International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 4, Issue 2, pp: (186-192), Month: October 2016 - March 2017, Available at: www.researchpublish.com

Systematic Review of Sensitive Biomarkers of Graves' Disease

[1]ALANAZI, ABDULLAH MOFAREH M, [2]ALANAZI, MUNEEF SUWAILEM A, [3]ALSHAMMARI, BADER OBAID K, [4]ALMATRAFI, ABDULAZIZ RAMDAN H, [5]ALENEZI, ABDULLAH MUNIF, [6]ALANAZI THAMER THEYAB M., [7]ALANAZI, NASSER SALEM M

Abstract: **Graves' disease (GD) is an autoimmune disorder, which is brought on by unusual hereditary changes, consisting of modifications in the expression levels of specific human cellular genes, and different ecological aspects, such as smoking cigarettes. This systematic review study was aimed to determine the most sensitive biomarkers used to predict and diagnosis of GD through a evidence based studies. We conducted electronic bibliographic research independently according to the validated methods of the Preferred Reporting Items for Systematic Reviews (20) using the following databases: Medline, Embase, Web of Science, and The Cochrane Library. The database search (date range, 1970–2016) was performed using the following MeSH search terms: ''Graves' disease,'' ''toxic goiter,'' and ''biomarker.'' interleukin-2, interleukin-10, genetic polymorphism. Direct proof revealed that OPN may cause distinction of Th17 cells in the peripheral blood and thyroid glands or draw in Th17 migration to thyroid glands of GD patients. The relationships in between OPN and CCL20/CCR6/Th17 axis in GD still have to be examined.**

Keywords: **Graves' disease (GD), Sensitive Biomarkers.**

1. INTRODUCTION

Graves' disease (GD) is an autoimmune disorder, which is brought on by unusual hereditary changes, consisting of modifications in the expression levels of specific human cellular genes, and different ecological aspects, such as smoking cigarettes (1). GD primarily impacts the thyroid, often leading to overactive and bigger thyroid glands, in addition to a number of signs, consisting of muscle sleeping disorders, irritation and weak point (2,3). Presently the frequency of GD is 0.5 % of the population and is the underlying etiology for 50-- 80 % of cases of hyperthyroidism (4). GD is not just related to a reduction in lifestyle, however if left neglected, it can result in heart disease, consisting of atrial fibrillation, cardiomyopathy, and heart disease (5,6). In addition, GD might impact the eyes, leading to exophthalmos, or other systems of the body, consisting of the skin, heart, blood circulation and nerve system. As much as 2% of the female population is impacted by GD, with a female-to-male ratio in between 5:1 and 10:1 (7,8). Interactions in between ecological aspects and hereditary elements might increase the threat of GD (9,10).

Previous research studies have actually determined ~ 20 hereditary polymorphisms that are related to GD, consisting of genes connected with the thyroid or associated with autoimmune reactions (11,12). T assistant type 1 (Th1) and Th2 serum cytokines have actually been shown to be associated with the advancement of GD (13-15). Interleukin (IL)-2, a cytokine signaling particle, is a protein controling the activities of lymphocytes that are associated with resistance. IL-2 is needed for the expansion and distinction of human T cells into effector cells (16). A previous research study reported that the serum concentrations of IL-2 were increased in patients with vitiligo, which is a gotten depigmenting condition related to GD and identified by the loss of practical melanocytes (17).

IL-10 is an anti-inflammatory cytokine, likewise referred to as a human cytokine synthesis repressive element, which provides pleiotropic impacts in swelling and immunoregulation. IL-10 hinders the expression levels of Th1 cytokines, significant histocompatibility complex class II antigens and costimulatory particles on macrophages (18). In addition, IL-

10 helps B-cell antibody, survival and expansion production and impacts the performance of particular cellular paths. It hinders the activities of nuclear factor-κB and modifies the JAK-STAT signaling path (18). A previous research study on a murine design suggested that IL-10 shortage minimizes the induction of anti-thyroid stimulating hormonal agent receptor antibodies; hence, IL-10 plays an essential function in the advancement of GD in mice (19).

