INTRODUCTION

Anatomy of the thyroid gland

The thyroid gland is a butterfly-shaped organ and is composed of two cone-like lobes or wings, lobus dexter (right lobe) and lobus sinister (left lobe), connected via the isthmus.

The gland is situated on the front of the neck, lying against and around the larynx and trachea, reaching posteriorly the oesophagus and carotid sheath. It starts cranially at the oblique line on the thyroid cartilage and extends inferiorly to approximately the fifth or sixth tracheal ring. It is difficult to demarcate the gland's upper and lower border with vertebral levels because it moves position in relation to these during swallowing. (1)

Physiology of the thyroid gland

The primary role of thyroid is production of the hormones triiodothyronine (T_3), thyroxine (T_4), and calcitonin which are involved in the regulation of a number of physiological processes, including metabolism and calcium balance. T3 most notably affects body temperature and heart rate, T4 most notably affects metabolism, and both affect growth. Calcitonin, works with parathyroid hormone to regulate calcium balance. It promotes bone formation, lowering the calcium and phosphorus levels in the blood by blocking the function of osteoclasts and promoting the function of osteoblasts. (2)

Thyroid hormones (T_4 and T_3) are produced by the follicular cells of the thyroid gland. Their synthesis is dependent on the availability of exogenous iodine. Thyroxine is produced by attaching iodine atoms to the ring structures of tyrosine molecules. Tyrosines are provided from a large glycoprotein called thyroglobulin, which is synthesized by thyroid epithelial cells. A molecule of thyroglobulin contains 134 tyrosines, although only a handful of these are actually used to synthesize T4 and T3.Thyroxine (T_4) contains four iodine atoms. Triiodothyronine (T_3) is identical to T_4, but it has one less iodine atom per molecule.T3 and T4 are called iodothyronines. Iodide is actively absorbed from the bloodstream by a process called iodide trapping. In this process, sodium is cotransported with iodide from the basolateral side of the membrane into the cell and then concentrated in the thyroid follicles to about thirty times its concentration in the blood. Via a reaction with the enzyme thyroperoxidase, iodine is bound to tyrosine residues in the thyroglobulin molecules, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). Linking two moieties of DIT produces thyroxine. Combining one particle of MIT and one particle of DIT produces triiodothyronine.(3)

Proteases digest iodinated thyroglobulin, releasing the hormones T_4 and T_3, the biologically active agents central to metabolic regulation.

When T3 andT4 are released into the circulation, they combine with plasma proteins, mainly Thyronine Binding Globulin (TBG). A small proportion of T3 and T4 also bind to albumin and prealbumin. Less than 1% of the iodothyronines are free (unbound) in the

plasma. Estrogens increase the synthesis of TBG and decrease the clearance of the iodothyronines. In states where there are high levels of circulating estrogens (i.e. pregnancy), there are high levels of circulating iodothyronines. [4]

In the peripheral tissues, T4 is converted into the more active iodothyronine T3. This is brought about by a deiodination reaction. T3 is eight times more potent hormone than T4 but it has a shorter half-life. There is another important conversion in the periphery where T4 is deiodinated to an inactive iodothyronine called reverse T3 (rT3). The precise role of rT3 is not fully understood, but it is thought to regulate the amount of active iodothyronines in the periphery.[5]

