

RECOMMENDATIONS

1. In view of this finding, thyroid function and anti-thyroid antibodies tests should be performed as part of the biochemical and immunological profile in RA patients.
2. Long term clinical follow-up studies of patients with rheumatoid arthritis and abnormal thyroid function tests are needed to relate the laboratory results to the clinical status, and to determine the relevance of the results to the management of these patients

REFERENCES

1. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence studies. *Arch Int Med* 2000; 160:526-34.
2. Schott M, Scherbaum WA. Autoimmune thyroid disease. *Dtsch Arztebl* 2006; 103(45):A 3023-32.
3. Swain M, Swain T, Mohanty BK. Autoimmune thyroid disorders-An update. *Indian J Clin Biochem* 2005; 20:9-17.
4. Larry J, Weetman AP. Disorders of the thyroid gland. In: Brunwald E, Fauci A (ed). *Harrison's principles of internal medicine*. 15th ed. Vol.2. New York, USA: McGraw-Hill Publication; 2001. 2060-84.
5. Yaqub A, Choudhry MI, Wheaton J, Gress T. Post ablative hypothyroidism. *W V Med J* 2011;107(2):37-40.
6. Ajjan RA, Kemp EH, Waterman EA, Waston PF, Endo T, Onaya T, et al. Detection of binding and blocking auto antibodies to the human sodium iodide transporter in patients with autoimmune thyroid disease. *J Clin Endocrinol Metab* 2000; 85: 2020-7.
7. Weetman, AP, McGregor AM. Autoimmune thyroid disease: Further developments in our understanding. *Endocr Rev* 1994; 15: 788-30.
8. Dittmar M, Kahaly GJ. Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. *J Clin Endocrinol Metab* 2003;88(7):2983-92.
9. Weetman AP. Endocrinology. In: Lechler RI, Warrens A (eds). *Handbook of HLA and disease*. 2nded. London: Academic Press; 2000;20(1):9-17.
10. Wan Q, Shah R, Panos JC, Giraldo AA, David CS, Kong YC. HLA-DR and HLA-DQ polymorphism in human thyroglobulin-induced autoimmune thyroiditis. *Hum Immunol* 2002; 63(4):301-10.
11. Falgarone G, Heshmati HM, Cohen R, Reach G. Role of emotional stress in the pathophysiology of Graves' disease. *Euro J Endocrinol* 2013;168:13–8.
12. Bartalena L, Bogazzi F, Tanda ML. Cigarette smoking and the thyroid. *Eur J Immunol* 1995; 133: 507-12.
13. Huang C, Fresca D, Jokic D, Wang X. Postpartum graves' hyperthyroidism in hashimoto's hypothyroidism. *Thyroid Sci* 2011; 6(3):1-5.
14. Strieder TG, Prummel MF, Tijssen JG, Endert E, Wiersinga WM. Risk factors for and prevalence of thyroid disorders in a crosssectional study among healthy female relatives of patients with autoimmune thyroid disorder. *Clin Endocrinol (Oxf)* 2003; 59(3): 396-401.
15. Kumar V. 24: the endocrine system. In: Kumar V, Abbas AK, Fausto N, Aster J (eds). *Robbins and Cotran pathologic mechanisms of disease*. 8thed. Philadelphia: Elsevier; 2010. 1112–3.