This systematic review study was aimed to determine the most sensitive biomarkers used to predict and diagnosis of GD through a evidence based studies.

2. METHODOLOGY

Study design:

Systematic review study was conducted Search strategy:

We conducted electronic bibliographic research independently according to the validated methods of the Preferred Reporting Items for Systematic Reviews (20) using the following databases: Medline, Embase, Web of Science, and The Cochrane Library. The database search (date range, 1970–2016) was performed using the following MeSH search terms: ‘‘Graves’ disease,’’ ‘‘toxic goiter,’’ and ‘‘biomarker.’’ interleukin-2, interleukin-10, genetic polymorphism. These terms and combinations thereof were also used as key words. Special database functions, such as ‘‘related articles’’ and ‘‘explosion,’’ were used to maximize the search. To minimize retrieval bias, a manual search of the bibliographies of each article obtained from the database search was performed using the Google Scholar database.

Data collection: Using a structured data abstraction form, different authors extracted the data from the included studies, and another independent author checked the extracted data. Disagreements were resolved through discussion and if necessary by involving another independent author.

3. RESULTS AND DISCUSSION

Thyroid-Stimulating Autoantibodies as a biomarker for GD:

The thyrotropin receptor, also known as the thyroid-stimulating hormone receptor (TSHR), is the primary antigen of Graves’s disease. Stimulating TSHR antibodies are the cause of thyroid overstimulation and were originally called long-acting thyroid stimulators due to their prolonged action.

We identified a very large mulicenter study (21) involving overall of 422 serum samples were acquired from 308 pediatric patients and healthy control kids hired from 7 European and american scholastic recommendation centers this multicenter cross-sectional research study is the biggest assessment of TSHR antibodies in kids and teenagers with GD done to this day and shows the outstanding level of sensitivity, uniqueness, and reproducibility of this unique TSHR antibody bioassay. In addition to being a helpful biomarker for illness activity, TSAb likewise associated with the existence of GO independent of thyroid function, recommending a possible causal function of TSAb in the immunopathogenesis of GO and in the advancement of the scientific phenotype of thyroid eye illness with proptosis. In a number of pediatric patients with GD, many samples were offered, and all were evaluated. In the European centers, the medical diagnosis of GD was believed on the basis of a normal scientific discussion, the existence of a diffusely bigger thyroid gland, and proof of extrathyroidal participation, if present, and was validated by the common ultrasound image consisting of considerably improved perfusion of the thyroid gland on Doppler assessment. In Boston, the medical diagnosis of GD was based upon those particular scientific image and the existence of TSHR antibodies (binding assay); radionuclide thyroid uptake and scan or a thyroid ultrasound was carried out when the medical diagnosis was uncertain. All pediatric patients with GD were evaluated for symptoms and signs of orbital participation. GO was identified inning accordance with the suggestions of the European Group on Graves' Orbitopathy (EUGOGO) The scientists evaluated 422 serum samples from 157 kids with GD along with serum samples from 101 control people with other thyroid and nonthyroid autoimmune illness (ie, Hashimoto's thyroiditis, nonautoimmune hyperthyroidism, type 1 diabetes, and juvenile arthritis), and from 50 healthy kids. The scientists compared the level of sensitivity and uniqueness of TSAbs to TBII (21).

In 82 kids with Graves' illness who had actually not formerly been dealt with, TSAb levels were 100% particular and delicate, and had 100% favorable and unfavorable predictive worths. In contrast, corresponding steps for the more extensively utilized TBII evaluation were 92.68% (P= 0.031), 100%, 100%, and 96.15%, respectively, recommending that TSAb levels had a considerably greater level of sensitivity than TBII levels (21).