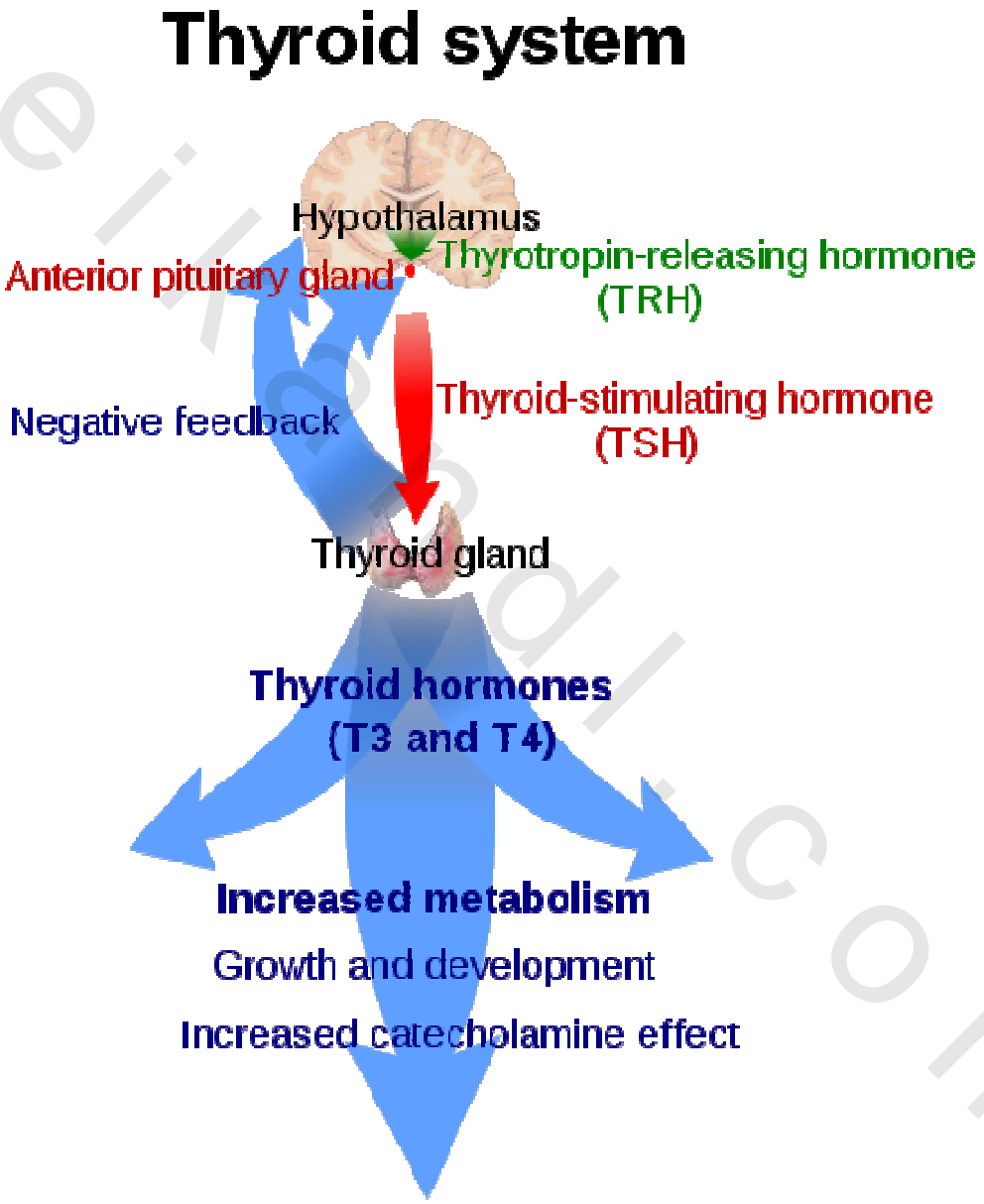

Figure1.The system of thyroid hormones: T3 and T4. [7]

Physiological effects of thyroid hormones:

Essentially all cells in the body are target cells of triiodothyronine .Once triiodothyronine is inside a cell, it enters the nucleus, where it binds to proteins known as nuclear receptor .The triiodothyronine-receptor complexes then bind to deoxyribonucleic acid (DNA) molecules .This results in an increase in the rate at which the affected DNA molecules are transcribed to produce messenger ribonucleic acid(mRNA) molecules and an increase in the rate of synthesis of the protein translation (coded for by the DNA (by way of the mRNA).[5-7]

Among the body functions which depend on normal thyroid secretion:

I- Metabolism:

- The basal metabolic rate: BMR is the number of calories of heat that must be produced per hour by catabolism to keep the body alive and healthy. The thyroid hormones have a direct relationship to this rate, in that T3 and T4 molecules influence every one of the trillion of cells in our bodies. They make them speed up their release of energy from foods, through the process of cellular metabolism. This essentially sets into action a series of other hormones, neurotransmitters, and enzymes, like a domino effect.
- A major function of the thyroid hormones is to increase body heat production by increasing the oxygen consumption and ATP hydrolysis in the muscles. This creates the energy needed for muscle contractions to make body heat. This is vital to homeostasis, since humans need to be at a constant temperature (a steady 37.0 °C (98.6 °F). [7]

- **Carbohydrate metabolism:**

Thyroxine influences the following activities in human body:

1- Increases utilization of glucose inside the cells to release metabolic energy.
2- Activates glycogenolysis in liver and muscles to generate more energy.
3- Increases glucose synthesis from non-carbohydrate sources i.e gluconeogensis.
4- Speeds up the absorption of glucose by walls of the intestine. [7,8]

- **Lipid metabolism:**

Thyroid hormones affect synthesis, mobilization and degradation of lipids, although degradation is influenced more than synthesis. The main and best-known effects on lipid metabolism include:

1. Enhanced utilization of lipid substrates.
2. Increase in the synthesis and mobilization of triglycerides stored in adipose tissue
3. Increase in the concentration of non-esterified fatty acids (NEFA).
4. Increase of lipoprotein-lipase activity.

Severe hypothyroidism is usually associated with an increased serum concentration of total cholesterol and atherogenic lipoproteins. Even in subclinical hypothyroidism, which is characterized by raised serum TSH levels with normal

serum thyroid hormone concentrations, mild hyperlipidemia is present and may contribute to an increased risk of atherogenesis. [7,9]

- **Protein metabolism:**

T3 stimulates both protein degradation and protein synthesis however, it more extensively increases protein degradation, especially in muscle. High levels of thyroid hormone are associated with muscle wasting and decreased muscle strength. In children low levels of thyroid hormone can impair growth because of its effects on protein metabolism. [7,10]

II- Cardiovascular system:

Thyroid hormones increases heart rate, cardiac contractility and cardiac output. They also promote vasodilation, which leads to enhanced blood flow to many organs. [7,10]

III- Central nervous system:

- Critical for normal CNS neuronal development
- Enhances wakefulness and alertness
- Enhances memory and learning capacity
- Required for normal emotional tone
- Increase speed and amplitude of peripheral nerve reflexes[7,10]

IV-Reproductive system:

- Required for normal follicular development and ovulation in the female
- Required for the normal maintenance of pregnancy
- Required for normal spermatogenesis in the male[7,10]

V-BONE GROWTH:

Thyroid hormones are important for optimal bone growth both in humans and rats. Three different possible mechanisms for stimulation of longitudinal bone growth have been demonstrated. Thyroid hormones have been shown to:

1- Stimulate GH secretion.
2- Thyroid hormones increased IGF-I mRNA in hypophysectomized rats and stimulated IGF-I production in perfused rat livers, suggesting that thyroid hormones increase the circulating levels of IGF-I.
3- A direct effect of thyroid hormones on the growth-plate has also been shown. In hypophysectomized rats, thyroid hormones stimulate longitudinal bone growth and are required for the formation of hypertrophic cells in normal rats. (11)

Regulation of T3 and T4 production

Thyroid hormone synthesis and secretion is regulated by two main mechanisms:

1- An "auto-regulation" mechanism,

Which reflects the available levels of iodine as low iodide levels increase iodine transport into follicular cells and high iodide levels decrease iodine transport into follicular cells. Thus, there is negative feedback regulation of iodide transport by iodide

2- Neuroendocrine Regulation of Thyroid Hormones:

Thyroid-stimulating hormone (TSH) is produced by thyrotroph cells of the anterior pituitary.