References

16. Bahn RS. Clinical review 157: Pathophysiology of Graves' ophthalmopathy: the cycle of disease. *J Clin Endocrinol Metab* 2003;88(5):1939-46.
17. Armengol MP, Juan M, Lucas-Martin A, Fernandez-Figueras MT, Jaraquemada D, Gallart T, et al. Thyroid autoimmune disease: demonstration of thyroid antigen-specific B cells and recombination-activating gene expression in chemokine-containing active intrathyroidal germinal centers. *Am J Pathol* 2001;159(3):861-73.
18. Marazuela M, Garcia-Lopez MA, Figueroa-Vega N, de la Fuente H, Alvarado-Sanchez B, Monsivais-Urenda A, et al. Regulatory T cells in human autoimmune thyroid disease. *J Clin Endocrinol Metab* 2006;91(9):3639-46.
19. Prasad KV, Prabhakar BS. Apoptosis and autoimmune disorders. *Autoimmunity* 2003; 36(6-7):323-30.
20. Ruf J, Carayon P. Structural and functional aspects of thyroid peroxidase. *Arch Biochem Biophys* 2006; 445 (2): 269–77.
21. Silva LM, Chavez J, Canalli MH, Zanetti CR. Determination of IgG subclasses and avidity of antithyroid peroxidase antibodies in patients with subclinical hypothyroidism - a comparison with patients with overt hypothyroidism. *Horm Res* 2003;59(3):118-24.
22. Kohno Y, Yamaguchi F, Saito K, Niimi H, Nishikawa T, Hosoya T. Anti-thyroid peroxidase antibodies in sera from healthy subjects and from patients with chronic thyroiditis: differences in the ability to inhibit thyroid peroxidase activities. *Clin Exp Immunol* 1991;85(3):459-63.
23. Pendersen IB, Knudsen N, Jorgensen T, et al. Thyroid peroxidase and thyroglobulin antibodies in a large survey of population with mild and moderate iodine deficiency. *Clin Endocrinol (OXF)* 2003;58:36.
24. Collison KS, Banga JP, Barnett PS, Huang GC, McGregor AM. Autoantibody stimulation of the human thyrotropin receptor: Regulation of adenylate cyclase activity, Thyroglobulin and thyroid peroxidase mRNA levels in primary cultures of Graves' thyroid tissue. *Clin Exp Immunol* 1991; 86: 61-5.
25. Spencer CA. thyroglobulin. In: Braver-Man LE, Utiger LD (eds). *Werner and Ingbar's the thyroid: a fundamental and clinical text*. 8th ed. Philadelphia: Lippincott Williams and Wilkins; 2000. 402.
26. Ghoraishian SM, Hekmati Moghaddam SH, Afkhami-Ardekani M. Relationship between Anti-Thyroid Peroxidase Antibody and Thyroid Function Test. *Iran J Immunol* 2006;3(3):146-9.
27. Kindt TJ, RA Goldsby, Osborne BA. *Kuby immunology*. New York: W.H. Freeman; 2007.
28. Mariotti S, Barbesino G, Caturegli P, Marinó M, Manetti L, Pacini F, et al. Assay of thyroglobulin in serum with thyroglobulin auto antibodies :an un obtainable goal?. *J Clin Endocrinol Metab* 1995;80:468-72.

