



# **Autoimmune Thyroiditis Among Ionizing Radiation Exposed Workers in Cardiac Catheterization Units.**

**Thesis**

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# الالتهاب المناعي في الغدة الدرقية بين العاملين المعرضين للاشعاع المؤين في وحدات قسطرة القلب

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## **LIST OF ABBREVIATIONS**

<b>SI :</b>	International system of units
<b>AITD :</b>	Autoimmune thyroid disease
<b>ANC :</b>	Absolute neutrophil count
<b>Anti-TPO :</b>	Anti-thyroxiperoxidase
<b>APC :</b>	Antigen presenting cells
<b>ARS:</b>	Acute radiation syndrome
<b>BCL :</b>	B cell lymphoma
<b>Bq :</b>	Becquerel
<b>C :</b>	Complement
<b>cAMP :</b>	cyclic adenosine monophosphate
<b>CD :</b>	Cluster Differentiation
<b>Ci :</b>	Curie
<b>CT :</b>	Computed Tomography
<b>CTLA :</b>	Cytotoxic T-lymphocyte association-protein
<b>CVD :</b>	Cardiovascular disease
<b>DC :</b>	Dendritic cells
<b>DNA :</b>	Deoxyribo nucleic acid
<b>Dps :</b>	Disintegration per second
<b>E</b>	Effective dose
<b>ECLIA :</b>	Electro-Chemi-Luminescence Immuno-Assay
<b>EDTA :</b>	Ethylene diamine tetra acetate
<b>ELISA :</b>	Enzyme-Linked Immuno-Sorbent Assay
<b>ERCP :</b>	Endoscopic Retrograde Cholangio-Pancreatography
<b>Fc :</b>	Fragment crystalizable
<b>FNAb :</b>	Fine needle aspiration biopsy
<b>GD :</b>	Graves' disease
<b>GJIC :</b>	Gap-Junction Intracellular Communication
<b>GM-CSF :</b>	Granulocyte-Macrophage Colony-Stimulating Factor
<b>Gy :</b>	Gray
<b>HD-IR :</b>	High dose ionizing radiation
<b>HLA :</b>	Human leukocyte Antigen

<b>HLADR :</b>	Human Leukocyte Antigen-antigen D Related
<b>HRP :</b>	Horseradish peroxidase
<b>HT:</b>	Hashimoto's thyroiditis
<b>ICRP :</b>	International Commission on Radiological Protection
<b>ICs :</b>	Interventional cardiologists
<b>IFN<math>\gamma</math> :</b>	Interferon $\gamma$
<b>Ig :</b>	Immunoglobulin
<b>IL :</b>	Interleukin
<b>IR :</b>	Ionizing radiation
<b>KD :</b>	Kilodalton
<b>LD :</b>	Lethal dose
<b>LDR :</b>	Low dose radiation
<b>LET :</b>	Linear energy transfer
<b>MHC :</b>	Major histocompatibility complex
<b>NK :</b>	Natural killer
<b>PBS :</b>	Phosphate-buffered saline
<b>PCI :</b>	Percutaneous coronary intervention
<b>PCNA :</b>	Proliferating cell nuclear antigen
<b>PIP2 :</b>	Phosphatidyl inositol-bisphosphate
<b>PPT :</b>	Post partum thyroiditis
<b>PTH :</b>	Parathyroid hormone
<b>PTPN :</b>	protein tyrosine phosphatases non-receptor
<b>Rad :</b>	Radiation absorbed dose
<b>Rem :</b>	Roentgen equivalent man
<b>RF :</b>	Radiofrequency
<b>ROS :</b>	Reactive oxygen species
<b>Sv :</b>	Sievert
<b>T3 :</b>	Triiodothyronine
<b>T4 :</b>	Thyroxin
<b>TAO :</b>	Thyroid associated orbitopathy
<b>TBAbs :</b>	Thyroid stimulation-Blocking Antibodies
<b>TBS :</b>	Tris-buffered saline
<b>Tc :</b>	Technetium

<b>TCR :</b>	T-cell Receptor
<b>Tg :</b>	Thyroglobin
<b>Th :</b>	T helper
<b>TIPS :</b>	Transjugular intrahepatic portosystemic shunt
<b>TLD :</b>	Thermo-luminescent dosimeter
<b>TMB :</b>	Tetra-methyl benzidine
<b>TNF :</b>	Tumor necrosis factor
<b>TRAIL :</b>	TNF-related apoptosis-inducing ligand
<b>TRH :</b>	Thyrotrophin-releasing hormone
<b>TSAbs :</b>	Thyroid Stimulating Auto-antibodies
<b>TSH :</b>	Thyroid stimulating hormone
<b>TSH-R :</b>	Thyroid stimulating hormone receptor
<b>UR I:</b>	Upper respiratory tract infection
<b>WR :</b>	Radiation weighting factor