TSH is a glycoprotein hormone composed of two subunits; alpha subunit and beta subunit, which gives specificity of receptor binding and biological activity.

Effect of TSH on follicular cells of the thyroid:

Increases iodide transport into follicular cells, Increases production and iodination of thyroglobulin and Increases endocytosis of colloid from lumen into follicular cells.

TSH release is influenced by hypothalamic TRH, and by thyroid hormones themselves.

Thyroid hormones exert negative feedback on TSH release at the level of the anterior pituitary through: Inhibition of TSH synthesis and decrease in pituitary receptors for TRH.

Other Factors Regulating Thyroid Hormone Levels:

- Diet: a high carbohydrate diet increases T3 levels, resulting in increased metabolic rate (diet-induced thermogenesis).
- Low carbohydrate diets decrease T3 levels, resulting in decreased metabolic rate.
- Any condition that increases body energy requirements (*e.g.*, pregnancy, prolonged cold) stimulates hypothalamus TRH (12)

Thyroid gland disorders:

Thyroid disorders include hyperthyroidism (abnormally increased activity), hypothyroidism (abnormally decreased activity) thyroiditis and thyroid nodules, which are generally benign thyroid neoplasms, but may be malignancies. All these disorders may give rise to goiter, that is, an enlarged thyroid.

1- Hyperthyroidism:

The most common thyroid disorders that result in hyperthyroidism include:

- Graves' disease: Graves' disease is also known as 'Toxic Diffuse Goiter' and it is the most common cause of hyperthyroidism in the United States. Graves' disease is an auto immune disease in which the body's immune system starts producing an antibody called as the 'thyroid stimulating immunoglobulin' or TSI. These antibodies mimic the action of Thyroid Stimulating Hormone (TSH) and cause the thyroid to produce too much of thyroid hormones The cause of Graves' disease is thought to be related to many factors including genes, gender, stress, pregnancy, and possibly infections. Symptoms of Graves' disease include goiter, problems conceiving a child, lighter menstrual flow and less frequent periods, weight loss, frequent bowel movements, heart palpitations, thinning of hair, brittle hair, hand tremors, problems sleeping, heat insensitivity, increased sweating, eye changes (exophthalmos), and reddening and thickening of the skin on the shins and top of the feet (pretibial myxedema).[13]
- Toxic adenomas: A benign growth within the thyroid gland. It may be associated with excessive thyroid hormone secretion, this becomes more likely if the nodule is larger that 3 cm. When there is a single nodule that is independently producing thyroid hormones, it is called a functioning nodule. If there is more than one functioning nodule, the term toxic, multinodular goiter is used. Functioning nodules may be readily detected with a thyroid scan. [13,14]
- Thyroiditis: Inflammation of the thyroid gland may occur after a viral illness (subacute thyroiditis). This condition is association with a fever and a sore throat that is often painful on swallowing. The thyroid gland is also tender to touch. There may be generalized neck aches and pains. Inflammation of the gland with an accumulation of white blood cells known as lymphocytes (lymphocytic thyroiditis) may also occur. In both of these conditions, the inflammation leaves the thyroid gland "leaky," so that the amount of thyroid hormone entering the blood is increased. Lymphocytic thyroiditis is most common after a pregnancy and can actually occur in up to 8% of women after delivery. In these cases, the hyperthyroid phase can last from 4 to 12 weeks and is often followed by a hypothyroid (low thyroid output) phase that can last for up to 6 months. The majority of affected women return to a state of normal thyroid function. Thyroiditis can be diagnosed by a thyroid scan. [13,14]
- Cancer thyroid: Papillary carcinoma, Follicular carcinoma, Undifferentiated (anaplastic) carcinoma and metastatic tumors[13,14]
- Drug induced: Amiodarone, an anti-arrhythmic drug, is structurally similar to thyroxin and may cause either under- or over activity of the thyroid, interferon-alpha, Excess iodine, as may occur in people taking certain expectorants, or iodine-containing contrast agents for x-ray studies may cause hyperthyroidism. [18]
- Secondary Hyperthyroidsm:

1. TSH secreting pituitary adenoma.
2. Pituitary resistance to T3and T4.
3. Chorionicgonadotropin-secreting tumors.
4. Gestational thyrotoxicosis. [13,14]

Early symptoms of hyper thyroidism include: Tremors, Excessive sweating, Smooth velvety skin, Rapid heart rate, Enlarged thyroid gland, Puffiness around the eyes and staring look.
As the disease progresses, symptoms of hyperthyroidism are all related to an increased metabolic rate and may include:

- Irregular heart rhythms and heart failure
- "Thyroid storm" - high blood pressure, fever, and heart failure
- Mental changes, such as confusion and delirium[13,14]

2- Hypothyroidism:

Causes of hypothyroidism include:

