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The Immune System which Adversely Alter Thyroid Functions: A Review on the Concept of Autoimmunity

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Abstract: The immune system protect individual from many pathogens exists within our environment and in human body, by destroying them through molecular and cellular mechanism of B and T cells of immune system. Autoimmunity is an adverse relation of immune system against non-foreign substances leaving behind either alters the normal function or destroying the tissue involved. Autoimmunity occur in genetically predispose persons with familial connections. The autoimmunity to the thyroid gland mainly consists of Hashimoto thyroiditis and Grave's disease, the two end of spectrum in thyroid function of hypo and hyperactivity, respectively. The thyroid stimulating hormone receptor, thyroglobuline, enzymes of thyroid hormones synthesis are targeted by autoantibodies and cell-mediated reactions. The aim of this review is to explore the studies reported on the autoimmunity to the thyroid gland.

Key words: Immune system, autoimmunity, thyroid gland, Hashimoto disease, Graves disease

INTRODUCTION

The immune system play an important role in destroying many human pathogens existed in our environment and within the human body, otherwise these pathogen causes pathological damages, which hurt the various organism within the body. The immune system does its responsibility through the two mechanisms which are called innate and adaptive immunity. In practice the innate immune system face antigen first and the various pathogens are meeting the innate immune system. Prior to face adaptive immunity. Within the body when the adaptive immune system is activated through a pathogen the latter, antigen mostly is destroyed through a complex reactions which happen within the immune system on meeting an antigen (Jiang and Chess, 2006; Nelson, 2004; Kroneberg et al., 1986).

The above mentioned two systems do their function through many biochemical molecules and different cells existed in the immune systems the soluble molecules are lysozyme, complement, acute phase proteins, interferon and different antibody and the participated cells immune systems are phagocytes, natural killer cells and T-lymphocytes respectively. On condition an antigen enter the first line of barrier the body which is the epithelial surface of various organs, the phagocyte cells encounter the antigens and subsequently the pathogen can be destroyed, through a complex reaction within the immune system (Schwarz and Bhandoola, 2006).

The cells within the immune system contains of lymphoid and myeloid sub-division producing lymphocytes and phagocytes. The lymphocytes also contain B and T-cells. The T and B come from Thymus and Bone marrow respectively and either of B and T cells have their own specific antigen receptor and on binding antigen to these receptors, cellular activation occur within the immune system, to destroy the encountering antigens, with the coordination exist between T and B cells of immune system (Weigle, 1975; Li et al., 2006).

Autoimmunity: Also it is absolutely clear the immune deficiency in human leave the individual defenseless against many antigen present in our environment which can be a topic for other study, but the other undesired upper end of spectrum which is the main subject behind this present review and it is the activity of immune system against body own tissues which causes tremendous problems, through the unwanted reaction of both B and T-cells by producing various antibodies by B-cells and many reactive T-cells against its own tissues (Sakaguchi, 2005; Weetman et al., 1990; Misaki et al., 1984) which many diseases and abnormalities can be produce by the unwanted immune reactions, which are called autoimmune diseases. In such disease the immune system are activated, producing many antibodies and activated T-cells which can be targeted at various part of the cells organelles, such as different enzymes, key macromolecules, hormone receptors and cell nucleus.
Genetic in autoimmunity: The base for autoimmunity is genetic and there are many studies indicating the development of autoimmune disease originating from evidence of association with human lymphocyte antigens. Other studies indicated that there are few genetic factors associated with developing autoimmunity whether it is either organ or non-organ specific. The autoimmunity to the thyroid diseases proved to be familial (Kite and Wittebisky, 1968; Bartel, 1941; Brix et al., 1998a; Brix et al., 2000; Nagayama et al., 1989). There are studies indicating the Graves disease and Hashimoto's thyroiditis are thyroid disorder with genetic predisposition (Epstein, 1999; Klavinskas et al., 1988; Nagasaka et al., 2000; Brix et al., 2001; Ringold et al., 2002), the high level of serum antibodies was found in sera belongs to the patients relatives, with a documented thyroid diseases (Hall et al., 1960; Zeitlin et al., 2007; Stenzszyk et al., 1985).

