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Causes of Hypothyroidism

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1. Introduction

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone or its effects on peripheral tissues. It usually is caused by an insufficient production of thyroid hormone by thyroid gland (primary hypothyroidism), but it could be also caused by inadequate secretion of either thyrotropin (ie. thyroid-stimulating hormone-TSH) from the pituitary gland (secondary hypothyroidism) or thyrotropin-releasing hormone (TRH) from the hypothalamus (tertiary hypothyroidism) (Bharaktiya, 2011).

Mixedema (previously a sinonim for hypothyroidism) is reffered to a skin and subcutaneous tissue changes in severe hypothyroid patients.

Hypothyroidism is a very common condition. It is estimated that about 2% of adult women and about 0,1-0,2% of men have clinical hypothyroidism, while the prevalence of subclinical disease is more frequent, up to 9% of adult population (Canaris et al., 2000; Danese et al., 1996 ; Vanderpump et al., 1995). The incidence however increases with age (Bharaktiya, 20111). The prevalence of hypothyroidism in newborns (congenital hypothyroidism) is about 1:3500 (LaFranchi, 1999).

2. Causes of hypothyroidism

The most common cause of hypothyroidism in adults may be summarised as follows (McPhee & Bauer, 1997):

1. Congenital:
   a. aplasia, hypoplasia, thyroid ectopy
   b. defect of hormones' synthesis and effects
2. Acquired:
   a. autoimmune thyroiditis
   b. iodide deficient diet
   c. thyroid ablation (as a consequence of radiation, surgical interventions etc)
3. Pharmacological: iodide, propylthiouracil, methimazole, lithium, thiocyanate etc

The most common cause of hypothyroidism in adults is autoimmune thyroid disease (AITD) where autoimmune thyroiditis (AT) is one of the entities. AT can begin suddenly or it can develop slowly over the years. The most frequent forms are Hashimoto's thyroiditis and atrophic thyroiditis (American Thyroid Association, 2008).

The second frequent cause is a thyroid ablation as a consequence of surgical removal of part or all of the gland in case of thyroid nodules, thyroid cancer, or Graves' disease. If part of the gland is left, it may be able to make enough thyroid hormone to keep blood levels normal. It is necessary that at least 90% of the gland be destroyed in order to develop hypothyroidism (American Thyroid Association, 2008).

Another cause of thyroid ablation is the radiation treatment during radiotherapy of neck for patients with Hodgkin's lymphoma, or cancers of the head or neck, or the use of radioactive iodine (I-131) in some patients with Graves' disease, nodular goiter, or thyroid cancer (American Thyroid Association, 2008).

Third most common are all causes of congenital hypothyroidism (in newborns), where one could find newborns without a thyroid (aplasia) or with only a partly formed one (hypoplasia). There are also babies with partial or all thyroid tissue in the wrong place (ectopic thyroid) or in some cases the thyroid is in place, but biosynthetic enzymes are defective (American Thyroid Association, 2008).

Although autoimmune thyroiditis is the most frequent cause of hypothyroidism, there are also a few forms of infective processes in thyroid. According to the duration, infective thyroiditis could be acute (generally caused by bacteria) or subacute (generally caused by viral agents). During the course of infective thyroiditis there could be a transient episode of thyroid hormones liberation in circulation from destroyed or damaged thyroid cells, called thyrotoxicosis. Subsequently if more than 90% of thyroid tissue is destroyed, hypothyroidism develops (McPhee & Bauer, 2007).

In some cases, medicines could be the cause of hypothyroidism, usually by interfering with normal thyroid hormone synthesis. Very often it is found in patients taking amiodarone, lithium, interferon alpha, and interleukin-2. These drugs are most likely to trigger hypothyroidism in patients who have a genetic tendency to develop AITD (American Thyroid Association, 2008). Potassium perchlorate could be used to treat thyrotoxicosis and hypothyroidism induced by amiodarone (Wolff, 1998). Perchlorate is a competitive inhibitor of the sodium-iodide symporter (NIS) that can suppress T3 and T4 production. Also, the drugs used for the hyperthyroidism treatment such as methimazole and propylthiouracil, could cause hypothyroidism.