- Hashimoto's thyroiditis: In this autoimmune disorder, the body attacks thyroid tissue. The tissue eventually dies and stops producing hormones.[13]
- Surgical removal of the thyroid gland: Removing all or a large portion of the thyroid gland can diminish or halt hormone production. [13]
- Radiation therapy: Radiation used to treat cancers of the head and neck can affect the thyroid gland and may lead to hypothyroidism. [13]
- Severe iodine deficiency: In some areas where there is an iodine deficiency in the diet, severe hypothyroidism can be seen in 5% to 15% of the population. Severe iodine deficiency is also seen in remote mountain areas[13]
- Drug induced: the use of lithium as a treatment for certain psychiatric conditions is an example of drug-induced hypothyroidism. Almost half of all people who take lithium may develop an enlarged thyroid, although less than a quarter of them will actually develop symptoms of hypothyroidism. Also the use of the iodine-containing drug (amiodarone) for heart arrhythmias. In addition, drugs used in treatment of hyperthyroidism (propylthiouracil) can also impair thyroid function and cause hypothyroidism. [18]

Typical symptoms of hypothyroidism are abnormal weight gain, tiredness, baldness, cold intolerance, and bradycardia. [15]

Negative feedback mechanisms result in growth of the thyroid gland when thyroid hormones are being produced in sufficiently low quantities, as a mean of increasing the thyroid output; however, when hypothyroidism is caused by iodine insufficiency, the thyroid is unable to produce T_3 and T_4 and as a result, the thyroid may continue to grow to form a non-toxic goiter. It is termed non-toxic as it does not produce toxic quantities of thyroid hormones, despite its size. [15,16]

The incidence of thyroid disorders is increasing all over the world. As many as 50% of people in the community have microscopic nodules, 3.5% have occult papillary carcinoma, 15% have palpable goiters, 10% demonstrate an abnormal

thyroid-stimulating hormone level, and 5% of women have overt hypothyroidism or hyperthyroidism[17]

These high incidence of thyroid disorders suggested that there are hidden factors of thyroid disorders. Exposure to certain toxic chemicals may be one of these factors. [17] Over the last several decades, evidence has begun to emerge suggesting that there may be a connection between occupational exposure to certain toxic substances and thyroid diseases, including cancer and autoimmune thyroid disorder. [18]

In 2005, researchers at the Institute of Epidemiology and Social Medicine in Greifswald, Germany published the results of a study that found a connection between exposure to occupational hazards and thyroid autoimmune disorders. In the research, it was found that workers whose jobs involved a risk of exposure to ionizing radiation were at higher risk of developing autoimmune thyroid disease. Especially female workers who reported a history of on-the-job exposure to ionizing radiation were at particularly high risk of developing signs of thyroid autoimmunity. The researchers also suggested that these results may be an indication that occupational exposure may be the "missing link" that explains the sharp increase in the prevalence of thyroid autoimmune disorders over the last several decades. [19]

Another study identified that occupational risk factors are associated with thyroid cancer. Like thyroid autoimmune disorder, the incidence of thyroid cancer cases have skyrocketed in recent years, prompting some scientists to surmise that environmental factors -- including exposure to dangerous substances in the workplace -- may be to blame. [18]

After analyzing the health data and work histories of a number of thyroid cancer patients, the researchers identified a number of risk factors that seemed to place workers at greater risk of developing the disease. Chief among these risk factors were occupational exposure to electromagnetic fields and industrial chemicals. [19]

Among the toxic substances that affect thyroid functions are perchlorate[20], thiocyanate[21], DDT[22] and lead. [23]

Perchlorate is a potent competitive inhibitor of the thyroid sodium-iodide symporter. Thus, it has been used to treat hyperthyroidism since the 1950s. At very high doses (70,000–300,000 ppb) the administration of potassium perchlorate was considered the standard of care in the United States, and remains the approved pharmacologic intervention for many countries. Perchlorate, in large amounts, interferes with iodine uptake into the thyroid gland. [20]

Thiocyanate [SCN-] is a complex anion which is a potent inhibitor of iodide transport. It is the detoxification product of cyanide and can easily be measured in body fluids. Consumption of naturally occurring goitrogens, certain environmental toxins and cigarette smoke can significantly increase SCN- concentrations to levels potentially capable of affecting the thyroid gland. Goiter endemics were reported to develop when the critical urinary iodine/ SCN- ratio decreases below 3 microg iodine per mg SCN-. Iodine

supplementation completely reverses the goitrogenic influence of SCN-. SCN- is also generated from cigarette smoking as a detoxifying product of cyanide. During the past two decades many reports dealt with the possible effects of cigarette smoking on thyroid hormone synthesis, thyroid gland size and thyroid autoimmunity including infiltrative ophtalmopathy of Graves' disease. (21)

Among many different pesticides, the thyroid-disrupting effects of dichlorodiphenyltrichloroethane (DDT) is the most studied. DDT exposure of birds decreased T4 or increased thyroid weight and reduced colloid content of the follicles. However, other studies found no measurable thyroid effects. Concentration of DDT correlated negatively to TT3 and free T3 in seals, whereas a study of sea-gulls showed no correlations with TSH. (22)

Lead

Lead is a chemical element in the carbon group with symbol Pb (from Latin: plumbum) and atomic number 82. Lead is a soft and malleable metal, which is regarded as a heavy and poor metal. Metallic lead has a bluish-white color after being freshly cut, but it soon tarnishes to a dull grayish color when exposed to air. Lead has a shiny chrome-silver luster when it is melted into a liquid. (24)

Forms of Lead:

Lead exists in both organic and inorganic forms.

Inorganic lead:

The lead compounds that don't contain carbon found in old paint, soil, and various products like cans, bright red and yellow paints is inorganic lead.(25,26)

Organic Lead

Leaded gasoline contained organic lead that contains carbon. However, since the elimination of lead from gasoline in the U.S. starting in 1976, exposure to organic lead is generally limited to an occupational context. However, organic lead can be more toxic than inorganic lead because the body more readily absorbs it. Potential exposures to organic lead should be taken very seriously. (25,26)

- **Routes of exposure:**

Lead can be absorbed through:

1- Ingestion into the gut: Lead paint is the major source of lead exposure for children. As lead paint deteriorates, it peels, is pulverized into dust and then enters the body through hand-to-mouth contact or through contaminated food or water. Ingesting certain home remedy medicines may also expose people to lead or lead compounds. Lead can be ingested through fruits and vegetables contaminated by high levels of lead in the soils they were grown in. Soil is contaminated through particulate accumulation from lead in pipes, lead paint and residual emissions from leaded gasoline.

