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

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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 Hashimato 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, Hashimato 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 tatter, 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 produced by the unwanted immune reactions, with 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

(Holborow, 1960; Mansourian *et al*., 2007; Chiovato *et al*., 1993; Mariorri *et al*., 1987). These damages can be either specific or non-specific. The thyroid autoimmunity are specific autoimmune diseases and the thyroid gland various cells and organelles are targeted by the individual immune systems and the thyroid function seriously affected leaving the patients with hypothyroidism in Hashimato and hyperthyroidism in Grave's disease (Okita *et al*., 1980; Aoki and Degroot, 1979).

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 Witebsky, 1968; Bartel, 1941; Brix *et al*., 1998a; Brix *et al*., 2000; Nagayama *et al*., 1989). There are studies indicating the Graves disease and Hashimato's thyroiditis are thyroid disorder with genetic predisposition (Epstein, 1999; Klavinskis *et al*., 1988; Nagasaka *et al*., 2000; Brix *et al*., 2001; Ringold *et al*., 2002), the high level of serum antibodies was found in serums belongs to the patients relatives, with a documented thyroid diseases (Hall *et al*., 1960; Zeitlin *et al*., 2007; Stenszky *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 Hashimato 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; Stenszky *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 McGrgor, 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 infraction is now an instrumental to diagnose, treat and manage the cardiovascular patients (Crile, 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 auto immune 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) Hashimato'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 autoimmunities 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; Kajantie *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 hyperthyrodism 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 autoimmunity 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 he accompanied by cholesterol elevation (Galesanu *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, b; 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 tridiothyronin (T3) in addition to latter hormones, the thyroid produce 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 macroprotien 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 c AMP 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; Metcalfer *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; Sakaguchi, 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 autoimmunity. 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 Hashimato 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).

Hashimato thyroiditis: Hashimato 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 Hashimato's disease includes: fatigue weight gain, depression, gastrointestinal, abnormality, intolerance to cold constipation, dry skin and hair, speech and vision abnormalities. Those Hashimato'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 Hashimato'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; Mclachian and Rapoport, 1992; Tomer, 1997; Lindberg *et al*., 2001; Noma *et al*., 1982; Pop *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 Hashimato, 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: Grave'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 peroxidease (TPO) enzyme are found, within the serum of effected persons (Di Cerbo *et al*., 1995; Sawai and Degroot, 2000; Davies *et al*., 1993; Caso-Pleaez *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 autoantibody 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 T4 and T3 through the stimulation of many enzymes responsible for hormone production. TSI is not under the negative conyr T4 and T3, therefore the syntheses of T4 and T3 are continued. In healthy persons when T4 and T3 are elevated the negative feed -back 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 the at same times the raised autoantibody against the TSH receptor blocks the TSH receptor in such way that even TSH can not binds to the TSH receptor and consequently the production of T4 and T3 are halted and hypothyroidism occur (Tonacchera *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 (Shahmohammadi *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 Paloya, 1973; Woolner *et al*., 1959; Giani *et al*., 1996; Bach, 2002; Smyth *et al*., 1998).

CONCLUSIONS

The review's main points are as follow:

- The importance of immune system in protecting the individual from invading foreign pathogen described
- The adverse effect of autoimmunity 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 recpector and thyroid peroxidase enzyme, involved in T4 and T3 production
- Hashimato 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

REFERENCES

Amino, N., H. Mori, Y. Iwatani, S. Asari, Y. Izumiguchi and K. Miyai, 1982. Peripheral K lymphocytes in autoimmune thyroid disease: Decrease in Graves disease and increase in Hashimotos disease. J. Clin. Endocrinol. Metab., 54: 587-591.

Aoki, N. and L. Degroot, 1979. Lymphocyte blastogenic response to human thyroglobulin in Graves disease, Hashimatos thyroiditis and metastatic thyroid cancer. Clin. Exp. Immune., 38: 523-523.

Bach, J.F., 2002. The effect of infections on susceptibility to autoimmune and allergic diseases. N. Engl. J. Med., 347: 911-920.