There are also reports of simultaneous incidence of autoimmune thyroid disorder and other autoimmune diseases. Examples of such a diseases are the existence thyroid and stomach antibodies in first degree relatives with Hashimoto thyroiditis (Bartel, 1941; Brix et al., 2001; Philips et al., 1991, 1993; Ringold et al., 2002; Hall et al., 1960; Zeitlin et al., 2008; Pop et al., 1998; Weetman and McGregor, 1994; Parkes et al., 1996; Yanagawa et al., 1993; Stenzszyk et al., 1985).

Also nearly all types autoimmune diseases demonstrate some correlation with human lymphocyte antigen specificity, but it should be mentioned ethnicity also play a role on the level of autoimmunity (Chen et al., 1999; Weetman and McGregor, 1994; Tomer et al., 1997; Shields et al., 1994).

Diagnostic role of autoimmunity: There are three indications for the presence of autoantibodies and other autoimmunity determinants with individual serum which can be summarized as follow: (1) The raising autoantibodies which are the main determinant factors for disease onset. (2) There may be an abnormality in which through its process and the damages predispose the individual to produce autoantibodies and finally. (3) There may be an pathogen which cause the disease and the production of antibodies as well. In clinical practice all of above three possibilities are routinely should be investigated for the management and treatment of patients. The elevation of antibodies in various autoimmune disorder and antibodies raised secondary to some diseases such as myocardial infarction is now an instrumental to diagnose, treat and manage the cardiovascular patients (Cryle, 1954; Hubble, 1959; Buchanan et al., 1961; Mulhern et al., 1996; Jenkins and Weetman, 2002; Irvine et al., 1965; Doniach et al., 1963; Hjort et al., 1963).

Thyroid autoimmune diseases: Various type of autoimmune diseases in the thyroid gland can be sub-divided as follow: (1) Grave's disease, with thyroid enlargement, resulting with hyperthyroidism and its subsequent clinical consequence (Sanders et al., 2003; Chazenbalk et al., 2002, 2004; Chen et al., 2003). (2) Hashimoto's thyroiditis accompanied with goiter, resulting in hypothyroidism or thyroid function remain with normal range and euthyroid state (Suzuki et al., 1980; Blanchin et al., 2007; Weetman et al., 1989; Beierwaltes et al., 1968).

Also the autoimmunites to the thyroid gland are well documented and categorized, but there are still some thyroid dysfunctions which can be labeled as transient thyroid dysfunction which can happen, on its own, or may be occurred during a particular physiological state, such as pregnancy and depression (Hidaka et al., 1992; Bogner et al., 1995; Weetman, 2001; Poppe et al., 2003; Pratt et al., 1993; Kong et al., 2009; Holmes et al., 1977; Rapopott et al., 1998; Woolner et al., 1959). In our study of thyroid function in pregnancy, we found there is a high prevalence of thyroid dysfunction during pregnancy although we did not measure the thyroid antibodies in pregnant women's, but the growing fetus can be an antigenic determinant in production of antibody within the thyroid gland during the pregnancy, which has been reported by other studies (Mansourian, 2010b; Mansourian et al., 2010; Shahmohammadi et al., 2008; Brix et al., 1998b). It is indicated in some pregnancies, postpartum women and in either neonatal by hyperthyroidism or hypothyroidism the elevation of auto antibodies were observed (Mansourian et al., 2010; Pratt et al., 1993; Poppe et al., 2003; Gribetz et al., 1954; Jansson et al., 1984; Kajartie et al., 2006; Radetti et al., 2007). It has also been recommended by many studies, that the maternal serum concentration of autoantibodies should be measured during the clinical investigation of thyroid function test in routine thyroid function assessment of suspected subjects, pregnancies and in
newborns in addition to other thyroid function test, such as thyroid stimulating hormone and thyroxin and triiodothyronine, (Mansourian, 2010b; Radetti et al., 2007; Kajantie et al., 2006).

In addition either of hyperthyroidism and hypothyroidism have many other metabolic disorder. dyslipidemia is among such abnormalities. It has been shown that in hypothyroidism, the cholesterol and low density lipoprotein level are increased (Mansourian, 2010a; Mansourian et al., 2008).