## **ABSTRACT**

**Introduction:** It is well known that ionizing radiation IR exposure increases the risk of thyroid cancer; however less is known about its role in development of autoimmune thyroiditis. **Objective:** To assess the effects of occupational exposure to ionizing radiation on thyroid functions and the possibility of having autoimmune thyroiditis. **Methods:** a group of 47 cardiac catheterization workers (19 physicians, 15 nurses and 13 technicians) and another 47 job, age, and sex matched controls were subjected to investigating the serum level of T3, T4, TSH, anti-TPO, Th<sub>1</sub> cytokines (IL2, IFN $\gamma$ ), Th<sub>2</sub> cytokines (IL10) and CD4%. Area monitoring of IR was also done using portable dose rate meter to measure local scattered radiation. Besides, annual personal exposure was monitored by TLD readings over the last 3 years **Results:** Area monitoring showed high level of scattered ionizing radiation inside the cardiac catheterization rooms, although dosimeter readings were within the acceptable level over the three years. Statistically significant higher level of serum TSH, anti-TPO, IL2, IFN $\gamma$  along with statistically significant lower levels of T3, IL10 and CD4% were found among the exposed compared to control groups ( $P < 0.05$ ). Significant positive correlation was detected between the level of anti-TPO and each of cumulative exposure index (CMI) ( $r = 0.378$   $P < 0.05$ ), TSH ( $r = 0.876$   $P < 0.001$ ), IL2 ( $r = 0.847$   $P < 0.001$ ), and IFN  $\gamma$  ( $r = 0.685$   $P < 0.001$ ). Moreover, a significant negative correlation was found between anti-TPO and each of T3 ( $r = -0.814$   $P < 0.001$ ) and T4 ( $r = -0.324$   $P < 0.05$ ). ANOVA and Post Hoc tests showed significantly higher level of anti-TPO and Th<sub>1</sub> cytokines with significantly lower levels of T3, CD4% and IL10 among the physicians compared to control group **Conclusion:** Autoimmune thyroiditis might be one of the hazards that can be attributed to occupational exposure to ionizing radiation especially in cardiac catheterization units.

**Key words:** Ionizing radiation- Autoimmune thyroiditis- T3- T4- TSH- Anti-TPO- IL2- IFN $\gamma$ -IL10 - CD4%.

### Introduction

Medical exposure from X-rays and nuclear medicine is the largest man-made source of radiation exposure (**Mettler et al., 2009**). Such exposure is of significant concern for interventional cardiologists due to increasing workloads and complexity of procedures over the last decade (**Cousins et al., 2013**). Moreover, those interventional cardiologists encounter much more radiation exposure than most other medical staff due to their working position close to the X-ray beam and the patient (the source of scatter radiation) ( **Rehani and Ortiz-Lopez, 2006**).

Radiation exposure can exert a number of adverse effects on many tissues in the body. One of the target organs for radiation-related damage is the thyroid gland as it receives a considerable radiation dose from scattered radiation probably due to its anatomical site (**Eheman et al., 2003**).

There is a general consensus that there is a high prevalence of thyroid cancer, thyroid nodules formation and thyroiditis in workers who were occupationally exposed to radiation, particularly among X-ray workers and other health staff exposed to radiation in laboratories (**Paolo et al., 2005**). Furthermore, autoimmune thyroid disease has been linked to therapeutic medical radiation, as well as environmental radiation exposure but the mechanisms and pathways involved in that relation remain not well clear (**Brent, 2010**).

Autoimmune thyroid disease is the most common organ-specific autoimmune disease and characterized by the presence auto-antibodies directed against several major thyroid antigen. Among those, are the Anti-TPO auto-antibodies which found in over 90% of patients with autoimmune hypothyroidism and 70% of patient with Graves' disease (**Hawa et al., 2006**).

Moreover, a dose-response relation between radiation exposure and the prevalence of positive anti-thyroxiperoxidase antibodies was found in some studies (**Vo lzke et al., 2005**).

Also, the role of cytokines in the development of autoimmune thyroid disorders has been widely explained (**Stassi and de Maria, 2002**). In case of Hashimoto's thyroiditis, a Th<sub>1</sub> disease, the cytokine IFN $\gamma$  appears to play a crucial role in the pathology of the disease while in the Graves' disease, a Th<sub>2</sub> disease, the cytokines IL4 and IL-10 are responsible for the pathology. However, these cytokines could be up- or down-regulated by low dose radiation (LDR) (**Hayashi et al., 2005**).