In 1998 it is estimated that about one third of world's population lived in iodine-deficient areas, primarily in Africa, Southeast and Central Asia, but also in some European countries (like Germany, Belgium, France and Italy) (Dunn, 1996). Since iodine is the essential factor for thyroid hormone synthesis and it is concentrated in thyroid, any disequilibrium (too much or too little) in circulating iodine levels could cause or worsen hypothyroidism. Since more than 90% of dietary iodine is excreted in the urine, the World Health Organization (WHO) has determined 100mcg/L of urinary iodine as cut-off level for iodine deficiency (WHO, UNICEF & ICCID, 2001). In areas of the world with very low iodine intake in the

diet (like India, Chile, Ecuador, Himalayas), severe hypothyroidism can be seen in 5% to 15% of the population (Mathur, 2011).

If the pituitary or hypothalamus are damaged by a tumor, radiation, or surgery, hypothyroidism could be developed (secondary or tertiary hypothyroidism, respectively), characterized by diminished both, TSH and thyroid hormone levels.

Finally, in some cases the deposit of abnormal substances in the thyroid, could be the cause of hypothyroidism. For example, in the course of amyloidosis there can be deposit of amyloid protein, in the course of sarcoidosis there can form granulomas, and in the course of hemochromatosis there can be deposit iron (American Thyroid Association, 2008)

3. Pathogenesis of autoimmune thyroid disease (AITD)

3.1 The role of genetic factors in the development of AITD

It is generally believed that AITD is a complex of several entities that could overlap: Hashimoto's thyroiditis (HT), Graves' disease (GD) and orbitopathy. The majority of autoimmune endocrinopathies are inherited as complex genetic traits, with multiple genetic and environmental factors interactions which confer susceptibility to such disorders. The genetic factors remain largely unknown, with the exception of the human leukocyte antigen (HLA). It is known that AITD are more frequent in families with HLA DR3 and DR5 HLA alleles. Predominantly involved are women. Indeed, HT is 5 to 10 times more common in women than in men. Since the basis for autoimmune diseases may have a common origin, it is possible that patients with HT or their first degree relatives, have one or more other autoimmune diseases such as type 1 diabetes mellitus or pernicious anemia (with antibodies against gastric parietal cells or B12) (Mathur, 2011).

In recent years however, considerable efforts have been made to discover other genetic factors responsible for autoimmune endocrinopathies (Vaidya & Pearce, 2004). There are several studies confirming that genetic polymorphism of the cytotoxic T lymphocyte antigen (CTLA)-4 alleles on 2q33 chromosome have been associated with HT (Awata et al., 1998; Donner et al., 1997; Nithiyananthan et al., 2002; Tomoyose et al., 2002). CTLA-4 is a co-stimulatory molecule expressed on the surface of activated T cells (Brunet et al., 1987). CTLA-4 (49) A/G allele was significantly more frequent in the group of HT patients compared to the healthy controls. Additionally, linkage and association of CTLA-4 with the presence of thyroid antibodies have also been reported (Tomer et al., 2001; Zaletel et al., 2002).

3.2 Autoimmune mechanisms

The thyroid is a major target for autoimmune disease, as exemplified by autoimmune thyroiditis (which include HT type 1 and 2, and atrophic thyroiditis), and GD with opposite clinical outcomes. Both diseases, but particularly HT, are characterized by lymphocytic infiltration of the gland which can result in tissue destruction, fibrosis and hypothyroidism. The follicular spaces shrink and colloid is absent or sparse. Fibrosis may be completely absent or present in degrees ranging from slight to moderate. Heuer and coll. (Bernet et al., 1996; Heuer et al., 1996) found increased expression of IFN-gamma, IL-2 and CD25 positive T cells in the thyroid specimens of patients with HT.