It should be noted, in thyroid disorder caused by autoimmune and subsequent dyslipidemia which can be its adverse effect, should be taken into account, due to the cardiovascular abnormalities and particularly the atherosclerosis, which many be accompanied by cholesterol elevation (Galesani et al., 2004; Vala, 2001; Mansourian, 2010b). In a study and review by author it was stated that lipid disorder among thyroid patients and thyroid hormone alteration frequently seen during pregnancy (Mansourian, 2010b; Pratt et al., 1993; Poppe et al., 2003) but on the same time as thyroid hormones assessments is carried out, thyroid auto antibodies, iodine, lipid profile, assessment of pregnant women in particular and other suspected individuals should be evaluated for any thyroid disorder and possible side effect of dyslipidemia resulted from thyroid malfunctions (Mansourian, 2010a; Marjani et al., 2008; Mansourian et al., 2008). There are also some experimental studies on the induction of autoimmunity by thyroid injury, which can be a topic for studies in humans (Bagchi et al., 1995; Flynn et al., 2007).

Autoimmunity to the thyroid gland

Thyroid gland: Thyroid gland is the largest of endocrine glands in human weighted approximately about 20 g located in front of the neck. This gland produces the two most important hormones required for body’s metabolism namely thyroxin (T4) and triiodothyronin (T3) in addition to latter hormones, the thyroid produces Calcitonin, responsible for calcium and bone metabolism. The reactions, which finally produce T4 and T3, begin with the absorption and maintains of iodine and preparation of this element to participate in the structure of organic molecules on the thyroglobulin macromolecule, there for the first step in synthesis of T4 and T4 is the absorption and transferring the iodine on the thyroids residue on the thyroglobulin.

The topic of iodine deficiency in human have been the corner stone of many research about thyroid disorder, in fact one of the first primary tool to diagnose the hypothyroidism is the assessment of iodine status. In our earlier study, we found that iodine deficiency can be manifested the base for some thyroid disorder, the findings which have been reported by many other studies (Mansourian et al., 2007). It was already mentioned in experimental studies the elevated iodine itself which can be observed in thyroid injury can be a base for autoimmunity to the thyroid gland (Bagchi et al., 1995; Flynn et al., 2007; Zois et al., 2006).

Thyroglobulin (Tg) is produced when iodine added on the thyrosil residue of this latter macroprotein within the thyroid gland. All these reaction leading to production of T4 and T3 do take place by the action of thyroid stimulation hormone (TSH), not only TSH facilitate the thyroid hormone synthesis, through the activation of, many enzymes with the thyroid gland such as thyroxine peroxidase and other enzymes of iodine oxidation, but the thyroid enlargement also carried out by TSH. This latter hormone does all these physiological and biochemical functions through cAMP. When TSH binds to the THS receptor on the thyroid gland the sequence of event happen, on the receptor which located on the membrane, leading to the production of cAMP, a second messenger responsible for all the events in the thyroid gland and TSH functions. Therefore, it is the TSH receptor which locate in the center of thyroid function and any unwanted stimulation TSH or blocking of TSH receptor, result in over activation or suppression of thyroid hormone production due to the alteration happen in the level of cAMP concentration in the thyroid gland (Tonacchera et al., 1996; Prabhakar et al., 1997). Autoimmunity to the thyroid genetically, predisposes individuals; finally leave the patients with the consequence of thyroid disorders. It should be mentioned also that it is not only the TSH receptor, which can be targeted by the immune system, but also as it was mentioned earlier T-cell mediated responses and cell destruction can be associated with thyroid autoimmunity (Collins and Gough, 2002; Metealf er et al., 1997; Weetman et al., 1982).

The molecular bases for autoimmunity to the thyroid gland: T-cell and B-cell, which mainly originated from Thymus and Bone marrow cell are behaved to destroy only individual foreign antigens in a complex molecular mechanism and through other pathways, the immune system, behaved in such way to recognize the non-foreign antigen, within the thyroid, in other word the body’s thyroid own cells and tissues are protected by the immune system and it behaved to recognized the self thyroid antigens. Only on condition that the immune system does not recognize and discriminate the thyroid non-foreign antigen, only on that condition the
predispose persons thyroid will be attacked by self
immune system, with all its adverse effects, on the thyroid
metabolism. Such immunity against persons own thyroid
is called thyroid autoimmunity, it means a molecule within
the person thyroid is considered a foreign molecule and
the immune system begin to react against that molecule
(Weetman et al., 1982; Drehage, 1996; Owen and Smart,
1985; Benvenga et al., 1987; Sakuguchi, 2005;
Shields et al., 1994; Tomer et al., 1997; Lamki et al., 1973;
McIntosh et al., 1993). In fact that molecule stimulates
all the reactions required by the immune system to
destroy the normal procedures of the thyroid gland
molecules and reactions. There are many reports,
indicating the gender play an important role in triggering
the autoimmune. Thyroid autoimmunity proved to be
sex-related and high incidence of autoantibodies were
found among females (Mansourian et al., 2010). In fact
also in our study we did not measure the level of
autoantibodies in our women sample population but
incidence of thyroid disorder and in particular
hypothyroidism was more common among females
(Mansourian et al., 2008).