2- Inhalation: especially for workers in lead-related occupations. Almost all inhaled lead is absorbed into the body, it's rate is 20–70% for ingested lead; children absorb more than adults.
3. Dermal contact: may be significant for a narrow category of people working with organic lead compounds, but is of little concern for general population. [27,28]

Lead-containing products

Lead can be found in products such as kohl, an ancient cosmetic from the Middle East, South Asia, and parts of Africa that has many names; and in some toys.[29] In 2007, millions of toys made in China were recalled from multiple countries owing to safety hazards including lead paint.[30] Vinyl mini-blinds, found especially in older housing, may contain lead.[31] Lead is commonly incorporated into herbal remedies such as Indian Ayurvedic preparations and remedies of Chinese origin.[32][48][52] There are also risks of elevated blood lead levels caused by folk remedies like *azarcon* and *greta*, which each contain about 95% lead and used to treat constipation.[48] Ingestion of metallic lead, such as small lead fishing lures, increases blood lead levels and can be fatal.[33][34][35][36] Ingestion of lead-contaminated food is also a threat. Ceramic glaze often contains lead, and dishes that have been improperly fired can leach the metal into food, potentially causing severe poisoning.[37] In some places, the solder in cans used for food contains lead.[52] When manufacturing medical instruments and hardware, solder containing lead may be present.[38] People who eat animals hunted with lead bullets may be at risk for lead exposure.[39] Bullets lodged in the body rarely cause significant levels of lead poisoning,[40][41] but bullets lodged in the joints are the exception, as they deteriorate and release lead into the body over time.[42]

In adults, occupational exposure is the main cause of lead poisoning. [43] Parents who are exposed to lead in the workplace can bring lead dust home on clothes or skin and expose their children.[54]People can be exposed when working in facilities that produce a variety of lead-containing products.

Industrial uses of lead:

Lead was one of the earliest metals discovered by humans. Due to its corrosion-resistive property, the Romans used it to make water pipes and for lining baths. Later, it was used to cover ship hulls. Around 4,000 years ago, the Chinese started using lead to forge coins. Moreover, lead was used for roofing and construction purposes because of its high fire and water-resistive properties. In ancient times, lead was also widely used in decorative objects. With the passage of time, the uses of lead have grown to a wider aspect. Lead, in one form or the other, is present all round us.

In Batteries

The most important use of lead is seen in the automobile industry in the form of batteries. [46]

In Ammunition

Lead is used for making bullets and shots for firearms. [44,52]

In Sailing Ballast

Due to its high density, weight-to-volume ratio, and resistance against corrosion, lead is used for the ballast keel of sailboats and scuba diving weight belts.[45]

As a Coloring Pigment

White lead, lead sulfate, and lead chromate are used as coloring elements in paints and ceramic glazes, notably in the colors red and yellow.[54]

As Soldering Material

Due to its low melting temperature and wide availability, lead, along with tin and other alloys, act as the most commonly used solder material for electronics.[45]

As an Anti-knock Agent

Tetraethyl lead is utilized as an anti-knock additive for aviation fuel in piston-driven aircraft. Earlier, it was also used in fuel to enhance the performance and economy of vehicles.[45]

In Sheathing and Insulation

Lead is commonly used as the most cost-effective stabilizer in polyvinyl chloride (PVC) plastic, which covers electrical cords. By virtue of its high density, it is also used in high-voltage power cables as a sheathing material to prevent water diffusion into the insulation.[45]

Radiation Shielding

Lead is used in aprons to shield patients during X-rays. It is also an effective metal against gamma radiation. [52]

In Roofing

Due to its water-resistive property, lead sheets are utilized in the construction industry for weathering, roofing and cladding, to prevent water penetration. [45]

In Semiconductors

Lead telluride, lead antimonide, and lead selenide are some of the lead-based semiconductors which are used in photovoltaic (solar energy) cells and infrared detectors. [44,45]

Fate of lead in the body:

In adults, about 35–40% of inhaled lead dust is deposited in the lungs, and about 95% of that goes into the bloodstream. [47] Of ingested inorganic lead, about 15% is absorbed, but this percentage is higher in children, pregnant women, and people with

deficiencies of calcium, zinc, or iron. [48] Children and infants may absorb about 50% of ingested lead. [49]

The main body compartments that store lead are the blood, soft tissues, and bone; the half-life of lead in these tissues is measured in weeks for blood, months for soft tissues, and years for bone.[48] Lead in the bones, teeth, hair, and nails is bound tightly and not available to other tissues, and is generally thought not to be harmful.[50] In adults, 94% of absorbed lead is deposited in the bones and teeth, but children only store 70% in this manner, a fact which may partially account for the more serious health effects on children.[51] The estimated half-life of lead in bone is 20 to 30 years, and bone can introduce lead into the bloodstream long after the initial exposure is gone.[52] The half-life of lead in the blood in men is about 40 days, but it may be longer in children and pregnant women, whose bones are undergoing remodeling, which allows the lead to be continuously re-introduced into the bloodstream.[51] Also, if lead exposure takes place over years, clearance is much slower, partly due to the re-release of lead from bone.[53] Many other tissues store lead, but those with the highest concentrations (other than blood, bone, and teeth) are the brain, spleen, kidneys, liver, and lungs.[54] It is removed from the body very slowly, mainly through urine.[55] Smaller amounts of lead are also eliminated through the feces, and very small amounts in hair, nails, and sweat.[56]