References

29. Philips D, Prentice L, Upadhyaya M, Lunt P, Chamberlain S, Roberts DF, et al. Autosomal dominant inheritance of autoantibodies thyroid peroxidase and thyroglobulin: studies in families not selected for autoimmune thyroid disease. *J Clin Endocrinol Metab* 1991; 72: 973-5.
30. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf)* 1995;43(1):55-68.
31. Latif R, Morshed SA, Zaidi M, Davies TF. The thyroid-stimulating hormone receptor: impact of thyroid-stimulating hormone and thyroid-stimulating hormone receptor antibodies on multimerization, cleavage, and signaling. *Endocrinol Metab Clin North Am* 2009; 38:319-41.
32. Rapoport B, McLachlan SM. The thyrotropin receptor in Graves' disease. *Thyroid* 2007; 17:911-922.
33. Barbesino G, Tomer Y. Clinical utility of TSH receptor antibodies. *J Clin Endocrinol Metab* 2013;98(6):2247-55.
34. Schott M, Morgenthaler NG, Fritzen R, Feldkamp J, Willenberg HS, Scherbaum WA, et al. Levels of autoantibodies against human TSH receptor predict relapse of hyperthyroidism in graves' disease. *Horm Metab Res* 2004;(36):92-6.
35. Costagliola S, Morgenthaler NG, Hoermann R, Badenhop K, Struck J, Freitag D, et al. Second generation assay for thyrotropin receptor antibodies has superior diagnostic sensitivity for Graves' disease. *J Clin Endocrinol Metab* 1999;84:90-7.
36. Brent GA. Clinical practice Graves' disease. *N Engl J Med* 2008;358:2594-605.
37. Orgiazzi J. Anti-TSH receptor antibodies in clinical practice. *Endocrinol Metab Clin North Am* 2000; 29: 339-55.
38. Eckstein AK , Plicht M , Lax H, Hirche H, Quadbeck B, Mann K, et al. Clinical results of anti inflammatory therapy in graves' ophthalmopathy and association with thyroidal auto antibodies. *Clin Endocrinol (oxf)* 2004;(61):612-8.
39. Eckstein AK, Plicht M, Lax H, Neuhäuser M, Mann K, Lederbogen S, et al. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. *J Clin Endocrinol Metab* 2006;91:3464-70.
40. Crisanti P, Omri B, Hughes E, Meduri G, Hery C, Clauser E, et al . The expression of thyrotropin receptor in the brain. *Endocrinology* 2001; 142:812–22.
41. Graves PN, Davies TF. New insights into the thyroid-stimulating hormone receptor: the major antigen of Graves' disease. *Endocrinol Metab Clin North Am* 2000; 29:267–86.
42. Chin HS, Chin DKH, Morgenthaler NG, Vassart G, Costagliola S. Rarity of anti-Na⁺/I⁻ transporter (NIS) antibody with iodide uptake inhibiting activity in autoimmune thyroid diseases (AITD). *J Clin Endocrin Metab* 2000;85:3937-40.

References

43. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T4, and thyroid antibodies in the United states population (1988 to 1994): National health and Nutrition Examination Durvey (NHALES III). *J Clin Endocrinol Metab* 2002; 87:489-99.
44. Dayan CM, Daniels GH. Chronic autoimmune thyroiditis. *N Engl J Med* 1996;335:99–107.
45. Vanderpump MP, Tunbridge WM. Epidemiology and prevention of clinical and subclinical hypothyroidism. *Thyroid* 2002; 12:839-47.
46. Jenkins RC, Weetman AP. Disease associations with autoimmune thyroid disease. *Thyroid* 2002; 12:977-88.
47. Einarsdottir E, Soderstrom I, Lofgren-Burstrom A, Haraldsson S, Nilsson-Ardnor S, Penha-Goncalves C, et al. The CTLA4 region as a general autoimmunity factor: an extended pedigree provides evidence for synergy with the HLA locus in the etiology of type 1 diabetes mellitus, Hashimoto's thyroiditis and Graves' disease. *Eur J Hum Genet* 2003, 11:81-4.
48. Cao L, Wang F, Yang QG, Jiang W, Wang C, Chen YP, et al. Reduced thyroid hormones with increased hippocampal SNAP-25 and Munc18-1 might involve cognitive impairment during aging. *Behav Brain Res* 2012; 229(1):131-7.
49. Klein I, Danzi S. Thyroid disease and the heart. *Circulation* 2007; 116:1725.
50. Taddei S, Caraccio N, Viridis A, Dardano A, Versari D, Ghiadoni L, et al. Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. *J Clin Endocrinol Metab* 2003; 88:3731-7.
51. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med* 2001; 344:501-9.
52. Felz MW, Forren AC. Profound hypothyroidism—a clinical review with eight recent cases: is it right before our eyes? *South Med J* 2004;97:490-8.
53. Chen JL, Chiu HW, Tseng YJ, Chu WC. Hyperthyroidism is characterized by both increased sympathetic and decreased vagal modulation of heart rate: evidence from spectral analysis of heart rate variability. *Clin Endocrinol (Oxf)* 2006;64(6):611-6.
54. Boelaert K, Newby PR, Simmonds MJ, Holder RL, Carr-Smith JD, Heward JM, et al. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med* 2010;123(2):183.e1–9.
55. Ebert EC. The thyroid and the gut. *J Clin Gastroenterol* 2010;44(6):402–6.
56. Hegazi MO, El-sonbaty MR. Unusual presentations of hyperthyroidism. In: Mertens L, Bogaert J (eds). *Handbook of hyperthyroidism: etiology, diagnosis and treatment*. New York: Nova Publishers; 2011. 265–70.
57. Klein I, Danzi S. Thyroid disease and the heart. *Circulation* 2007;116(15):1725–35.