A considerably higher portion of kids with Graves' illness were TSAb favorable than TBII favorable (94% vs 87.9%; P< 0.039), as were a higher portion of the 263 samples from the kids with Graves' illness (94% vs 89%; P< 0.0075). On the other hand, all control kids and kids with other thyroid and nonthyroid autoimmune illness were TSAb and TBII unfavorable, recommending that TSAb evaluation is "an appropriate test for distinguishing these conditions from Graves' illness (21). TSAb levels-- however not TBII levels-- were substantially greater amongst kids with Graves' illness and orbital illness compared to those without orbital illness (P< 0.001) (21). After an average of 3 years of treatment, patients with Graves' illness without orbital illness revealed a higher decline in TSAb levels compared with patients with orbital disease (69% vs 20% decrease;*P*<0.001) **(Figure1)** (21)**.**

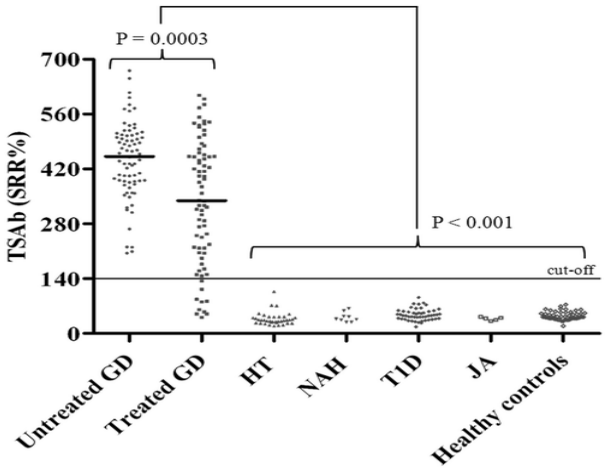

Figure 1. Serum TSAb levels shown as dot plots in all patients of each study group and in healthy euthyroid control children. Median (range) serum TSAb levels were in 82 untreated pediatric patients with GD (SRR%, 447; range, 142–671), in 75 treated GD patients (with various thyroid functions) (339; 41–608), in 37 patients with HT (34; 19–107), in nine patients with NAH (37; 29–58), in 50 patients with T1D (46; 17–92), in five patients with JA (39; 32–42), and in 50 euthyroid healthy controls (42; 19–74). The line at 140 SRR% indicates the assay cutoff. A significant difference was obtained between untreated and treated pediatric patients (*P* = .0003) and in all patients with GD vs the various non-GD collectives (*P* < .001). The median value in the untreated and treated patients with GD is shown as a bold horizontal line (21).

Chemokine (C-C motif) ligand 20 (CCL20) and Osteopontin (OPN) a sensetive biomarkers for GD:

CCL20 comes from CC chemokine family. The significant function of chemokines is to function as a chemoattractant to guide cell migration. Chemokines are divided into the inflammatory or hemeostatic classification by their function (22). Homeostatic chemokines, such as CCL20, are constitutively produced in specific tissues and are accountable for basal leukocyte migration. Inflammatory chemokines, for instance, CCL2, cxcl10 and ccl3, rise by proinflammatory stimuli and assist manage adaptive and inherent immune actions (23). Direct proof revealed that OPN may cause distinction of Th17 cells in the peripheral blood and thyroid glands or draw in Th17 migration to thyroid glands of GD patients. The relationship in between OPN and CCL20/CCR6/Th17 axis in GD still have to be examined. More work on assessment of cytokines present in thyroid glands rather than flowing cytokines might supply more uncomplicated proofs about the association in between OPN and CCL20 in GD (22). Newest research studies recommended that osteopontin (OPN) caused Th17 reactions through amplification of IL-17 production, which moderated unfavorable impacts in several sclerosis (MS) and RA (24,25). OPN, a crucial proinflammatory cytokine with pleiotropic functions, has actually been firmly connected to lots of autoimmune illness, such as MS, RA and systemic lupus erythematosus (SLE) (26-31). Our previous research study suggested that OPN was exceedingly produced in GD patients and acted through the NF-κB path to improve the production of proinflammatory cytokines and chemokines (32). Since of its capability to improve the production of IFN-γ from T cells and IL-12 production from macrophages (33), OPN is categorized as a Th1 cytokine.