Mechanism of toxicity:

Lead and other heavy metals create reactive radicals which damage cell structures including DNA and cell membranes.[57] Lead also interferes with DNA transcription, enzymes that help in the synthesis of vitamin D, and enzymes that maintain the integrity of the cell membrane.[54] Anemia may result when the cell membranes of red blood cells become more fragile as the result of damage to their membranes.[58] Lead interferes with metabolism of bones and teeth [59] and alters the permeability of blood vessels and collagen synthesis [43]. Lead also interferes with the normal metabolism of calcium in cells and causes it to build up within them.[60]

The primary cause of lead's toxicity is its interference with a variety of enzymes because it binds to sulfhydryl groups found on many enzymes.[55] Part of lead's toxicity results from its ability to mimic other metals that take part in biological processes, which act as cofactors in many enzymatic reactions, displacing them at the enzymes on which they act.[54] Lead is able to bind to and interact with many of the same enzymes as these metals but, due to its differing chemistry, does not properly function as a cofactor, thus interfering with the enzyme's ability to catalyze its normal reaction or reactions. Among the essential metals with which lead interacts are calcium, iron, and zinc.[56]

Health effects of lead:

1-Acute poisoning:

1- Neurological signs: Pain, muscle weakness, paraesthesia, and, rarely, symptoms associated with encephalitis.[61]
2- Gastrointestinal problems: Abdominal pain, nausea, vomiting, diarrhea, ,constipation. astringency "dry mouth",a metallic taste and poor appetite.[62]

3- Absorption of large amounts of lead over a short time can cause shock due to loss of water from the gastrointestinal tract. (62)
4- Hemolysis due to acute poisoning can cause anemia and hemoglobinuria.(62)
5- kidney damage and decrease urine output.(62)

6- People who survive after acute poisoning often go on to present with symptoms of chronic poisoning.(62)

2- Chronic poisoning:

1- Children:

A fetus developing in the uterus of a woman who has elevated blood lead level is also susceptible to lead poisoning by intrauterine exposure, and is at greater risk of being born prematurely or with a low birth weight.(63)

Children are more at risk for lead poisoning because their smaller bodies are in a continuous state of growth and development.(64) Lead is absorbed at a faster rate compared to adults, and causes more physical harm than to older people. Furthermore, children, especially as they are learning to crawl and walk, are constantly on the floor and therefore more prone to ingesting and inhaling dust that is contaminated with lead.(65)

The classic signs and symptoms in children are loss of appetite, abdominal pain, vomiting, weight loss, constipation, anemia, kidney failure, irritability, lethargy, learning disabilities, and behavioral problems.(64) Slow development of normal childhood behaviors, such as talking and use of words, and permanent intellectual disability are both commonly seen.(63) Although less common, it is possible for fingernails to develop leukonychia striata if exposed to abnormally high lead concentrations.(66)

2- Adults:

Renal system

Kidney damage occurs with exposure to high levels of lead, and evidence suggests that lower levels can damage kidneys as well.(49) The toxic effect of lead causes nephropathy and may cause Fanconi syndrome, in which the proximal tubular function of the kidney is impaired. (50) Long-term exposure at levels lower than those that cause lead nephropathy have also been reported as nephrotoxic in patients from developed countries that had chronic kidney disease or were at risk because of hypertension or diabetes mellitus. (67) Lead poisoning inhibits excretion of urate and causes a predisposition for gout. (68)(69)(70)

Nervous system

Lead affects the peripheral nervous system (especially motor nerves) and the central nervous system.(54) Peripheral nervous system effects are more prominent in adults and central nervous system effects are more prominent in children.(74) Lead causes the axons of nerve cells to degenerate and lose their myelin coats.(54)

The brain is the organ most sensitive to lead exposure.(73) Lead is able to pass through the endothelial cells at the blood brain barrier because it can substitute for calcium

ions and be uptaken by Calcium-ATPase pumps.[75] Lead poisoning interferes with the normal development of a child's brain and nervous system; therefore children are at greater risk of lead neurotoxicity than adults are.[76] Lead exposure in young children has been linked to learning disabilities, [77] Increased blood lead level in children has been correlated with decreases in intelligence, nonverbal reasoning, short-term memory, attention, reading and arithmetic ability, fine motor skills, emotional regulation, and social engagement.[78]

High blood lead levels in adults are also associated with decreases in cognitive performance and with psychiatric symptoms such as depression and anxiety.[79]

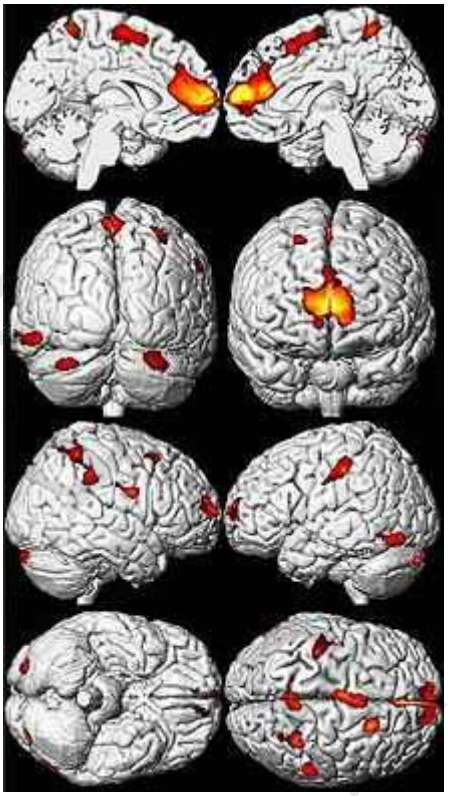

Figure (2): MRI picture of the brain of an adult who exposed to lead during childhood.