Bagchi, N., T.R. Brown and R.S. Sundick, 1995. Thyroid cell inuury is an initial event in the induction of autoimmune thyroiditis by iodine in obese strain chikens. Endocrinol., 136: 5054-5060.

Bartalena, L., F. Bogazzi, F. Pecori and E. Martino, 1996. Graves disease occurring after subacute thyroiditis: Report of a case and review of the literature. Thyroid, 6: 345-348.

Bartel, E.D., 1941. Heredity in Graves Disease. Enjnar Munksgaards Forlag, Copenhagen, Denmark.

Beierwaltes, W.H., R.H. Nishyama and D. Thyroiditis, 1968. Occurrence and similarity to Hashimotos struma. Endocrinol., 83: 501-508.

Benvenga, S. and F. Trinarchi, 2008. Changed presentation of Hashimotos thyroiditis in North-Easternb Sicilt and Calabria Southern Ital based on a 31- year experience. Thyroid., 18: 429-441.

Benvenga, S., F. Trimarchi and J. Robbins, 1987. Circulating thyroid hormone autoantibodies. J. Endcrinol. Invest., 10: 605-619.

Blanchin, S., C. Coffin, F. Viader, J. Ruf and P. Carayon *et al*., 2007. Antithyroperoxidase antibodies from patients with Hashimato encephalopathy bind to cerebellar astrocytes. J. Neuroimmunol., 192: 13-20.

Bogner, U., H. Schleusener and J.R. Wall, 1984. Antibody dependent cell mediated cytotoxicity against human thyroif cells in Hashimotos thyroiditis but not Graves disease. J. Clin. Endocrinol. Metab., 59: 734-738.

Bogner, U., L. Hegedus, J.M. Hansen, R. Finke and H. Schleusener, 1995. Thyroid cytotoxic antibodies in atrophic and goitrous autoimmune thyroiditis. Europ. J. Endocrinol., 132: 69-74.

Brix, T.H., K.O. Kyvik and L. Hegedus, 1998a. What is the evidence of genetic factors in the etiology of Graves disease? A brief review. Thyroid., 8: 727-734.

Brix, T.H., K. Christensen, N.V. Holm, B. Harvald and L.A. Hegedus, 1998b. Population- based study of Graves disease in Danish twins. Clin. Endocrinol., 48: 397-400.

Brix, T., K.O. Kyvik and L. Hegedus, 2000. A population-based study of chronic autoimmune hypothyroidism in Danish twins. J. Clin. Endocrinol. Metab., 85: 536-539.

Brix, T.H., K.O. Kyvik, K. Christensen and L. Hegedus, 2001. Evidence for a major role of heterdity in Graves disease: A population- based study of two Danish twin cohorths. J. Clin. Endocrinol. Metab., 86: 930-936.

Buchanan, W.W., J. Crooks, W.D. Alexande, D.A. Kouteras, E.J.M. Wayne and K.G. Gray, 1961. Association of Hashimotos and rheumatoid arthritis. Lancet, 1: 245-245.

Caso- Pleaez, E., A.M. McGregor and J.P. Banga, 1995. A polyclonal T cell repertoire of V-alpha and V-beta T cell receptor gene families in intrathyroidal T lymphocytes of Graves disease patients. Scand. J. Immunol., 14: 141-147.

Chazenbalk, G.D., P. Pichurin, C.R. Chen, F. Latrofa, A.P. Johnstone, S.M. Mclachian and B. Rapoport, 2002. Thyroid- stimoulating autoantibodies in Graves disease preferentially recognize the free A subunit, not the thyrotropin holoreceptor. J. Clin. Invest., 110: 209-217.

Chazenbalk, G.D., F. Latrofa, S.M. Mclachlan and B. Rappoport, 2004. Thyroid stimulation does not require antibodies with identical epitopes but does involve recognition of a critical conformation at the N terminus the thyrotropin A- subinit. J. Clin. Endcrinol. Metab., 89: 1988-1993.

Chen, Q.Y., W. Huang, J.X. She, F. Baxter, R. Volpe and N.K. Maclaren, 1999. HLA-DRB1*03/DRB3*0101 and DRB3*0202 are susceptibility genes for Graves disease in North American Caucasians, whereas DRB1*07 is protective. J. Clin. Endocrinol. Metab., 84: 3182-3186.