We recognized an essential research study (34) concerning CCL20 The patients in this research study were hired from the outpatient Department of Ruijin Hospital connected to Shang-hai Jiao Tong University. Fifty without treatment GD patients (uGD), 15 euthyroid GD patients (eGD), 12 TRAb-negative GD patients (nGD) and 35 age and gender matched healthy control donors (hCD) were picked. The requirements for choice of neglected Graves' illness patients consists of the following: patients are naïve to any treatment; the existence of common signs, such as heat intolerance, tiredness, increased hunger, increased sweating, weight-loss, muscle weak point, and tremblings; thyroid gland was diffusely bigger; lab medical diagnosis consisting of reduced serum delicate TSH (sTSH), increased totally free triiodothyronine

(FT3), thyroxine (FT4) and TSH receptor antibody (TRAb). eGD patients were uGD patients treated with methimazole (MMI) for 1-3 months till reaching typical TSH, FT3, and FT4 worths as the euthyroid state however TRAb level was simply somewhat reduced compared with preliminary GD patients. nGD patients were uGD patients treated with MMI for 1-2 years up until TSH, FT3, FT4 in addition to TRAb reduced to regular variety and preserved steady for a minimum of 3 months. hCDs were registered based upon history, regular health examination, measurements of thyroid hormonal agents, and thyroid autoantibodies, thyroid ultrasonography and left out the existence of thyroid conditions. the research study discovered plasma CCL20 levels in uGD patients were substantially greater than those from healthy control donors. [typical, 10.32 (interquartile variety, 6.815-- 15.97) pg/ml determined in 50 uGD patients versus 5.143 (interquartile variety 2.712-- 7.892) pg/ml determined in 35 hCD; P< 0.05] Compared to uGD patients, plasma CCL20 levels were minimized in eGD patients [3.940 (interquartile variety 2.059-- 8.969) pg/ml, P< 0.05] and nGD patients [5.006 (interquartile variety 2.993-- 8.673) pg/ml, P< 0.05] Regularly, CCL20 mRNA expression in CD4+ T cells increased in uGD patients compared with healthy topics however more reduced in GD remission patients (**Figure 2**). plasma concentrations of OPN were considerably increased in uGD patients compared to hCD [135.7 (interquartile variety 112.9-- 186.5) ng/ml determined in uGD patients versus 59.41 (interquartile variety 42.03-- 81.53) ng/ml determined in hCD; P< 0.001). We discovered that OPN level substantially decreased after medical treatment in eGD patients [88.86 (interquartile range 69.5–115.5) ng/ml, *P*<0.01] and nGD patients [78.91 (interquartile range 49.85–90.75) ng/ml, *P*<0.001] compared with uGD patients.

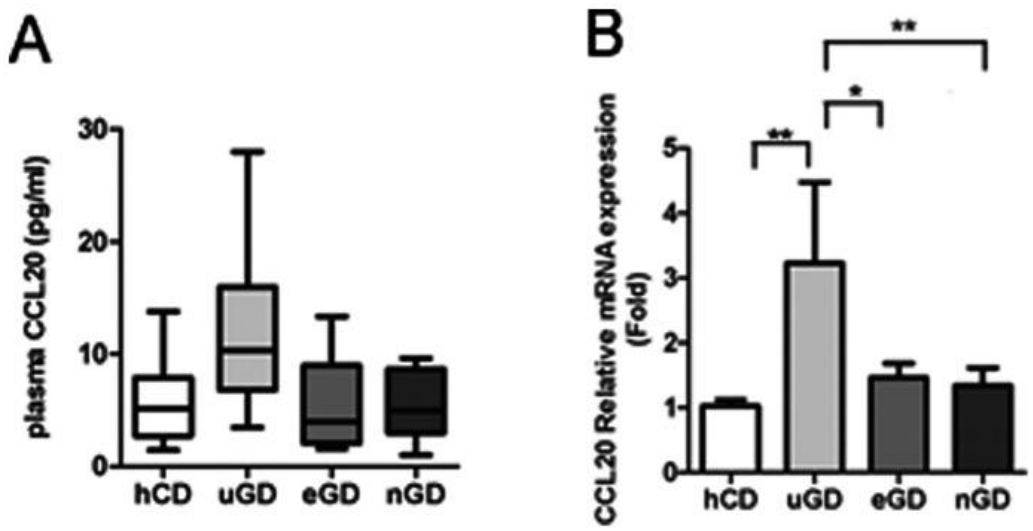

Figure 2: (A) Distribution of plasma CCL20 levels in 35 healthy control donors, 50 untreated GD patients, 15 euthyroid GD patients and 12 TRAb-negative GD patients. Median values, interquartile ranges and ranges are denoted by horizontal bars, boxes and vertical bars, respectively. (B) CCL20 mRNA levels in CD4+T cells from healthy controls, uGD, eGD and nGD patients. Data were presented as mean±SEM.*, *P*<0.05; **, *P*<0.01 (34).