Although the two disorders, HT and GD, have striking differences in clinical symptoms, they share the same histopathological features: lymphocytic infiltration and aberrant expression of HLA class II molecules on thyrocytes (Bernet et al., 1996). It is possible that HT and GD are caused by a similar immunologic dysfunction because similar autoantibodies (Abs) have been found in these patients.

The cause of the autoimmune process is probably a combination of an inherited tendency and an as yet unknown trigger (American Thyroid Association, 2008). Previous studies have shown that HLA class II–expressing thyrocytes could stimulate the proliferation of autologous T cells grown from thyroid glands during autoimmune diseases (Dayan et al., 1991; Londei et al., 1984; Weetman et al., 1986). Local up-regulation of the antigen-presenting function on thyrocytes may be an early event in the development of AITD (Dayan et al., 1991). Autoantigen presentation by thyrocytes is more efficient than by professional antigen-presenting cells (APC), because the thyroid autoantigens thyroid peroxidase and thyrotropin (TSH) receptor are membrane proteins. These proteins can be recycled and presented by class II molecules, and the effective concentration of these antigens on thyroid epithelial cells may be higher than when picked up by other antigen-presenting cells (Feldmann et al., 1992). However, lack of expression of costimulators such as B7.1 (CD80) or B7.2 (CD86) by thyrocytes undermines their ability to present antigens. Instead, class II–expressing thyrocytes may induce tolerance in autoreactive CD4+T cells (Matsuoka et al., 1996).

On the other hand, increased expression of intercellular adhesion molecule-1 (ICAM-1) has been shown present in specimens from patients with HT, while expression was less or absent in GD (Bagnasco et al., 1991; Ciampolillo et al., 1993; Pesce et al., 2002; Weetman et al., 1990). ICAM-1 is a member of the Ig gene superfamily and present on the surface of various cell types, serves as a ligand for lymphocyte function associated antigen-1 (LFA-1), and can be induced by various stimuli, such as cytokines (IL-1, tumor necrosis factor [TNF]-alpha, interferon [IFN]-gamma), hormones, cellular stresses (H_2O_2), and other environmental factors (Roebuck & Finnegan, 1999). Upon up-regulation it promotes cell–cell interactions, providing intense signals to the immune system that cause the T cells to home in on the inflamed site (Bonita et al., 2002).

An earlier investigation had found that elevated (rather than reduced) plasma levels of soluble CTLA-4 (sCTLA-4) protein were more frequent in patients with AITD than in healthy controls (Oaks & Hallett, 2000). CTLA-4 molecule, together with CD28 co-stimulatory molecule (both expressed on the T cell surface), plays a critical role in the T cell response to antigen presentation. For T cell activation two signals are needed: TCR engages antigen (the first signal), which is bound to a HLA class II molecule on the surface of an APC, and a co-stimulatory signal, that could be stimulatory or inhibitory. This stimulatory second signal is provided mainly by the interaction of CD28 with its ligands, B7.1 (CD80) and B7.2 (CD86) on APC. CTLA-4 also binds to the same B7 ligands (CD80 and CD86) but it delivers inhibitory signals to T-cell activation (Walunas et al., 1994). In the absence of a stimulatory second signal, the antigen–TCR engagement is ineffective, and causes functional inactivation of the T cell (anergy) or induces apoptosis of the cell (Alegre et al., 2001).

Soluble CTLA4 molecules (sCTLA4), more frequently found in AITD patients, could compete with membrane-bound CTLA-4 for CD80 / CD86-binding sites and cause a

reduction of inhibitory signaling (Vaida & Pearce, 2004). Thus, autoreactive T cells will become activated leading to autoimmune process. The altered levels of sCTLA-4 could lead to either blockade of available B7 ligands, leading to a decreased stimulatory signal (if sCTLA-4 is increased), or to an inability of membranous CTLA-4 to bind the B7 ligand, leading to subsequently less inhibitory signal (if sCTLA-4 is decreased).