References

58. Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, et al. Prevalence and Natural History of Graves' Orbitopathy in a Large Series of Patients with Newly Diagnosed Graves' Hyperthyroidism Seen at a Single Center. *J Clin Endocrinol Metab* 2013; 98(4):1443-9.
59. Konuk EB, Konuk O, Misirlioglu M, Menevse A, Unal M. Expression of cyclooxygenase-2 in orbital fibroadipose connective tissues of Graves' ophthalmopathy patients. *Eur J Endocrinol* 2006;155(5):681-5.
60. Anderson CK, Miller OF 3rd. Triad of exophthalmos, pretibial myxedema, and acropachy in a patient with Graves' disease. *J Am Acad Dermatol* 2003; 48(6):970-2.
61. Wikland B, Sandberg PO, Wallinder H . Subchemical hypothyroidism. *Lancet* 2003; 361(9365): 1305.
62. Kim PS, Dunn AD, Dunn JT. Altered immunoreactivity of thyroglobulin in thyroid disease. *J Clin Endocrinol Metab* 1988; 67:161-8.
63. Coles AJ, Wing M, Smith S, Coraddu F, Greer S, Taylor C, et al. Pulsed monoclonal antibody treatment and autoimmune thyroid disease in multiple sclerosis. *Lancet* 1999; 354: 1691–5.
64. Ross DS. Syndromes of thyrotoxicosis with low radioactive iodine uptake. *Endocrinol Metab Clin North Am* 1998; 27: 169–85.
65. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, et al. Guidelines Committee, National Academy of Clinical Biochemistry Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease .*Thyroid* 2003; 13 (1): 3-126.
66. Stephen A, Falk MDS. Diagnostic imaging in thyroid diseases *Endocrinology and Surgery* 1995; 7:81.
67. Ruchaa M, Szczepanek E. Thyroid ultrasound-a piece of cake? *Endokrynol Pol* 2010; 61:330-44.
68. Anderson L, Middleton WD, Teefey SA, Reading CC, Langer JE, Desser T, et al. Hashimoto thyroiditis: part 1,sonographic analysis of the nodular form of hashimoto thyroiditis. *AJR Am J Roentgenol* 2010;195:208-15.

References

69. Anderson L, Middleton WD, Teefey SA, Reading CC, Langer JE, Desser T, et al. Hashimoto thyroiditis: Part 2, sonographic analysis of benign and malignant nodules in patients with diffuse Hashimoto thyroiditis. *AJR Am J Roentgenol* 2010;195:216-22.
70. Fatourechi V, Aniszewski JP, Fatourechi GZ, Atkinson EJ, Jacobsen SJ. Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmsted County, Minnesota, study. *J Clin Endocrinol Metab* 2003;88:2100-5.
71. Zantut-Wittmann DE, Persoli L, Tambascia MA, Fischer E, Franco Maldonado D, Costa AM, et al. HLA-DRB1*04 and HLA-DQB1*03 association with the atrophic but not with the goitrous form of chronic autoimmune thyroiditis in a Brazilian population. *Horm Metab Res* 2004; 36:492-500.
72. Chabchoub G, Mnif M, Maalej A, Charfi N, Ayadi H, Abid M. Epidemiologic study of autoimmune thyroid disease in south Tunisia. *Ann Endocrinol (Paris)* 2006; 67:591-5.
73. Lahner H, Quadbeck B, Janssen OE, Mann K. Diagnosis and treatment of autoimmune thyroiditis. *MMW Fortschr Med* 2004; 146: 28-30.
74. Farwell AP, Braverman LE. Inflammatory thyroid disorders. *Otolaryngol Clin North Am* 1996; 29:541-56.
75. Schubert MF, Kountz DS. Thyroiditis: a disease with many faces. *Postgrad Med* 1995;98:101-12.
76. Sachs HC. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. *Pediatrics* 2013; 132(3):e796-809.
77. Roti E, Emerson CH. Clinical review 29: postpartum thyroiditis. *J Clin Endocrinol Metab* 1992; 74:3-5.
78. Singer PA. Thyroiditis: acute, subacute, and chronic. *Med Clin North Am* 1991; 75:61-77.
79. Nassar MM, Dickinson AJ, Neoh C, Powell C, Buck D, Galal E, et al. Parameters predicting outcomes of strabismus surgery in the management of Graves' ophthalmopathy. *J AAPOS* 2009;13(3):236-40.
80. Ujhelyi B, Erdei A, Galuska L, Varga J, Szabados L, Balazs E, et al. Retrobulbar ^{99m}Tc-diethylenetriamine-pentaacetic-acid uptake may predict the effectiveness of immunosuppressive therapy in Graves' ophthalmopathy. *Thyroid* 2009;19(4):375-80.
81. Dodds NI, Atcha AW, Birchall D, Jackson A. Use of high-resolution MRI of the optic nerve in Graves' ophthalmopathy. *Br J Radiol* 2009;82(979):541-4.