The autoimmunity in thyroid mainly consists of
Hashimoto thyroiditis and Grave’s disease. The two
end of thyroid diseases spectrum leaving the patients
in hypothyroid and hyper thyroid conditions,
respectively (Endo et al., 1983; Amino et al., 1982;
Bogner et al., 1984).

Hashimoto thyroiditis: Hashimoto thyroiditis is an
autoimmune thyroid disease. In this thyroid disorder, the
immune system activated against self- organ and attack,
the thyroid gland. The consequence of thyroid attack by
the immune system is the reduction of thyroid hormone
synthesis and thyroid gland in compensation to this latter
reaction continue to produce hormone to reach to the
normal level, which the body required for that level of
thyroid hormone, by doing so the thyroid gland enlarged
and it is developed into goiter, this type of goiter which
the body gain normal level of thyroid hormones is called
simple goiter, it means, it is only the enlargement of
thyroid gland without any toxicity due to the enhanced
production and the hyperplasia of the gland, but the
thyroid finally enter into hyperthyroid state
(Buchanan et al., 1961; Fatourechi et al., 1971; Eason,
1928; Suzuki et al., 1980; Benvenga and Trinarchi, 2008;
Pearce et al., 2003).

The side- effects of Hashimoto’s disease includes:
fatigue weight gain, depression, gastrointestinal,
abnormality, intolerance to cold constipation, dry skin and
hair, speech and vision abnormalities. Those Hashimoto’s
patients without any successful treatment, eventually
face, reduction in their heart rate, drop in their body
temperature and their eye become puffy around their eyes.
If the Hashimoto’s disease remain untreated and in
advance cases, it will end up with heart failure. the
molecular and cellular mechanism behind cell destruction
with the thyroid gland, is a combination of T-cell
autoimmunity activity in the thyroid accompanied with
autoantibodies raised against thyroglobulin, thyroid
peroxidase enzymes (Kohno et al., 1988; Protmann et al.,
1985; Melachian and Raperport, 1992; Tomer, 1997;
Lindberg et al., 2001; Noma et al., 1982; Fep et al., 1998;
Okamoto et al., 1989). It seems that T-cell destruction is
step forward for the production of autoantibodies against
the thyroglobulin and the thyroid peroxidase enzymes
(Komiya et al., 2001). T-cell autoimmunity seems to be
adversely effect the thyroid cells and it seems this
procedure is the first step toward the creation of goiter in
the thyroid gland, with the infiltration of lymphocyte and
production of compensatory thyroid cells, leading to the
hypothyroid and enlargement of thyroid gland the raised
autoantibodies within patient’s thyroid gland, also
accompanied with T-cell mediate cell destruction in the
thyroid gland with reduction of thyroid hormone
synthesis, but as it was mentioned earlier, it is the T-cell
mediated autoimmunity against the thyroid gland which
fundamentally destroy the thyroid cells and these reaction
predispose the gland to face eventually the inflammation
seen in Hashimato’s disease, with associated syndrome
(Komiya et al., 2001). It is reported also the Hashimoto,
disease can be accompanied with some cancer of thyroid
gland. Graver’s disease a topic which should have been
taken seriously for the management of Hashimato patients
(Woolner et al., 1959; Holmes et al., 1977; Giani et al.,
1996; Smyth et al., 1998; Kohn et al., 1997; DeGroot et al.,
1997; Dailey et al., 1955; Giani et al., 1996).