Interleukin-2 (IL-2) and interleukin-10 (IL-10) as biomarkers of Graves' disease:

To determine whether the serum levels of IL-2 and IL-10 were altered in the GD patients when compared with the healthy controls, we identified a study (35) which aimed to determine whether the expression levels of interleukin (IL)-2 and IL-10 may be used as biological markers in Graves' disease (GD) patients. An overall of 256 people, consisting of 118 GD patients and 138 healthy people, were registered into the research study. Blood samples were gathered from each patient and healthy person, which were then subjected to enzyme-linked immunosorbent assay (ELISA). Overall RNA and overall proteins were figured out utilizing reverse transcription-quantitative polymerase domino effect (RT-qPCR) and western blot analysis, respectively. In addition, constraint piece length polymorphism (RFLP) analysis was carried out to discover the existence of hereditary polymorphisms.blood (1 ml) was gathered from all the patients and healthy people, followed by centrifugation for serum separation and decision of the serum levels utilizing ELISA. As displayed in (**Figure3**), the ELISA results exposed a 7-fold and 5.2-fold boost in the IL-2 and IL-10 serum levels, respectively, when compared to the healthy controls. These outcomes suggested that the IL-2 and IL-10 expression levels were modified in the GD patients(35).

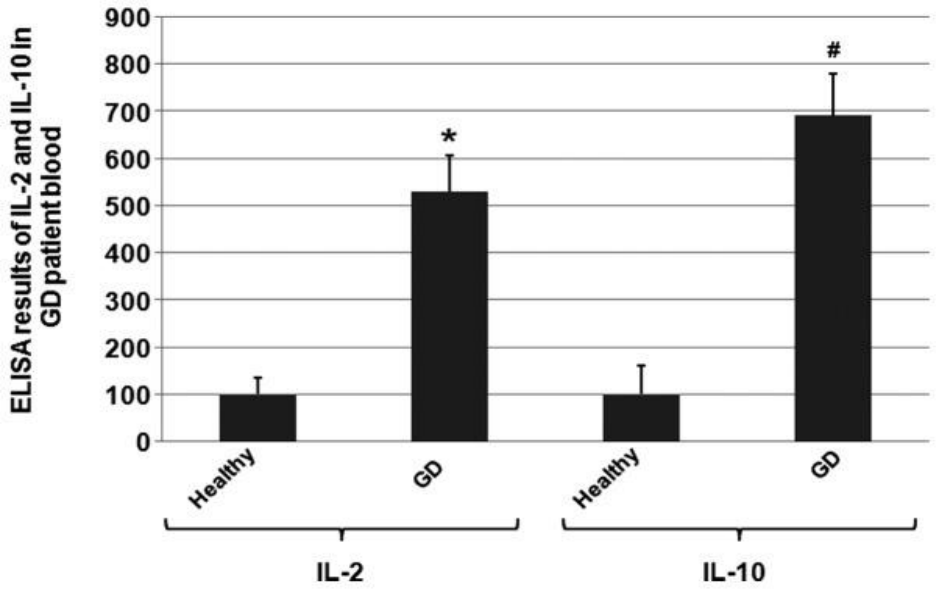

Figure3: Expression levels of IL-2 and IL-10 in the blood of the GD patients and healthy controls, determined by ELISA. The data (mean ± standard deviation) were obtained from four independent experiments and calculated against the ratios of the reading obtained from the healthy control groups, which was set to 100. *P<0.05, IL-2 vs. control; and #P<0.05, IL-10 vs. control. IL, interleukin; GD, Graves' disease.

REFERENCES

[1] Menconi F, Marcocci C, Marinò M. Diagnosis and classification of Graves' disease. Autoimmun Rev.2014;13:398–402. doi: 10.1016/j.autrev.2014.01.013.