References

82. Meurisse M, Gollogly L, Degauque C, Fumal I, Defechereux T, Hamoir E. Iatrogenic thyrotoxicosis: causal circumstances, pathophysiology, and principles of treatment-review of the literature. *World J Surg* 2000 ;24(11):1377-85.
83. Newman CM, Price A, Davies DW, Gray TA, Weetman AP. Amiodarone and the thyroid: A practical guide to the management of thyroid dysfunction induced by amiodarone therapy. *Heart* 1998;79:121-7.
84. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. *N Engl J Med* 2003; 348:2646.
85. Scott DL, Symmons DP, Coulton BL, Popert AJ. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987; 1:1108-11.
86. Mitchell DM, Spitz PW, Young DY, Bloch DA, McShane DJ, Fries JF. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986; 29: 706-14.
87. Pincus T, Callahan LF, Sale WG, Brooks AL, Payne LE, Vaughn WK. Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. *Arthritis Rheum* 1984;27:864-72.
88. Isomaki H. Long-term outcome of rheumatoid arthritis. *Scand J Rheumatol Suppl* 1992; 95:3-8.
89. Wolfe F. The natural history of rheumatoid arthritis. *J Rheumatol Suppl* 1996;44:13-22.
90. Aho K, Heliövaara M, Maatela J, Tuomi T, Palosuo T. Rheumatoid factors antedating clinical rheumatoid arthritis. *J Rheumatol* 1991; 18:1282-4.
91. Aho K, von Essen R, Kurki P, Palosuo T, Heliövaara M. Antikeratin antibody and antiperinuclear factor as markers for subclinical rheumatoid disease process. *J Rheumatol* 1993;20:1278-81.
92. Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum* 2004; 50:380-6.
93. Rantapaa-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum* 2003; 48:2741-9.
94. Firestein GS. Evolving concepts of rheumatoid arthritis. *Nature* 2003;423;356-61.
95. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for the treatment of rheumatoid arthritis. *Lancet* 2007; 370:1861-74.
96. Bohndorf K, Schalm J. Diagnostic radiography in rheumatoid arthritis: benefits and limitations. *Baillieres Clin Rheumatol* 1996; 10:399-407.