Chen, C.R., P. Pichurin, C.R. Chen, F. Latrofa, A.P. Johnstone, S.M. Mclachian and B. Raporter,q 2003. Thyroid reporter autoantigen in Gravers disease in the culprit as well as the victim. J. Clin. Invest., 111: 897-1904.

Chiovato, L., P. Bassi, F. Santini, C. Mammoli, P. Lapi, P. Carayon and A. Pinchera, 1993. Antibodies producing complement- mediated thyroid cytotoxicity in patients with atrophic or goitrous auto immune thyroiditis. J. Clin. Endocrinol. Metab., 77: 1700-1705.

Collins, J. and S. Gough, 2002. Autoimmunity in thyroid disease. Eur. J. Nucl. Med. Mol. Imaging., 29: 417-424.

Crile, G. Jr., 1954. The treatment of diseases of the thyroid gland. Ann. R. Coll. Surg. Engl., 14: 158-158.

Dailey, M.E., S. Lindsay and R. Skahen, 1955. Relation of thyroid neoplasms to Hasgimatos disease of the thyroid gland. Arch. Surg., 70: 291-297.

Davies, T.F., E.S. Concepcion, A. Ben-Nun, P. Graves and G. Tatjan, 1993. T-cell receptor V gene use in autoimmune thyroid disease: Direct assessment by thyroid aspiration. J. Clin. Endocrinol. Metab., 76: 660-666.

DeGroot, L.J. and E. Paloya, 1973. Thyroid carcinoma and adiation. A Chicago endemic. J. Amer. Med. Assn., 225: 487-491.

DeGroot, L.I., K. Hoye, S. Refetoff, A.J. Van Herle, G.T. Asteris and H. Rochman, 1997. Serum antigens and antibodies in the diagnosis of thuroid cancer. J. Clin. Endocrimol. Metab., 45: 1220-1223.

Dechairo, B.M., D. Zabaneh, J. Collins, O. Brand and G.L. Dawson *et al*., 2005. Association of the TSHR gene with Graves disease: The first disease specific locus. Eur. J. Hum. Gemet., 31: 1223-1230.

Di Cerbo, A., R. Di Paola, M. Bonati, M. Zingrillo, V. De Filippis and D. Corda, 1995. Subgroups of Graves patients identified on the basis of the biochemical activities of their immunoglobulins. J. Clin. Endpcrinol. Metab., 80: 2785-2790.

Doniach, D., I.M. Roitt and K.B. Taylor, 1963. Auto immune phenomena in pernicious anemia. Serological overlap thyroiditis, thyrotoxicosis and systemic lupus erythematosus. Br Med J., 1: 1374-1379.

Drehage, H.A., 1996. Autoimmunity and thyroid growh. Where do we stand? Europ. J. Immunol., 135: 39-45.

Eason, J., 1928. Correalation of Graver diseases and thyroiditis. Edinburgh. Med. J., 35: 169-169.

Endo, Y., Y. Aratake, I. Yamammoto, H. Nakagawa, T. Kuribayashi and S. Ohtaki, 1983. Peripheral K cells in Graves disease and Hashimotos thyroiditis in relation to circulating, immune complexes. Clin. Endocrinol., 18: 187-194.

Epstein, F.H., 1999. Molecular mimicry and autoimmunity. New Engl. J. Med., 341: 2068-2074.

Fatourechi, V., W.M. McConahey and L.B. Oolner, 1971. Hyperthyroidism associated with histilogic Hashimatos thyroiditi. Mato. Clin. Proc., 46: 682-682.

Flynn, J.C., C. Meroueh, D.P. Snower, C.S. David and Y.M. Kong, 2007. Depletion of CD4+CD25+regulatory T cells exacerbates sodium iodide- induced experimental autoimmune thyroiditis in human leucocyte antigen DR3 (DRB1*0301) transgenic class II- knock- out non- obese diabetic mice. Clin. Exp. Immunol., 147: 547-554.