[2] Park J, Kim JG, Park SP, Lee HW. Asymmetric chorea as presenting symptom in Graves' disease. Neurol Sci. 2012;33:343–345. doi: 10.1007/s10072-011-0679-0.

[3] Mohaseb K, Linder M, Rootman J, Wilkins GE, Schechter MT, Dolman PJ, Singer J. Development and validation of a patient symptom questionnaire to facilitate early diagnosis of thyroid-associated orbitopathy in graves' disease. Orbit. 2008;27:419–425. doi: 10.1080/01676830802414566.

[4] Brent GA. Clinical practice. Graves' disease. N Engl J Med. 2008;358:2594–605.

[5] Abraham-Nordling M, Wallin G, Tra¨isk F, et al. Thyroid-associated ophthalmopathy; quality of life follow-up of patients randomized to treatment with antithyroid drugs or radioiodine. Eur J Endocrinol. 2010;163:651–7.

[6] Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med. 2001;344:501–9.

[7] Imrie H, Vaidya B, Perros P, et al. Evidence for Graves' disease susceptibility locus at chromosome Xp11 in a United Kingdom population. J Clin Endocrinol Metab. 2001;86:626–630.

[8] Ngo ST, Stern FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocrinol.2014;35:347–369. doi: 10.1016/j.yfrne.2014.04.004.

[9] Rioux JD, Abbas AK. Paths to understanding the genetic basis of autoimmune disease. Nature.2005;435:584–589. doi: 10.1038/nature03723.

[10] Prummel MF, Strieder T, Wiersinga WM. The environment and autoimmune thyroid diseases. Eur J Endocrinol. 2004;150:605–618. doi: 10.1530/eje.0.1500605.

[11] Sorrentino R. Genetics of autoimmunity: an update. Immunol Lett. 2014;158:116–119. doi: 10.1016/j.imlet. 2013. 12. 005.

[12] Bordignon M, Bargagli E, Agostini Et Al C. TLR7 Gln11Leu single nucleotide polymorphism in patients with sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2013;30:157–161.

[13] Esfahanian F, Naimi E, Doroodgar F, Jadali Z. Th1/Th2 cytokines in patients with Graves' disease with or without ophthalmopathy. Iran J Allergy Asthma Immunol. 2013;12:168–175.

[14] Qin Q, Liu P, Liu L, et al. The increased but non-predominant expression of Th17- and Th1-specific cytokines in Hashimoto's thyroiditis but not in Graves' disease. Braz J Med Biol Res. 2012;45:1202–1208. doi: 10.1590/S0100-879X2012007500168.

[15] Antonelli A, Ferrari SM, Frascerra S, et al. Peroxisome proliferator-activated receptor α agonists modulate Th1 and Th2 chemokine secretion in normal thyrocytes and Graves' disease. Exp Cell Res.2011;317:1527–1533. doi: 10.1016/j.yexcr.2011.04.007.

[16] Ribot JC, Ribeiro ST, Correia DV, Sousa AE, Silva-Santos B. Human γδ thymocytes are functionally immature and differentiate into cytotoxic type 1 effector T cells upon IL-2/IL-15 signaling. J Immunol.2014;192:2237–2243. doi: 10.4049/jimmunol.1303119.

[17] Singh S, Singh U, Pandey SS. Serum concentration of IL-6, IL-2, TNF-α, and IFNγ in Vitiligo patients.Indian J Dermatol. 2012;57:12–14. doi: 10.4103/0019-5154.92668.

[18] Koh SJ, Kim JM, Kim IK, Ko SH, Kim JS. Anti-inflammatory mechanism of metformin and its effects in intestinal inflammation and colitis-associated colon cancer. J Gastroenterol Hepatol. 2014;29:502–510. doi: 10.1111/ jgh.12435.

[19] Ueki I, Abiru N, Kawagoe K, Nagayama Y. Interleukin 10 deficiency attenuates induction of anti-TSH receptor antibodies and hyperthyroidism in a mouse Graves' model. J Endocrinol. 2011;209:353–357. doi: 10.1530/JOE-11-0129.