References

97. Van der Heijde DM. Joint erosions and patients with early rheumatoid arthritis. *Br J Rheumatol* 1995; 34 (Suppl 2):74–8.
98. Plant MJ, Jones PW, Saklatvala J, Ollier WE, Dawes PT. Patterns of radiological progression in rheumatoid arthritis: results of an 8 year prospective study. *J Rheumatol* 1998; 25:417–26.
99. Wolfe F, Sharp JT. Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. *Arthritis Rheum* 1998;41:1571–82.
100. Machold KP, Stamm TA, Eberl GJ, Nell VK, Dunky A, Uffmann M, et al. Very recent onset arthritis: clinical, laboratory, and radiological findings during the first year of disease. *J Rheumatol* 2002;29:2278–87.
101. Bijlsma JW, Weinblatt ME. Optimal use of methotrexate: the advantages of tight control. *Ann Rheum Dis* 2007;66:1409–10.
102. Pincus T, Yazici Y, Sokka T, Aletaha D, Smolen JS. Methotrexate as the “anchor drug” for the treatment of early rheumatoid arthritis [review]. *Clin Exp Rheumatol* 2003;21 (Suppl 31):S179–85.
103. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. *Ann Rheum Dis* 2009; 68:1094–9.
104. Doan T, Massarotti E. Rheumatoid arthritis: an overview of new and emerging therapies. *J Clin Pharmacol* 2005;45:751–62.
105. Van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort C, van der Veen MJ, et al. The effectiveness of early treatment with “second-line” anti-rheumatic drugs: a randomized controlled trial. *Ann Intern Med* 1996;124:699–707.
106. Bukhari MA, Wiles NJ, Lunt M, Harrison BJ, Scott DG, Symmons DP, et al. Influence of disease-modifying therapy on radiographic outcome in inflammatory polyarthritis at five years: results from a large observational inception study. *Arthritis Rheum* 2003;48:46–53.
107. Van Dongen H, van Aken J, Lard LR, Visser K, Roday HK, Hulsmans HM, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double blind randomized, placebo-controlled trial. *Arthritis Rheum* 2007;56:1424–32.
108. Emery P. The Dunlop-Dottridge Lecture: prognosis in inflammatory arthritis: the value of HLA genotyping and the oncological analogy. *J Rheumatol* 1997;24: 1436–42.
109. Banal F, Dougados M, Combescure C, Gossec L. Sensitivity and specificity of the American College of Rheumatology 1987 criteria for the diagnosis of rheumatoid arthritis according to disease duration: a systematic literature review and meta-analysis. *Ann Rheum Dis* 2009; 68: 1184–91.
110. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31(3):315–24.

References

111. Aletaha D, Neogi T, Silman A, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69: 1580–8.
112. Hyrich KL, Symmons DP, Silman AJ. OMERACT 7 special interest group, reconciling subject differences in recruitment to clinical trials and clinical practice. *J Rheumatol* 2005; 32:2475-6.
113. Aletaha D, Neogi T, Silman A, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69: 1580–8.
114. Funovits J, Aletaha D, Bykerk V, Combe B, Dougados M, Emery P, et al. The 2010 American College of Rheumatology/European League against Rheumatism classification criteria for rheumatoid arthritis: methodological report phase I. *Ann Rheum Dis* 2010; 69:1589–95.
115. Neogi T, Aletaha D, Silman AJ, Naden RL, Felson DT, Aggarwal R, et al. The 2010 American College of Rheumatology/European League against Rheumatism classification criteria for rheumatoid arthritis: phase 2 methodological report. *Arthritis Rheum* 2010; 62:2582–91.
116. Smolen JS, Steiner G. Therapeutic strategies for rheumatoid arthritis. *Nat Rev Drug Discov* 2003;2:473-88.
117. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. *Lancet* 2007;370:1861-74.
118. McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. *Nat Rev Immunol* 2007;7:429-42.
119. Schett G. Cells of the synovium in rheumatoid arthritis. Osteoclasts. *Arthritis Res Ther* 2007;9:203.
120. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature* 2006; 441:235-8.
121. Harris ED. Clinical features of rheumatoid arthritis. In: Ruddy S, Harris ED, Sledge CB, Kelley WN (eds). *Kelley's textbook of rheumatology*. 7thed. Philadelphia: WB Saunders; 2005. 1043–78.
122. Akil M, Amos RS. ABC of rheumatology: rheumatoid arthritis—I, clinical features and diagnosis. *BMJ* 1995;310:587–90.
123. Colledge NR, Walker BR, Ralston S, Davidson S. *Davidson's principles and practice of medicine*. 21sted. Edinburgh: Churchill Livingstone/Elsevier; 2010.