Galesanu, C., N. Lisnic, R. Teslaru, L. Apostu and E. Zbranca *et al*., 2004. Lipidprofile in group of hypothyroidpatients Vs treated hypothyroidpatients. Rev. Med. Chir. Soc. Med. Nat. Lasi., 108: 554-560.

Giani, C., P. Fierabrancci, R. Bonacci, A. Gigoliotti and F. De Megri *et al*., 1996. Relationship between breast cancer and thyroid disease: Relevance of auto immune thyroid in breast maligany. J. Clin. Endocrinol. Metab., 81: 990-994.

Gribetz, D., N.B. Talbot and J.D. Crawford, 1954. Goiter due to lynphochtic thyroiditis (*Hashimatos struma*): Its occurrence in predolescent and adolescent girls N. Engl. J. Med., 250: 555-555.

Hall, R., S.G. Owen and G.A. Smart, 1960. Evidence for genetic predisposition to formation of formation of thyroid auto antibodies. Lancet, 2: 187-188.

Hidaka, Y., N. Amino, Y. Iwatani, T. Kaneda and M. Nasu *et al*., 1992. Increase in peripheral natural killer cell activity in patients with autoimmune thyroid disease. Autoimmunity, 11: 239-246.

Hjort, T., F. Jeppesen, K. Okholm and J. Temler, 1963. The Prognostic significance of thyroid autoantibodifes in the development of postoperative myxedema. Dan. Med. Bull., 10: 159-167.

Holborow, E.J., 1960. Serum anticlear factor and autoimmunity. Proc. R. Soc. Med., 53: 625-627.

Holmes, H.B., A.O. Kreutner and A.P.H. Brien, 1977. Hashimatos thyroiditis. Its relationship to other thyroid diseases. Surg. Gynecol. Obstet., 144: 887-887.

Hubble, D., 1959. The diagnosis and yreatment of auto immunizing thyroiditis. Scott. Med. J., 4: 55-55.

Irvine, W.J., S.H. Davies, S. Teitkbaum, I.W. Delamore and A.W. Wiliams, 1965. The clinical and pathological significance of gatric parietal cell antibodu. Ann. Acad. Sci., 124: 657-691.

Jansson, R., S. Bernader, A. Karlsson, K. Levin and G. Nilsson, 1984. Aytoimmune thyroid dysfunction in the postparyum period. J. Clin. Endocrinol. Metab., 58: 681-687.

Jenkins, R.C. and A.P. Weetman, 2002. Disease associations with auto immune thyroid disease. Thyroid., 12: 977-988.

Jiang, H. and L. Chess, 2006. Regulation of immune responses by T cells. New Engl. J. Med., 354: 1166-1176.

Kajantie, E., D.I. Philips, C. Osmond, D.J. Barker, T. Forsen and J.G. Erikson, 2006. Spontaneous htpothyroidism in adult women is predicted by small boy size a birth and during children. J. Clin. Endocrimol. Metab., 91: 4953-4956.

Kite, J.H. and E. Witebsky, 1968. Hereditary autoimmune thyroiditis in the fowl. Sci., 160: 1357-1358.

Klavinskis, L.S., A.L. Notkins and M.B.A. Otdstone, 1988. Persistent viral infection of the thyroid gland: Alteration of thyroid function in the absence of tissue injury. Endocrinology, 122: 567-575.

Kohn, L.D., K. Suzuki, W.H. Hoffman, D. Tonbaccini and N. Shimojo *et al*., 1997. Characterization of monoclonal thyroid- simulating and thyrotropin ginding- inhibiting auto antibodies from a Hashimatos patient whose children had intrauterine and neonatal thyroid disease. J. Clin. Endocrinol. Metab., 82: 3998-4002.

Kohno, Y., N. Naito, Y. Hiuama, N. Shimojo and N. Suzuki *et al*., 1988. Thyroglobulin and thyroid peroxidase share common epitopes recognize by autoantibodies in patients with chronic autommune thyroiditis. J. Clin. Endocrinol. Metab., 67: 899-907.

Komiya, I., T. Yamada, A. Sato, T. Koukinishimori and N. Takasu, 2001. Remissionand recurrence of hyperthyroid Graves disease during and after methimazole tratmeent when assessed by IgE and interlukin 13. J. Clin. Endocrinol. Metab., 86: 3540-3544.