The brains of adults who were exposed to lead during childhood show decreased volume, especially in the prefrontal cortex, on MRI. Areas of volume loss are shown in color over a template of a normal brain.[73]

Immune system:

Lead may also be harmful to the developing immune system, causing production of excessive inflammatory proteins; this mechanism may mean that lead exposure is a risk factor for asthma in children. [59] Lead exposure has also been associated with a decrease in activity of immune cells such as polymorph nuclear leukocytes. [59]

Respiratory system:

Lead exposure in work environment can cause a higher frequency of respiratory symptoms. Pulmonary function tests values were also significantly reduced among lead exposed workers indicating a permanent change of respiratory system. [80]

Hematological disorders:

One of the main causes for the pathology of lead is that it interferes with the activity of the essential enzyme delta-aminolevulinic acid dehydratase which is important in the biosynthesis of heme, the cofactor found in hemoglobin.[52] Lead also inhibits the enzyme ferrochelatase, another enzyme involved in the formation of heme.[51,52,81] Ferrochelatase catalyzes the joining of protoporphyrin and Fe^{2+} to form heme.[51,52,54] Lead's interference with heme synthesis results in production of zinc protoporphyrin and the development of anemia.[82]

Cardiovascular system:

A positive association of lead exposure with blood pressure has been identified in numerous studies in different settings, including prospective studies and in relatively homogeneous socioeconomic status groups. Several studies have identified a dose–response relationship. The hypertensive effects of lead have been confirmed in experimental models. Beyond hypertension, studies in general populations have identified a positive association of lead exposure with clinical cardiovascular outcomes (cardiovascular, coronary heart disease, and stroke mortality; and peripheral arterial disease), but the number of studies is small. In some studies these associations were observed at blood lead levels < 5 μg/dL.[71,72,83]

Endocrine system:

Studies on the effects of lead on the endocrine system are mainly based on occupationally lead-exposed workers and experimental animal models. Although evidence is conflicting, it has been reported that accumulation of lead affects the majority of the endocrine glands.

1-The hypothalamic-pituitary axis

Lead causes blunted GH and FSH/LH responses to GHRH, and GnRH stimulation, respectively. Suppressed GH release has been reported, probably caused by reduced synthesis of GHRH, inhibition of GHRH release or reduced somatotrope responsiveness. Higher levels of PRL in lead intoxication have been also reported. High LH and FSH levels are usually associated to normal testosterone concentrations, whereas in long-term exposed individuals' low testosterone levels do not induce high LH and FSH concentrations. These findings suggest that lead initially causes some subclinical testicular damage, followed by hypothalamic or pituitary disturbance when longer periods of exposure take place. [84]

2- Reproductive functions:

Lead affects both the male and female reproductive systems. In men, when blood lead levels exceed 40μg/dL, sperm count is reduced and changes occur in volume of sperm, their motility, and their morphology.[49] A pregnant woman's elevated blood lead level can lead to miscarriage, prematurity, low birth weight, and problems with

development during childhood.[78] Lead is able to pass through the placenta and into breast milk, and blood lead levels in mothers and infants are usually similar.[54] A foetus may be poisoned in utero if lead from the mother's bones is subsequently mobilized by the changes in metabolism due to pregnancy; increased calcium intake in pregnancy may help mitigate this phenomenon.[85]

3-The adrenal glands:

In the parenchyma of adrenals histological and cytological changes are demonstrated, causing changes in plasma basal and stress-mediated corticosteroid concentrations and reduced cytosolic and nuclear glucocorticoid receptor binding.[84]

4- Calcitropic hormones:

Lead toxicity involves alterations on calcitropic hormones' homeostasis, which increase the risk of skeletal disorders. [84]

5-Thyroid gland:

Thyroid hormone kinetics are also affected. Central defect of the thyroid axis or an alteration in T4 metabolism or binding to proteins may be involved in derangements in thyroid hormone action. [84]Moreover, it has been suggested that the nonspecific symptoms of inorganic lead intoxication are related to the effects of the blood lead on thyroid function. [86]

Diagnosis of lead toxicity:

Diagnosis includes determining the clinical signs and the medical history, with inquiry about possible routes of exposure.[87] Clinical toxicologists, medical specialists in the area of poisoning, may be involved in diagnosis and treatment. The main tool in diagnosing and assessing the severity of lead poisoning is laboratory analysis of the blood lead level (BLL).[88]

The current reference range for acceptable blood lead concentrations in healthy persons without excessive exposure to environmental sources of lead is less than 5 µg/dL for children[89] and 10 µg/dL for adults.[92]Previous to 2012 the value for children was 10 (µg/dl).[91] and less than 25 µg/dL for adults. [90]

The current biological exposure index (a level that should not be exceeded) for lead-exposed workers in the U.S. is 30 µg/dL in a random blood specimen.