References

124. Eustice C. What is rheumatoid lung disease?. Arthritis.about.com 2011. Available from:<http://arthritis.about.com/od/rheumatoidarthritis/a/rheumatoidlung.htm> [Accessed On: 3 Mar, 2014].
125. de Groot K. Renal manifestations in rheumatic diseases. *Internist (Berl)* 2007; 48(8): 779–85.
126. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum* 2008; 59 (12): 1690–7.
127. Gupta A, Fomberstein B. Evaluating cardiovascular risk in rheumatoid arthritis. *J Musculoskeletal Med* 2009; 26 (8): 481–94.
128. Rehman H. Hemolytic anemia following mycoplasma infection. *Inter J Hematol* 2008; 4 (1):1-2.
129. Balint GP, Balint PV. Felty's syndrome. *Best Pract Res Clin Rheumatol* 2004; 18 (5): 631–45.
130. Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum* 2006; 54 (3): 692–701.
131. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. *Clin Exp Rheumatol* 2005;23(5 Suppl 39):S93-9.
132. Swaak A. Anemia of chronic disease in patients with rheumatoid arthritis: aspects of prevalence, outcome, diagnosis, and the effect of treatment on disease activity. *J Rheumatol* 2006; 33:1467.
133. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999; 340:448.
134. Westwood OM, Nelson PN, Hay FC. Rheumatoid factors: what's new?. *Rheumatology (Oxford)* 2006; 45 (4): 379–85.
135. Whiting PF, Smidt N, Sterne JA, Harbord R, Burton A, Burke M, et al. Systematic review: accuracy of anti-citrullinated Peptide antibodies for diagnosing rheumatoid arthritis. *Ann Intern Med* 2010; 152:456.
136. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med* 2007; 146:797-808.
137. Luime JJ, Colin EM, Hazes JM, Lubberts E. Does anti-mutated citrullinated vimentin have additional value as a serological marker in the diagnostic and prognostic investigation of patients with rheumatoid arthritis?, a systematic review. *Ann Rheum Dis* 2010; 69:337--44.

References

138. Pinheiro GC, Scheinberg MA, Aparecida da Silva M, Maciel S. Anti-cyclic citrullinated peptide antibodies in advanced rheumatoid arthritis. *Ann Intern Med* 2003;139:234-5.
139. Alessandri C, Bombardieri M, Papa N, Cinquini M, Magrini L, Tincani A, et al. Decrease of anti-cyclic citrullinated peptide antibodies and rheumatoid factor following anti-TNFalpha therapy (infliximab) in rheumatoid arthritis is associated with clinical improvement. *Ann Rheum Dis* 2004;63:1218-21.
140. Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis. *Lancet* 2009; 373:659.
141. Khan MA. Update on spondyloarthropathies. *Ann Intern Med* 2002; 136:896-807.
142. Phan TG, Wong RC, Adelstein S. Autoantibodies to extractable nuclear antigens: making detection and interpretation more meaningful. *Clin Diagn Lab Immunol* 2002; 9:1.
143. Klarlund M, Østergaard M, Jensen KE, Madsen JL, Skjødt H, Lorenzen I. Magnetic resonance imaging, radiography, and scintigraphy of the finger joints: one year follow up of patients with early arthritis. *Ann Rheum Dis* 2000; 59: 521–8.
144. Watt I. Basic differential diagnosis of arthritis. *Eur Radiol* 1997; 7: 344–51.
145. Ødegaard S, Landewe R, van der Heijde D, Kvien TK, Mowinckel P, Uhlig T. Association of early radiographic damage with impaired physical function in rheumatoid arthritis: a ten-year, longitudinal observational study in 238 patients. *Arthritis Rheum* 2006; 54: 68–75.
146. Døhn UM, Ejbjerg BJ, Court-Payen M, Hasselquist M, Narvestad E, Szkudlarek M, et al. Are bone erosions detected by magnetic resonance imaging and ultrasonography true erosions? a comparison with computed tomography in rheumatoid arthritis metacarpophalangeal joints. *Arthritis Res Ther* 2006; 8(4): R110.
147. Østergaard M, Stoltenberg M, Løvgreen-Nielsen P, Volck B, Sonne-Holm S, Lorenzen I. Quantification of synovitis by MRI: correlation between dynamic and static gadolinium-enhanced magnetic resonance imaging and microscopic and macroscopic signs of synovial inflammation. *Magn Reson Imaging* 1998;16: 743–75.
148. Grassi W, Cervini C. Ultrasonography in rheumatology: an evolving technique. *Ann Rheum Dis* 1998; 57: 268–71.
149. Hau M, Kneitz C, Tony HP, eberle M, Jahns R, Jenett M High resolution ultrasound detects a decrease in pannus vascularization of small finger joints in patients with rheumatoid arthritis receiving treatment with soluble tumour necrosis factor alpha receptor (etanercept). *Ann Rheum Dis* 2002;61: 55–8.