Kondrashova, A., H. Visjari. A.M. Haapala, T. Seikari, P. Kulmala. J. Ilonen and H. Hyoty, 2008. Serological evidence of thyroid autoimmunity among schoolchildren in two different socioeconomic environments. J. Clin. Endocrinol. Metab., 93: 729-734.

Kong, Y.C., G.P. Morris, N.K. Brown, Y. Yan, J.C. Flynn and C.S. David, 2009. Autoimmune thyroiditis: A model uniquely suited to probe regulatory T cell function. J. Autoimmun., 33: 239-246.

Kroneberg, M., G. Siu, L.E. Hood and N. Shastri, 1986. The molecular genetics of the T- cell abtigen and T-cell antien recognition. Ann. Rev. Immunol., 4: 529-529.

Kung, A.W.C. and B.M. Jones, 1998. A Change from stimulatory to blocking antibody activity in Graves disease during pregnancy. J. Clin. Endocrinol. Metab., 83: 514-518.

Lamki, L., V.V. Row and R. Volpe, 1973. Cell mediated immunity in Graves disease and in Hashimotos thyroiditis as shown by the demonstration of migration inhibition factor (MIF). J. Clin. Endocrinol. Metab., 36: 358-364.

Li, J., D.R. Barreda, Y. Zhang, H. Boshra and A.E. Gelman *et al*., 2006. B-Lymphocytes from early vertebrates have potent phagocytes abilities. Nat. Immunol., 7: 1116-1124.

Libert, F., A. Lefort, C. Gerard, M. Parmentier and J. Perret *et al*., 1989. Cloning, sequencing and expression of the human thyrotropin (TSH) receptore: Evidence for binding of auto antibodies. Biochem. Biophys. Ren. Commun., 165: 1250-1255.

Lindberg, G., J. Svensson, U.B. Erisson, P. Nilsson, E. Svenonius and S.A. Ivarson, 2001. Comparision of some different methods for analysis of thyroid autoantibodies: Importance of thyroglobulin autoantibodies. Thyroid., 11: 265-269.

Mansourian, A.R., E.O. Ghaemi, A. Ahmadi, A. Saifi, A.V. Moradi and S. Bakhshandehnosrat, 2007. A survy of urinary iodine concentration in south east of Caspian Sea in northern Iran. Pak. J. Biol. Sci., 10: 2166-2171.

Mansourian, A.R., E. Ghaemi, A.R. Ahmadi, A. Marjani, A. saifi and S. Bakhshandehnosrat, 2008. Serum lipid level alteration in subclinical hypothyroidpatients in Gorgan (South east Caspian Sea). Chinese Clin. Med., 3: 206-221.

Mansourian, A.R., A.R. Ahmadi, H.R. Mansourian, A. Saifi, A. Marjani, G.R. Veghari and E. Ghaemi, 2010. Maternal thyroid stimulating hormone level during the first trimmester of pregnancies at thesouth east ofCaspian Sea in Iran. J. Clin. Diagnostioc. Res., 4: 2472-2477.

Mansourian, A.R., 2010a. The state of lipid profiles in sub clinical hypothyroidism: A review of Literature. Pak. J. Biol. Sci., 13: 556-562.

Mansourian, A.R., 2010b. Thyroid function tests during first trimester of pregnancy: A review of literature. Pak. J. Biol. Sci.,

Mariorri, S., S. Anelli, R. Ruf Bechi, B. Czarnocka, A. Lombardi, P. Carayon and A. Pinchera, 1987. Comparison of serum thyroid microsomal and thyroid peroxidase autoantibodies in thyroid diseases. J. Clin. Endocrinok. Metab., 65: 987-993.

Marjani, A., A.R. Mansourian, E.O. Ghaemi, A. Ahmadi and V. Khori, 2008. Lipid peroxidation in the serumof hypothyroid patients in Gorgan, south east of Caspian sea. Asian J. Cell. Biol., 3: 47-50.