Ionizing radiation can produce functional alteration of the immune system and breaks self -tolerance with induction of autoimmune disease among that is the thyroid gland which is one of the susceptible organs for the deleterious effect of ionizing radiation. However, the association and pathogenesis of radiation induce autoimmune thyroiditis is still not well clear, therefore, in this work we estimated the level of thyroid hormones, anti TPO and some cytokines searching for that association and possible immune mechanism.

## **Aim of the work**

The overall aim of this study is to investigate the effect of occupational exposure to ionizing radiation on the thyroid gland function and the risk for autoimmune thyroiditis development.

### **objectives:**

1. Assess radiation exposure among cardiac catheterization's workers.
2. Assess thyroid gland integrity among ionizing radiation exposed workers in cardiac catheterization units.
3. Assess the level of anti-thyroxiperoxiase antibody and its relation to radiation exposure.
4. Assess the balance between Th1 and Th2 immune response through measuring some related cytokines with investigating their relation to radiation exposure.

## **Background**

Radiation is the propagation or emission of energy in the form of particles or waves travelling through space. Electromagnetic radiation is a type of radiation in which there are self-propagating waves, and is further classified on the electromagnetic spectrum based on the wavelength, frequency, or energy of these waves, ranging from radio waves (highest wavelengths, lowest frequencies and energies) to gamma rays and X-rays (lowest wavelengths, highest frequencies and energies) (ARPANSA, 2011).

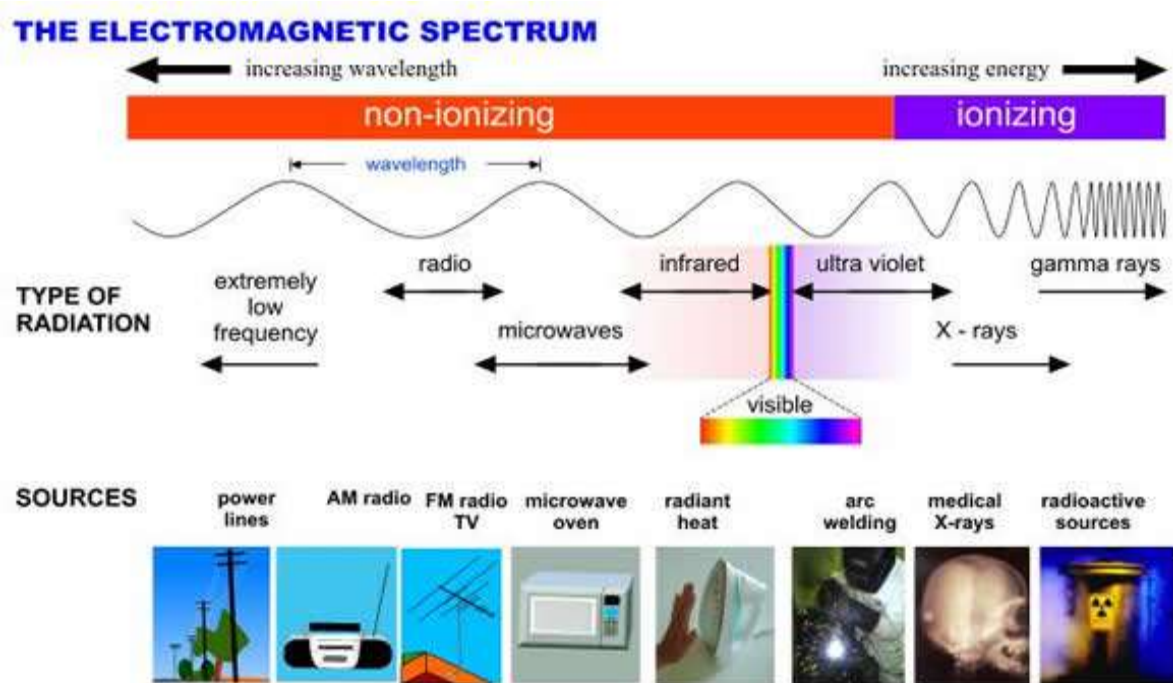


Figure (2:1): The electromagnetic spectrum, (ARPANSA, 2012).

Another classification of radiation is the distinction between ionizing and non-ionizing radiation. Ionizing radiation has enough energy to ionize atoms, e.g. to enable an electron to move out of its orbit, whereas non-ionizing radiation does not. Most types of electromagnetic radiation, such as visible light, are non-ionizing, but higher energy electromagnetic radiation such as gamma rays and X-rays is ionizing (ARPANSA, 2012).