3.3 The possible role of iodide excess on thyroid mild inflammation and the development of hypothyroidism

Many epidemiological studies have demonstrated the toxic effects of iodide excess on thyroid function. In one study, about 10% of European patients receiving 0.5 mg of iodide per day for 6 months developed lymphocytic infiltration of the thyroid gland, accompanied by hypothyroidism or less often hyperthyroidism. Both the infiltration and the hypofunction were reversible upon discontinuation of iodide (Kahaly et al., 1998). The thyroid response to excess iodide is known as thyroid autoregulation. Most commonly, studies that examined the effects of toxic doses of iodide were usually performed in Fisher's rat thyroid low-serum-5 (FRTL-5) cells, which can synthesize and secrete thyroglobulin (Tg), absorb and transport iodide, and produce thyroid peroxidase (Ambesi-Impiombato et al., 1980). Although iodide doses over 10 mM caused toxic effects on the thyroid gland in vivo (Li & Boyages, 1994), higher concentrations of iodide were needed in order to influence cell proliferation (Becks et al., 1987; Eng et al., 2001; Smerdely et al., 1993) or even to induce apoptosis (Smerdely et al., 1993; Vitale et al., 2000) in cell culture.

Possible sources of excess iodide for humans are: amiodarone, povidone-iodine, iodinated radiographic contrast media, Lugol's 5% solution (used as 0,1-0,3ml for the treatment of simple goiter, equivalent of 12,5-37,5 mg of iodine) (Gennaro, 1995), dry or powdered algae (in many vitamin-mineral supplements and preparations for weight-loosing programs and herbal products).

The U.S. recommended daily intake (RDI) for dietary iodine is 150 mcg for adults, 220 mcg for pregnant women, and 270 mcg during lactation (Surks et al., 2004). The safe upper limit has been set at 1,000 mcg (1 mg) as a result of studies assessing TSH levels with supplementation. Iodine intake over 1 mg daily could potentially contribute to an underlying thyroid pathology-AITD, or even could exacerbate nodularities in euthyroid individuals in those taking over 20 mg of iodide (Burgi et al., 2001; Dunn et al., 1998; Robison et al., 1998). Population studies have shown that an excess of iodine intake may increase the prevalence of autoimmune thyroiditis (HT and atrophic thyroiditis) in animals and humans, increasing the risk of clinically evident hypothyroidism (Teng et al., 2006).

Iodide excess could influence thyroid cell growth and immunological profile. It is known that Lugol's solution given a couple of days before surgery in GD patients reduced HLA class I and II mRNA expression in thyroid cells in vivo and in vitro (Schuppert et al., 1996). It has also been reported that ICAM-1 mRNA was doubled in suspensions of isolated human thyroid follicles incubated with 10 mM sodium iodide (NaI) (Yamazaki et al., 2003). Furthermore, iodide excess did not change Tg level in FRTL-5 cells (Pregliasco et al., 1996), but it inhibited iodine organification (Davies et al., 1989), thyroid hormone secretion (Sato et al., 1990), and

cAMP production and secretion (Miyazaki et al., 1999) in isolated human thyroid follicles. Recently, it was reported (Kostic et al., 2009) that iodide excess inhibited human primary thyroid cell proliferation and gradually increased ICAM-1 on cell surface. In the presence of low-dose IFN-gamma, KI additionally augmented ICAM-1 expression, and such effect could induce lymphocytic infiltration in the thyroid gland and secretion of proinflammatory cytokines. Decreased Tg production in the presence of KI excess and IFN-gamma could explain the development of hypothyroidism after iodide dietary addition in patients that already have lymphocytic infiltration and/or mild inflammation in the thyroid gland.

Among the subjects exposed to iodine supplementation for the prevention of iodine deficiency or fed diet with high iodine intake, besides a few cases of focal and reversible lymphocyte infiltration of the thyroid, severe cases of hypothyroidism, not reversed by the suspension of iodine administration, with severe lymphocyte infiltration and parenchymal destruction have been described.

Various animal strains genetically susceptible to autoimmune thyroiditis have been described, such as Cornell and obese strain (OS) chickens, BB/Worcester and Buffalo rats, and diabetic non-obese mice NOD.H-2h4.