Graves disease: Graver’s disease is an autoimmune
thyroid disorder, resulting in the over activity and the
elevated level of thyroid hormones much more than the
healthy body metabolism required, eventually lead to
weight loss, nervousness and increasing heart rate
intolerance to heat, sleeping problem.

Weakness, tremors, alteration in vision, with
eventual, ophthalmopathy. The bases for thyroid disorder
in this disease related to the over activity and unwanted
immunological reactions by the individual immune system.

The antibodies against peroxidase (TPO) enzyme are
found, within the serum of affected persons
(Di Cerbo et al., 1995; Sawai and Degroot, 2000;
Davies et al., 1993; Caso-Pleacz et al., 1995; Kite and
Witebsky, 1968; Tomer and Davies, 1993; McLachlan and Rapoport, 1992, 2004; Protmann et al., 1985; Kohno et al., 1988; Dechairo et al., 2005; Wong and Cheng, 2001; Kondrashova et al., 2008; Brix et al., 1998b; Vali et al., 2000). As it was mentioned earlier Graves disease is a familial disease and the genetic susceptibility lead the synthesis of autoantibodies against Tg and TPO. The other most autoimmune which is produced and targeted against thyroid gland is antibody against receptor of Thyroid Stimulating Hormone (TSH), the antibody against the TSH receptor which is also known as Thyroid Stimulating Immunoglobulin (TSI).

TSI binds to the receptor of TSH on the thyroid gland stimulate and mimic the physiological effect of TSH, producing cAMP the second messenger responsible for the enlargement of thyroid gland and also the elevated production of T3 and T4 through the stimulation of many enzymes responsible for hormone production. TSI is not under the negative conoyr T4 and T3, therefore the synthesis of T4 and T3 are continued. In healthy persons when T4 and T3 are elevated the negative feedback control the hormones production by sending the message to the hypothalamus and pituitary to slower down the release of TSH and consequently the production of T4 and T3 are reduced. Also it should be mentioned that at times the raised autoantibody against the TSH receptor blocks the TSH receptor in such a way that even TSH can not binds to the TSH receptor and consequently the production of T4 and T3 are halted and hyperthyroidism occur (Tonacci et al., 1996; Prabhakar et al., 1997; Libert et al., 1989; Nagayama et al., 1989).

In our earlier studies we found high incidence of hyperthyroidism, among pregnant women and also many of them remained at euthyroid state. In the latter study we argued the elevated thyroid hormone level was the physiological requirement pregnancy, but it seems further studies should have been done to clarify whether the hyperthyroidism or euthyroid condition observed during pregnancy are either the direct consequence of pregnancy or the raised autoantibodies against the thyroid gland enzymes and TSH receptor (Shalimohammadi et al., 2008; Kung and Jones, 1998; Pratt et al., 1993; Poppe et al., 2003). The feature related to the Grave’s disease is the production of autoantibodies and T-cell mediated on to autoimmune response.

It should be mentioned that many reports indicated the simultaneous incidence of autoimmunity to the thyroid gland with the gland hyper activities and the thyroid gland carcinoma, or even some infection within the thyroid gland (Tomer and Davies, 1993; Bartalena et al., 1996; Wenzel et al., 1988; DeGroot and Palaya, 1973; Woolner et al., 1959; Giani et al., 1996; Bach, 2002; Smyth et al., 1998).

**CONCLUSIONS**

The review’s main points are as follows:

- The importance of immune system in protecting the individual from invading foreign pathogen described
- The adverse effect of autoimmune against self-antigen explored
- Autoimmunity has a genetic background with familial connection
- The determination of autoantibodies measurements are valuable diagnostic tools in medical practice
- Autoimmunity to the thyroid gland can be assessed by measuring autoantibodies raised against thyroglobulin, TSH receptor and thyroid peroxidase enzyme, involved in T4 and T3 production
- Hashimoto thyroiditis and Grave’s disease are the two end of spectrum of hypo and hyperthyroidism in thyroid autoimmunity, respectively
- Although, the main focus was on the production of antibodies in thyroid autoimmunity but it should be remembered that autoantibodies within the thyroid gland are also produced not only by the autoimmunity to the gland but also some other diseases such as thyroid cancer and in during some pregnancies, the elevated autoantibodies to the thyroid gland has been detected therefore the assessment of thyroid autoimmunity status should have been taken into account when thyroid cancer and pregnancies are medically examined

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