McIntosh, R.S., N. Tandon, A.P. Pickerill, R. Davies, D. Barnett and A.P. Weetman, 1993. IL-2 receptor positive intrathyroidal lymphocytes in Graves disease: Analysis of V transcript microheterogeneity. J. Immunol., 91: 3884-3893.

Mclachian, S.M. and B. Rapoport, 1992. The molecular biology of thyroid peroxidase: Cloning, expression and role as autoantigen in autoimmune thyroid disease. Endocrine. Rev., 13: 192-206.

Mclachlan, S.M. and B. Rapoport, 2004. Why measure thyroglobulin autoantibodies rather than thyroid peroxidas autoantibodies? Thyroid., 14: 510-520.

Metcalfer, R.A., Y.S. Oh, C. Stroud, K. Arnold and A.P. Weetman, 1997. Analysis of antibody-dependent cell- mediated cytotoxicity in auto immune thyroid disease. Autoimmunity, 5: 65-72.

Misaki, T., J. Konishi, Y. Iida, K. Endo and K. Torizuka, 1984. Altered balance of immunoregulatory lymphocyte sybsets in autoimmunity thyroid disease. Acta. Endocrinol., 105: 200-204.

Mulhern, L.M., A.T. Masi and L.E. Shulman, 1996. Hashimato disease: A search for associated disorders in 170 clinically detected cases. Lancet, 2: 508-511.

Nagasaka, A., A. Nakai, N. Oda, M. Kotake, K. Iwase and S. Yoshida, 2000. Reverse transcriptase is elevated in the thyroid tissue from Graves disease patients. Clin. Endocrinol., 53: 155-159.

Nagayama, Y., K.D. Kaufman, P. Seto and B. Rapoport, 1989. Molecular cloning, sequence and functional expression of the cDNA for the human thyrortopin receptor. Biochem. Biophys. Res. Commun., 165: 1184-1190.

Nelson, B.H., 2004. IL-2, regulatory T cells, an tolerance. J. Immune., 172: 3983-3988.

Noma, T., J. Yata, Y. Shishiba and B. Inatsuki, 1982. *In vitro* detection of anti thyroglobulin antibody forming cells from the lymphocytes of chronic thyroiditis patients and analysis of their regulation. Clin. Exp. Immunol., 49: 565-571.

Okamoto, Y., N. Hamada, H. Saito, M. Ohno, J. Noh, L. Ito and H. Morii, 1989. Thyroid peroxidase activity inhibiting immunoglobulins in patients with auto immune thyroid disease. H. Clin. Endocrinol. Metab., 68: 730-734.

Okita, N., A. Kidd, V.V. Roww and R. Volpe, 1980. Sentiziation of T lymphocytes in Graves and Hashimatos diseases. J. Clin. Endoccrinol. Metab., 51: 316-316.

Owen, S.G. and G.A. Smart, 1985. Thyroid antibodies in myxedema. Lancet, 2: 1034-1034.

Parkes, A.B., C. Darke, S. Othman, M. Thomas and N. Young *et al*., 1996. Major histocompatibility complex class II and complement polymorphisms in postpartum thyroiditis. Europ. J. Endocrinol., 134: 449-453.

Pearce, E.N., A.P. Farwell and L.E. Braverman, 2003. Thyroiditis. N. Engl. J. Med., 348: 2646-2655.

Philips, D., L. Entice, M. Upadhyaya, P. Lunt and S. Chamberiain *et al*., 1991. Autosomal dominant inheritance of autonatibodies to thyroid peroxidase and thyroglobulin- studies in families not selected for autoimmune thyroid disease. J. Clin. Endocrinol. Metab., 72: 973-975.

Philips, D.I.W., D.C. Shields, J.M. Dougoujon, L. Prentice, P. McGuffin and B. Rees Smith, 1993. Complex segregation analysis of thyroid autoantibodies: Are they inherited as an autosomal dominant trait? Hum. Hered., 43: 141-146.

Pop, V.J., L.H. Maartens, G. Leusink, A.A. Van Son Konttnerus, A.M. Ward, R. Mercalfe and A.P. Weetman, 1998. Are auto immune thyroid dysfunction and depression related? J. Clin. Endocrinol. Metab., 83: 3194-3997.