NOD mice expressing the H-2Jg7 allele of MHC class II, are genetically predisposed to develop type I diabetes and other autoimmune diseases, such as spontaneous autoimmune thyroiditis, which appears with low incidence. On the contrary, transgenic mice NOD.H-2h4, expressing the H-2Ak allele on the NOD background, do not develop diabetes but develop, with higher frequency, a spontaneous autoimmune thyroiditis (SAT). Moreover, as in BB/Worcester rats, SAT is increased by the addition of iodide in the drinking water. In these animals, deletion of IFN-gamma is associated with a strong reduction of anti-TG antibodies and of thyroid infiltration with B, T and plasma cells.

High iodide doses transiently inhibit Tg iodination by thyroperoxidase (TPO) (Wolff-Chaikoff effect). This is because, at high iodide to Tg ratios (mM to microM), iodide peroxidation to molecular iodine (I2) by TPO prevails over iodination of tyrosyl residues of Tg (Km 6 x 10-3M and 8 x 10-5, respectively). The iodination of tyrosyl residues leads to the production of one mole of OH- ions per mole of tyrosyl residue formed, whereas the peroxidation of iodide to I2 leads to the formation of two moles of OH- ions per mole of I2 produced. Hydrogen peroxide (H2O2), produced by the NADPH-oxidase of the apical membrane of thyroid epithelial cells (TECs), is the limiting electron acceptor in the TPO-catalized reactions. Its production leads to the production of superoxide anion (O2-) as an intermediate. Excess I- ions inhibit both the enzymatic degradation of H2O2 by TPO and non enzymatic oxidation of H2O2 by I2.

However, in dog thyroid slices, iodide excess seems to inhibit H2O2 generation, through the formation of oxidized iodine compounds. Thus, excess iodide inhibits thyroid functions by multiple mechanisms, which include, besides true anion effects, the oxidative modification and/or iodination of important enzymes, the inhibitory effect of the products of the iodination or peroxidation of polyunsaturated fatty acid, which, in turn, can act as free radicals. An imbalanced production of free radicals and/or dysfunctions of enzymes involved in their detoxication, such as glutathione peroxidase, catalase and superoxide dismutase, have been associated with aging, neurodegenerative diseases, cancer and autoimmune diseases.

At persistingly high doses, iodide can determine thyroid involution. Preliminary studies showed the accumulation of lipid peroxidation products, with necrosis and inflammation of murine and human thyroid exposed to toxic iodide doses (23, 24). More recently, it has been demonstrated that thyroid cell apoptosis is the prevalent cause of TEC death in thyroid iodide-dependent involution in goitrogen-treated rats. However, TEC necrosis induced by iodide excess has been indicated as a preliminary step in a model of the development of autoimmune thyroiditis.

Iodide excess induces apoptosis in thyroid cultured cells, through a p53-independent oxidative mechanism. Diminished levels of bcl-2 gene expression and increased levels of bax gene expression have been found in the brain and the thyroid of guinea-pigs exposed to excess iodide. In OS chickens, the TEC damage, preceding the development of autoimmune thyroiditis, is mediated by the production of ROS. H2O2 induces apoptosis in cultured pig thyroid cells.

Cellular products of thyroid iodinated lipids include arachidonic acid derivatives, such as 6-iodo-5-hydroxy-8,11,14-eicosatrienoic acid and 14-iodo-15-hydroxy-5,8,11 eicosatrienoic acid (I-OH-A), and their respective delta and omega iodolactones (IL-d and IL-ω). IL-ω inhibits iodide organification in dog thyroid slices, by inhibiting H2O2 production (31). IL-ω and IL-d inhibit the proliferation of rat FRTL-5 cultured thyroid cells and cause the involution of thyroid in goitrogen-treated rats. IL-d inhibits inositol-3-phosphate production and EGF and beta FGF signal transduction in human and pig thyroid cells. 2-iodoesadecanal (2-IHDA), produced from the rat thyroid exposed to iodide, inhibits adenylate cyclase activity and cAMP-stimulated activities of NADPH oxidase and TPO. The non-iodinated products derived from arachidonic acid oxidation induce apoptosis in smooth muscle vessel cells. 4-Hydroxynonenal, the most important product of arachidonic acid oxidation, induces apoptosis in a number of cell types, including endotelial cells. As with iodide in the thyroid, it can do so through a p53-idependent mechanism