Blood lead concentrations in poisoning victims have ranged from 30->80 µg/dL in children exposed to lead paint in older houses, 77–104 µg/dL in persons working with pottery glazes, 90–137 µg/dL in individuals consuming contaminated herbal medicines, 109–139 µg/dL in indoor shooting range instructors and as high as 330 µg/dL in those drinking fruit juices from glazed earthenware containers. [93]

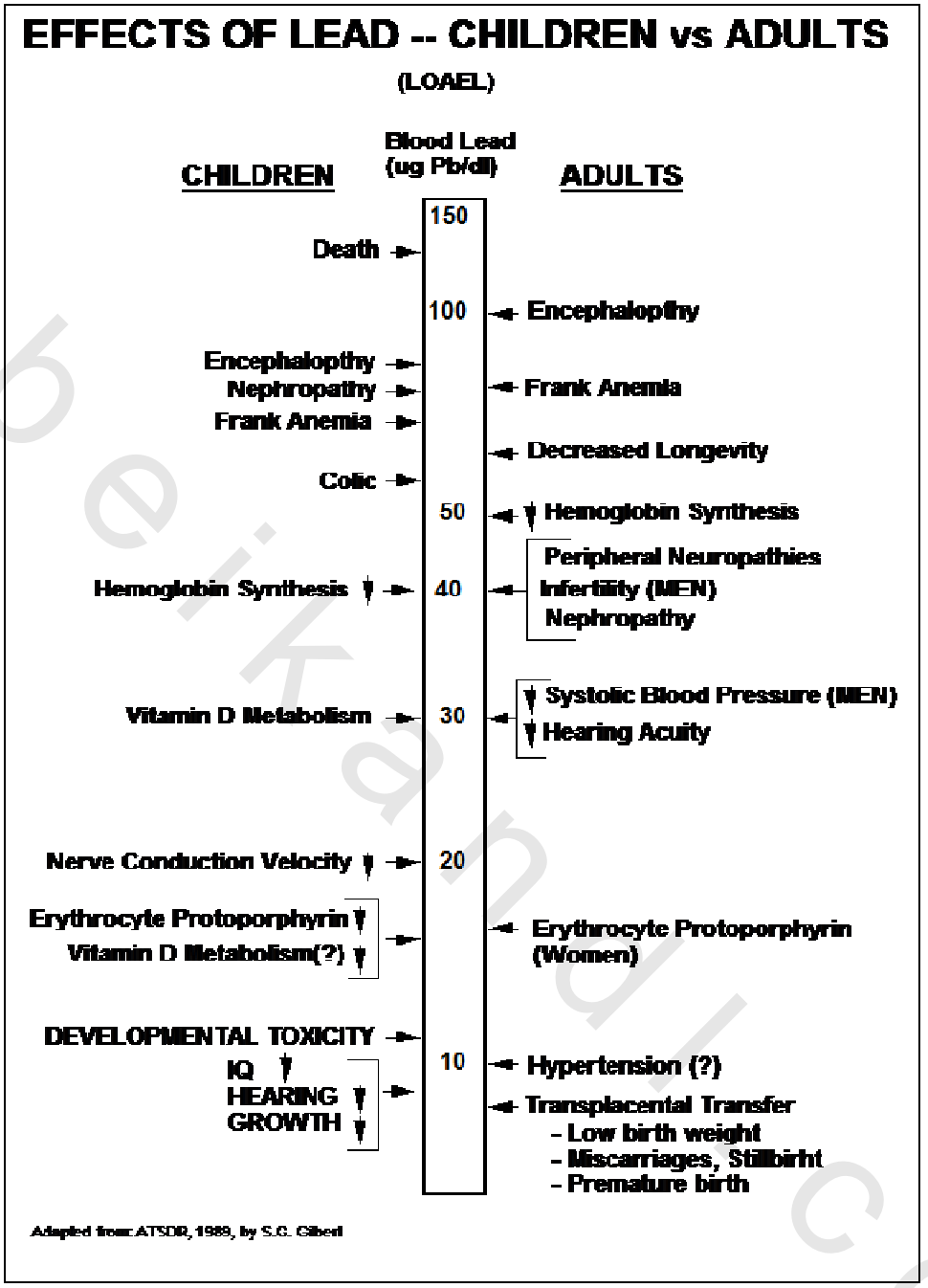

Figure 3. Effects of Blood Lead - Children vs. Adults. [94]

Prevention of lead induced toxicity

Preventive measures are preferred over the treatment regimens, considering the toxic effects of lead. This is due to the fact that once lead enters the body, it is almost impossible to remove it completely or to reverse its damaging effects on the body. A three-way measure as preliminary preventive approach towards lead toxicity was recommended. It includes Individual intervention, Preventive medicine strategy and Public health strategy. [29] Recommended steps by individuals to reduce the blood lead levels of children include increasing their

frequency of hand washing and their intake of calcium and iron, discouraging them from putting their hands to their mouths, vacuuming frequently, and eliminating the presence of lead-containing objects such as blinds and jewelers in the house. [95]

Preventive medicine strategy mainly aims at screening the blood levels of children that are at a high risk of lead exposure. If lead is detected in blood, medical intervention is carried out with the aim to control undesirable outcomes of poisoning and prevent further accumulation of lead. [88]

Public health strategy has a much larger sphere of influence and acts at a population level with a target to reduce the risk of lead exposure in habitable regions. Various preventive strategies have been suggested by the public health services for controlling lead. The most important of them include: prohibition of setting up industries dealing with lead close to habitable areas and completely banning the use of lead where appropriate replacement is available.[96]

Apart from the above mentioned preliminary strategies, nutrition also plays an important role in prevention of lead induced toxicity. Studies have shown that uptake of certain nutrients like mineral elements, flavonoids and vitamins can provide protection from the environmental lead as well as from the lead already present in the body. These nutrients play a pivotal role in restoring the imbalanced prooxidant/oxidant ratio that arises due to oxidative stress. Although the mechanism by which these nutrients restore the delicate prooxidant/oxidant ratio is still unclear, significant data are available suggesting a protective role of nutrients against lead poisoning. [97]

No available data about lead exposure in Egypt. Especially about workers in these fields and since thyroid disorders are common in our country we decided to be one of the first that study the relation between lead and thyroid.