atopic dermatitis. Total and specific serum IgE was measured and Complete Blood Count was also carried out.

Four *Malassezia* species were isolated from AD patients *M. globosa*, *M. furfur*, *M. sympodialis* and *M. obtusa*. The clinical isolates consisted of two bacterial strains, *S. aureus* and *S. epidermidis*.

The significant increase of AD severity seems to be more closely related to the prevalence of *S. aureus* and *Malassezia* on the skin of radiation workers. This was proved by the presence of high IgE and eosinophils in radiation workers. So, the interactions of low gamma radiation and skin seems to further complicate the risk of assessments of atopic dermatitis.

Key words: Atopic dermatitis, Radiation workers, Staphylococcus, *Malassezia*.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory disease causing intense pruritus with typical clinical features (**Orfali *et al.*, 2013**).

Atopic dermatitis (AD) is an itchy inflammatory skin disease with predilection for skin flexures. AD develops as a result of complex interaction of genetic, environmental and immunological factors. Disturbed skin function, infection and stress may be other important contributing factors. Early onset, concomitant asthma and family history of AD may predict a persistent course (**Williams and Wüthrich, 2000**).

Patients with AD usually exhibit defects in innate and acquired immune responses resulting in a heightened susceptibility to bacterial, fungal and viral infections, most notably colonization by *S. aureus*. Moreover, allergens expressed by the yeast *Malassezia furfur*, a component of normal skin flora, have also been implicated in disease pathogenesis in a subset of AD patients (**Baker, 2006**).

Microorganisms play an influential role in AD pathogenesis, interacting with disease susceptibility genes to cause initiation and/or exacerbation of disease activity. *Staphylococcus aureus* colonization of both lesions and clinically uninvolved skin has been demonstrated by many investigators. Also, the density of this organism in lesional skin correlates with the severity of inflammation; reduction in the density of *S. aureus* is associated with clinical improvement (**Williams *et al.*, 1990 and Nilsson *et al.*, 1992**).

Members of the genus *Malassezia*, lipophilic yeasts, colonize the skin of the head, neck, and shoulders of humans are considered to be one

of the factors that exacerbate AD, based on the finding that those patients (but not healthy subjects) have specific serum immunoglobulin E (IgE) antibodies against *Malassezia* (Werfel and Kapp, 1998).

The development and phenotypic expression of AD depend on a complex interaction between genetic and environmental factors (Watson and Kapur, 2011), including nutrition (Wang *et al.*, 2007).

On the other hand, the health risks of low doses of radiation could influence the occupational health of radiation workers. The worry about the indeterminate risks of low dose radiation should be integrated through collaboration between radiation biologists and epidemiologists, in order to provide an explanation of epidemiologic radiation effects.

The response of human skin to low dose radiations is a consequence of biological reactions including; genomic instability and bystander effects. This could be the predisposing factors for the emergence of premalignant skin lesions and premature skin aging; as well as higher susceptibility to bacterial and fungal infections (Hu *et al.*, 2012).

The ultimate response of cells and tissues to radiation injury is invariably dependent on the radiation dose and the ability of the cells to repair sub-lethal damage. High radiation doses usually result in mitotic arrest and high incidence of cell death, with little chance of regenerative cellular repopulation. Lower doses of radiation fail to produce cell killing, but succeed in producing radiation induced mutations and other molecular alteration resulting in cellular abnormalities that become inherited in the genetic cell line of the cells composing the tissue and ultimately produce tissue and organ abnormalities (El-Naggar, 2000).