Poppe, K., D. Glinoer, H. Tournate, P. Deveroey, A. Van Stierteghem, L. Kaufman and B. Velkeniers, 2003. Assisted reproduction and thyroid autoimmunity: An unfortunate combination? J. Clin. Endocrinol. Metab., 88: 4149-4152.

Prabhakar, B.S., J.L. Fan and G.S. Seetharamaiah, 1997. Thyrotropin- receptor- mediated diseases: A paradigm for receptor autoimmunity. Immune. Today, 18: 437-442.

Pratt, D.E., G. Kaberlein, A. Dudkiewicz, V. Karande and N. Gleicher, 1993. The association of anythyroides in eutyroid nonpregnant women with recurrent first trimester abortions the next pregnanc. Fittil. Steril., 60: 1001-1005.

Protmann, L., N. Hamada, G. Heinrich and L.J. DeGroat, 1985. Antithyroid peroxidase antibody in patient with autoimmunue thyroid disease: possible identity wit microsomal antibody. J. Clin. Endocrinol. Metab., 61: 1001-1003.

Radetti, G., A. Fanolla, L. appalardo and E. Gottardi, 2007. Prenaturity my be a risk factor for thyroid dysfunction in childhood. J. Clin. Endocrinol. Metab., 92: 155-159.

Rapopott, B., G.D. Chacenblack, J.C. Jaume and S.M. Mclachian, 1998. The thyrotrophine (TSH)-releasing hormone receptor: Interaction with TSH and autoantibodies. Endocrine. Rev., 19: 673-716.

Ringold, D.A., J.T. Nicoloff, M. Kesler, H. Davis, A. Hamilton and T. Mack, 2002. Further evidence for a strong influence on the development od autoimmune thyroid diseas: The California twin study. Thyrouid., 12: 647-653.

Sakaguchi, S., 2005. Naturally arising Foxp3- expressing CD25+ CD25+ regulatory T cells in immunological tolerance to self and non- self. Nat. Immune., 6: 345-352.

Sanders, J., M. Evans, L.D.K.E. Premawardhand, J. Defferyes, T. Richards, J. Furmaniak and B Rees Smith, 2003. Human, monoclonal thyroid stimulating antibody. Lancet, 362: 126-128.

Sawai, Y. and L.J. DeGroot, 2000. Binding of human thyrotropin receptor peptides to a Graves disease predisposing human leukocyte antigen class II molecule. J. Clin. Endocrinol. Metab., 85: 1176-1179.

Schwarz, B.A. and A. Bhandoola, 2006. Trafficking from Bone marrow to thymuss prerequisite for thymopoiesis. Immunol. Rev., 209: 47-57.

Shahmohammadi, F., A.R. Mansourian and H.R. Mansourian, 2008. Serum thyroidhormon level in women withnausea and vomiting in early pregnancy. J. Med. Sci., 8: 507-510.

Shields, D.C., S. Ratanachaiyavong, A.M. McGregor, A. Collins and N.E. Morton, 1994. Combined segregation and linkage analysis of Graves disease with a thyroid autoantibody diathesis. Am. J. Human Genet., 55: 540-554.

Smyth, P.P.A., S.G. Shering, M.T. Kilbane, M.J. Murray, E.W.M. McDermott, D.F. Smith and N.J. O'Higgins, 1998. Serum thyroid peroxiedase auto antibodies, thyroid volume and outocome breast caricinoma. J. Clin. Endocrinol. Met., 83: 2711-2716.

Stenszky, V., L. Kozma, C. Balazs, S. Rochitz, J.C. Bear and N.R. Farid, 1985. The genetics of Graves disease: HLA and disease susceptibility. J. Clin. Endocrinol. Metab., 61: 735-740.

Suzuki, S., M. Misunaga, Miyshi, S. Hirakw and O. Nakawa *et al*., 1980. Cytophilic antithyroglubulin antibody and antibody dependent monocyte mediated cyotoxity in Hashimatos thyroiditis. J. Clin. Endocrinol. Metab., 51: 446-446.