The current vision of the pathogenesis of autoimmunity favors the triggering role of the exposure of cryptic self epitopes. It has been demonstrated that a hormonogenic carboxy-terminal fragment of Tg , beginning at residue 2384, was released during enzymatic iodination or metal-catalyzed oxidation of Tg in vitro, as well as during oxidative stress in vivo. Because it was recognized by autoantibodies of patients affected with autoimmune thyroid disease (AITD), it was suggested that oxidative proteolysis can expose immunopathogenetic cryptic epitopes.

In vitro iodination of murine Tg , used to immunize susceptible rats, determined the transformation of a T-cell epitope (residues 2495-2511) from cryptic to immunodominant in vivo. It is well known that the iodination of Tg with TPO in vitro is accompanied by the formation of proteolytic peptides, whose amount is related to their iodine and hormone content.

Thyroid autoantigens could be also transferred to thyroidal dendritic cells (DC) and cross-presented to T lymphocytes. Apoptosis of TECs, induced by iodide excess, could play a pivotal role in this process. Apoptotic cells are a preferred source of antigens for cross-presentation, being captured by DCs via alpha(v)-beta5 or alpha(v)-beta 5 integrins and CD36. Although DC can cross-present both apoptotic and necrotic cells, MHC class II-restricted presentation can occur with both of them, while MHC class I-restricted

presentation can only occur with apoptotic cells. Moreover, even if immature DCs phagocytose efficiently both apoptotic and necrotic cells, the exposition to the latter is necessary in order to induce their maturation to APC, with optimal abilities of antigen processing and presentation and elevate levels of CD38, DC-LAMP, and CD40 and CD86 co-stimulatory molecules. Moreover, DC can cross-activate CTL by the internalization of heat shock proteins gp96 and Hsp70 loaded with antigenic peptides. Finally, the processing and the class II-restricted presentation are increased by receptor-mediated internalization of mannosylated antigens, such as Tg.

3.4 Other cell stressors that could induce hypothyroidism

It has been shown that human primary thyroid cells increase HLA-DR surface expression in response to a variety of cell stressors, such as IFN-gamma (Montani et al., 1998; Otten et al., 1998; Wu et al., 1999) and ionizing radiations (Czirjak et al., 1990) or transiently modify HLA-DR expression in vitro in the presence of iodide excess (Kostic et al., 2009). Recently, Kostic et al. (Kostic et al., 2010) showed that HLA-DR expression was also transiently increased 24 hours after UVC treatment of human primary thyroid cells in vitro, and subsequently returned to normal level 48 h after irradiation. This local up-regulation of antigen presenting function on thyrocytes in vivo could be sustained by a local inflammatory network (formed by cytokines and other cells of the immune system) and it may be an early event in the development of AITD (Botazzo et al., 1983; Liu et al., 2008).

Another consequence of UVC as physical mutagen is a cell cycle arrest or apoptosis induction in human primary thyroid cells. As already mentioned, the local up-regulation of HLA-DR by thyrocytes together with the expression of proteins from apoptotic cells may represent an early event in the development of AITD (Botazzo et al., 1983).

The model for the cellular response of human thyroid cells after UVC irradiation (Kostic et al., 2010) suggested that UV induced dimers lead to activation of p53 that is in turn able to induce G0 / G1 cell cycle arrest in order to repair DNA damage. Cells that are able to repair damaged DNA or that do not have a large DNA damage enter S phase of the cell cycle, but secondary lesions generated during replication, induce apoptosis. The cells that are severely damaged after UVC irradiation, diminish Bcl-2 expression in the mitochondria and start apoptosis.