[20] Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336-41.

[21] Diana T, Brown RS, Bossowski A, Segni M, Niedziela M, Koning J, et al. Clinical relevance of thyroid-stimulating autoantibodies in pediatric Graves' disease. A multicenter study. J Clin Endocrinol Metab (2014)99:1648–55.10.1210/jc.2013-4026.

[22] Le Y, Zhou Y, Iribarren P, Wang J (2004) Chemokines and chemokine receptors: their manifold roles in homeostasis and disease. Cell Mol Immunol 1: 95–104.

[23] Rotondi M, Chiovato L, Romagnani S, Serio M, Romagnani P (2007) Role of chemokines in endocrine autoimmune diseases. Endocr Rev 28: 492–520

[24] Murugaiyan G, Mittal A, Weiner HL (2008) Increased osteopontin expression in dendritic cells amplifies IL-17 production by CD4+ T cells in experimental autoimmune encephalomyelitis and in multiple sclerosis. J Immunol 181: 7480–7488.

[25] Chen G, Zhang X, Li R, Fang L, Niu X, et al. (2012) Role of osteopontin in synovial Th17 differentiation in rheumatoid arthritis. Arthritis Rheum 62: 2900–2908

[26] Wang KX, Denhardt DT (2008) Osteopontin: role in immune regulation and stress responses. Cytokine Growth Factor Rev 19: 333–345

[27] Ohshima S, Kobayashi H, Yamaguchi N, Nishioka K, Umeshita Sasai M, et al. (2002) Expression of osteopontin at sites of bone erosion in a murine experimental arthritis model of collagen-induced arthritis: possible involvement of osteopontin in bone destruction in arthritis. Arthritis Rheum 46: 1094–1101.

[28] Sakata M, Tsuruha JI, Masuko-Hongo K, Nakamura H, Matsui T, et al. (2001) Autoantibodies to osteopontin in patients with osteoarthritis and rheumatoid arthritis. J Rheumatol 28: 1492–1495.

[29] Niino M, Kikuchi S, Fukazawa T, Yabe I, Tashiro K (2003) Genetic polymorphisms of osteopontin in association with multiple sclerosis in Japanese patients. J Neuroimmunol 136: 125–129.

[30] Jansson M, Panoutsakopoulou V, Baker J, Klein L, Cantor H (2002) Cutting edge: attenuated experimental autoimmune encephalomyelitis in eta-1/osteopontin-deficient mice. J Immunol 168: 2096–2099.

[31] D'Alfonso S, Barizzone N, Giordano M, Chiocchetti A, Magnani C, et al. (2005) Two single-nucleotide polymorphisms in the 50 and 30 ends of the osteopontin gene contribute to susceptibility to systemic lupus erythematosus. Arthritis Rheum 52: 539–547.

[32] Xu L, Ma X, Wang Y, Li X, Qi Y, et al. (2011) The expression and pathophysiological role of osteopontin in Graves' disease. J Clin Endocrinol Metab 96(11): E1866–1870 [

[33] Sato T, Nakai T, Tamura N, Okamoto S, Matsuoka K, et al. (2005) Osteopontin/Eta-1 upregulated in Crohn's disease regulates the Th1 immune response. Gut 54: 1254–1262

[34] Xiaoli Li, Yicheng Qi, Xinran Ma,Fengjiao Huang, Hua Guo, Xiaohua Jiang, Jie Hong, Dongping Lin, Bin Cui, Guang Ning, Lingyan Xu, and Shu Wang. Chemokine (C-C Motif) Ligand 20, a Potential Biomarker for Graves' Disease, Is Regulated by Osteopontin. PLoS One. 2013; 8(5): e64277.. doi: 10.1371/journal.pone.0064277

[35] CUIGE LIANG, WENHUA DU, QINGYU DONG, XIAOMENG LIU, WENXIA LI, YUELI WANG, and GUANQI GAO. Expression levels and genetic polymorphisms of interleukin-2 and interleukin-10 as biomarkers of Graves' disease. Exp Ther Med. 2015 Mar; 9(3): 925–930.doi: 10.3892/etm.2015.2180.