Tomer, Y. and T.F. Davies, 1993. Infection, thyroid disease and autoimmunity. Endocrine. Rev., 14: 107-120.

Tomer, Y., 1997. Anti-thyroglobulin autoantibodies in autoimmune thyroid diseases: Cross-reactive or pathogenic. Clin. Immunol. Immunopathol., 82: 3-11.

Tomer, Y., G. Barbesino, M. Kedache, D.A. Greenbarg and T.F. Davies, 1997. Mapping of a major susceptibility locus for Graves disease (GD1) to chromosome 14q31. J. Clin. Endocrinol. Metab., 82: 1645-1648.

Tonacchera, M., J. Van Sande, J. Parma, L. Duprez and F. Cetani *et al*., 1996. TSH receptor and disease. Clin. Endocrinnol., 44: 621-633.

Vala, B.S., 2001. Endocrinology Andtheheart. In: Cardiology, Mickel, H., C. John and P. Di Marco (Eds.), Mosby, London.

Vali, M., N.R. Rose and P. Caturegil, 2000. Thyroglobulin as auntoantigen: Strucure- function relationships. Rew. Endocr. Met. Dis., 1: 69-77.

Weetman, A.P., AM McGregor, J.H. Lazarus and R. Hall, 1982. Thyroid antibodies are produced by thyroid derived lymphocytes. Clin. Exp. Immune., 48: 196-200.

Weetman, A.P., C.M. Black, S.B. Cohen, R. Tomlinson, J.P. Banaga and C.B. Reimer, 1989. Affinity purification of subckasses and the distrivution of thyroid auto- antibody reactivity in *Hashimatos thyroiditis*. Scand. J. Immonol., 30: 73-82.

Weetman, A.P., M.E. Yateman, P.A. Ealey, C.M. Black and C.B. Reimer *et al*., 1990. Thyroid stimulating antibody activity between different immunogolubin G Subclasses. J. Clin. Invest., 86: 723-727.

Weetman, A.P. and A.M. McGregor, 1994. Autoimmune thyroid disease: Further development in our understanding. Endocring Rev., 15: 788-830.

Weetman, A.P., 2001. Determinants of autoimmune thyroid disease. Nat. Immunol., 2: 769-770.

Weigle, W., 1975. Cyclicproduction of antibody as a regulatory mechanism in the immune response. Adv. Immol., 21: 87-87.

Wenzel, B.E., J. Heesemann, K.W. Wenzel and P.C. Scriba, 1988. Patients with autoimmune thyroid diseases have antibodies to plasmid encoded proteins of enteropathogenic Yersinia. J. Endocrinol. Invast., 11: 139-140.

Wong, G.W.K. and P.S. Cheng, 2001. Increasing incidence of childbooh Graves; disease in Hong Kong: A follow- up study. Clin. Endocrinol., 54: 547-550.

Woolner, L.B., W.M. McConahy and O.H. Beahr, 1959. Stroma lymphomatosa and related thyroidal disorders. J. Clin. Endpcrinol. Metab., 19: 53-61.

Yanagawa, T., A. Mangklabruks, Y.B. Chang, Y. Okamoto, M.E. Fisfalen, P.G. Curran and L.J. DeGoot, 1993. Human histocompatibility leukocyte antigen-DQA1*0501 allele associated with genetic susceptibility to Graves disease in a Caucasian population. J. Clin. Endocrinol. Metab., 76: 1569-1574.

Zeitlin, A.A., M.J. Simmonds and S.C. Gough, 2008. Genitic developments in autoimmune thyroid disease: An evolutionary process. Clin. Endocrinol., 68: 671-682.

Zeitlin, A.A., M.J. Simmonds, S.C. Gough, S. Blanchin and C. Coffin *et al*., 2007. Anti thyroperoxidase antibodies from patients with Hashimatos encephalopathy bind to cerebellar astrocytes. J. Neuroimmunol., 192: 13-20.

Zois, C., I. Sravrou, E. Svarna, K. Seferidis and A. Tsarsoulis, 2006. Natural Course of auto immune thyroiditis after elimination of iodine deficiency in north western Greece. Thyroid., 16: 289-293.