It has also been shown that in microgravity conditions the thyroid cells FRTL5 in culture do not respond to TSH treatment and present an irregular shape with condensed chromatin, a modification of the cell membrane with shedding of the TSH-receptor in the culture medium, and an increase of sphingomyelin-synthase and bax proteins. It is possible that microgravity induces a rearrangement of specific sections of the cell membrane, which act as platforms for molecular receptors, thus influencing thyroid cell function in astronauts during space missions.

It has been recently reported that FTRL-5 cells cultured in the presence or absence of TSH in the International Space Mission during the Eneide and Experia missions presented a similar cell growth pattern, which indicates an absence of response to TSH in space (Albi et al., 2010). It is difficult to establish whether this modification that occurs in space is due to cosmic radiation or microgravity.

It was previously reported that simulated weightlessness changed the cytoskeleton of normal thyroid cells (Infanger et al., 2004), increased the extracellular matrix proteins (Infanger et al., 2006), reduced thyroglobulin, FT3 and FT4 secretion, (Grimm et al., 2002), and induced apoptosis (Kossmehl et al., 2002, Grimm et al., 2002) of thyroid carcinoma cells. These data were supported by exposing mitochondria-rich thyroid carcinoma cells and normal thyroid cells to simulated microgravity conditions and obtaining apoptotic cells (Kossmehl et al., 2003). We reported for the first time the modifications of thyroid cells under real microgravity conditions.

We have shown that, in microgravity, the FRTL5 cells appeared aggregated and presented chromatin condensation, the TSH-induced cAMP production was significantly attenuated, and the TSHR was increased about 4.4 fold in the culture medium. At Earth's gravity, the TSHR was unaltered, and the cells responded to TSH treatment with normally high levels of cAMP production (Albi et al., 2011).

It is possible that the loss of TSHR from the cells in microgravity was due to the disorganization of microdomains within the cell membrane, depending on Sphingomyelin and Cholesterol incorporation from the culture medium that yielded a more rigid membrane structure. These data were consistent with the observation that a medium lacking TSH caused cessation of FRTL-5 cell proliferation due to the decrease in membrane lipid fluidity, which in turn was caused by an absolute increase of membrane cholesterol.

It has been shown that microgravity induced the FRTL5 cells treated with TSH to release Cholesterol and Sphingomyelin to the culture medium probably by modifying the microdomain structure (Albi et al., 2011). The lower amount of TSHR in the culture medium after TSH stimulation with respect to the TSH- samples may have been due to the fact that raft-TSHR complexes are regulated by TSH, which stimulates the formation of monomers and allows their rapid exit from the rafts (Latif et al., 2003). Therefore, the modification of lipid rafts consequent to the removal of Cholesterol and Sphingomyelin may have been preceded by a transfer of the receptor, which would explain the reduction but not the absence of the cAMP response. The disorganization of microdomains in microgravity was confirmed by the presence of caveolin 1 in the pellet obtained after fixation, which was absent in the samples maintained in Earth's gravity.

4. Types of AITD

The types of AITD may be summarised as follows:

- Type 1 (Thyroiditis chronica Hashimoto type 1):
  - euthyroidism with anti-TPO Abs and
  - 1A: with goiter;
  - 1B: without goiter
- Type 2 (Thyroiditis chronica Hashimoto type 2):
  - hypothyroidism with anti-TPO Abs and
  - 2A with goiter; 2B without goiter;
  - 2C transitory forms (postpartal hypothyroidism, Hashitoxicosis)
- Type 3 (Morbus Graves):
  - 3A hyperthyroidism with

- stimulating anti-TSH R Abs;
- anti-TPO Abs and anti-Tg Abs +/-
- 3B Euthyroidism with supressed TSH and anti-TSH R Abs
- 3C Hypothyroidism. Orbitopathy and anti-TPO Abs +/–

The Abs present in the sera of patients with AITD are only the witnesses of autoimmune destruction or activation of thyroid gland.

The most frequent in HT are Abs against thyroperoxidase (anti-TPO), Abs associated with euthyroidism (HT type 1) or hypothyroidism (HT type 2) and accompanied or not by goiter. On the other hand, in GD (AITD type 3) Abs against Tg (anti-Tg Abs) in AITD type 3A, and stimulating or inhibiting Abs against TSH receptor (anti-TSHR Abs) may also be found.

According to the prevalence of stimulating or blocking anti-TSHR Abs, GD patients could develop hyperthyroidism (stimulating anti-TSHR Abs), hypothyroidism (inhibiting anti-TSHR Abs) or be euthyroid (GD type 3B).

Of great interest is the relationship between Interferon and Autoimmune Thyroid Disease. Three different types of thyroid dysfunction associated with IFN treatment have been reported: (1) autoimmune (often subclinical) hypothyroidism; (2) destructive thyroiditis; and (3) Graves' hyperthyroidism.

These abnormalities can occur at any time during IFN therapy, from as early as 4 weeks until as late as 23 months after initiation, and there is no clear difference between the three types, with a median date of onset of 17 weeks after start of IFN treatment. Pooling of several studies shows that hypothyroidism seems to be more frequent than thyrotoxicosis.

The majority of patients with hypothyroidism also have TPO antibodies (87%), indicating the autoimmune nature of this event. According to most studies hypothyroidism can be transient, subsiding after discontinuation of IFN. In a large Italian survey, hypothyroidism was, however, permanent in 59% of the patients. A similar result was found in the review of the literature (Koh et al.), which showed that 56% of the patients had permanent hypothyroidism. In a recent long-term follow-up study, it was found (Carella et al.) that 10 of 36 (28%) TPO antibody-positive patients lost their antibodies at 6 years after discontinuation. On the other hand, 26 patients remained antibody-positive at that time, and subclinical hypothyroidism was detected in seven of them

5. Conclusion

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone. It usually is a primary process in which the thyroid gland produces insufficient amounts of thyroid hormone. It can also be secondary—that is, lack of thyroid hormone secretion due to inadequate secretion of either thyrotropin (ie, thyroid-stimulating hormone [TSH]) from the pituitary gland or thyrotropin-releasing hormone (TRH) from the hypothalamus (secondary or tertiary hypothyroidism). The patient's presentation may vary from asymptomatic to, rarely, coma with multisystem organ failure (myxedema coma).

Localized disease of the thyroid gland that results in decreased thyroid hormone production is the most common cause of hypothyroidism.

The most common cause of hypothyroidism in adults is autoimmune thyroid disease (AITD. The second frequent cause is a thyroid ablation as a consequence of surgical removal of part or all of the gland. Third most common are all causes of congenital hypothyroidism (in newborns). There are also a few forms of infective processes in thyroid.

In some cases, medicines could be the cause of hypothyroidism, usually by interfering with normal thyroid hormone synthesis.

Because all metabolically active cells require thyroid hormone, deficiency of the hormone has a wide range of effects. Systemic effects are due to either derangements in metabolic processes or direct effects by myxedematous infiltration (ie, accumulation of glucosaminoglycans in the tissues).

The myxedematous changes in the heart result in decreased contractility, cardiac enlargement, pericardial effusion, decreased pulse, and decreased cardiac output. In the GI tract, achlorhydria and decreased intestinal transit with gastric stasis can occur. Delayed puberty, anovulation, menstrual irregularities, and infertility are common. Decreased thyroid hormone effect can cause increased levels of total cholesterol and low-density lipoprotein (LDL) cholesterol and a possible change in high-density lipoprotein (HDL) cholesterol due to a change in metabolic clearance. In addition, hypothyroidism may result in an increase in insulin resistance.

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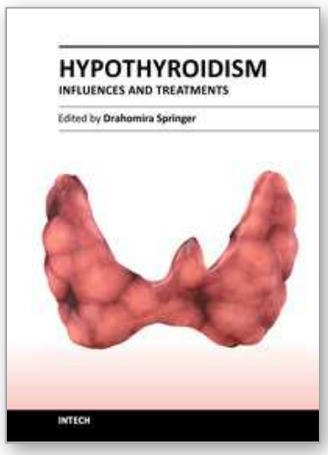
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Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

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