150. Terslev L, Torp-Pedersen S, Qvistgaard E, Danneskiold-Samsøe B, Bliddal H. Estimation of inflammation by Doppler ultrasound: quantitative changes after intra-articular treatment in rheumatoid arthritis. *Ann Rheum Dis* 2003; 62: 1049–53.
151. Backhaus M, Burmester GR, Sandrock D, Loreck D, Hess D, Scholz A, et al. Prospective two year follow up study comparing novel and conventional imaging procedures in patients with arthritic finger joints. *Ann Rheum Dis* 2002; 61: 895–904.
152. Swen WAA, Jacobs JWG, Hubach PCG, Klasens JH, Algra PR, Bijlsma JW. Comparison of sonography and magnetic resonance imaging for the diagnosis of partial tears of finger extensor tendons in rheumatoid arthritis. *Rheumatology* 2000; 39: 55–62.
153. Grassi W, Filippucci E, Farina A, Cervini C. Sonographic imaging of tendons. *Arthritis Rheum* 2000; 43: 969–76.
154. Strating MM, Van Schuur WH, Suurmeijer TP. Predictors of functional disability in rheumatoid arthritis: results from a 13-year prospective study. *Disabil Rehabil* 2007; 29(10):805–15.
155. Guillemin F, Gerard N, van Leeuwen M, Smedstad LM, Kvien TK, van den Heuvel W. Prognostic factors for joint destruction in rheumatoid arthritis: a prospective longitudinal study of 318 patients. *J Rheumatol* 2003;30(12):2585–9.
156. Dixey J, Solymossy C, Young A. Is it possible to predict radiological damage in early rheumatoid arthritis (RA)? A report on the occurrence, progression, and prognostic factors of radiological erosions over the first 3 years in 866 patients from the early RA study (ERAS). *J Rheumatol* 2004;31(Suppl 69): 48–54.
157. Uhlig T, Smedstad LM, Vaglum P. The course of rheumatoid arthritis and predictors of psychological, physical and radiographic outcome after 5 years of follow-up. *Rheumatology* 2000;39(7):732–41.
158. Forslind K, Ahlmen M, Eberhardt K, Hafström I, Svensson B. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: Role of antibodies to citrullinated peptides (anti-CCP). *Ann Rheum Dis* 2004;63(9):1090–5.
159. Herrero-Beaumont G, Bjerneboe O, Richarz U. Transdermal fentanyl for the treatment of pain caused by rheumatoid arthritis. *Rheumatol Int* 2004;24(6):325–32.
160. Berliner MN, Giesecke T, Bornhovd KD. Impact of transdermal fentanyl on quality of life in rheumatoid arthritis. *Clin J Pain* 2007;23(6):530–4.
161. Frank RG, Kashani JH, Parker JC, Beck NC, Brownlee-Duffeck M, Elliott TR, et al. Antidepressant analgesia in rheumatoid arthritis. *J Rheumatol* 1988; 15(11):1632–8.
162. Seideman P. Additive effect of combined naproxen and paracetamol in rheumatoid arthritis. *Br J Rheumatol* 1993;32(12):1077–82.

References

163. Shi W. Safety and efficacy of oral nonsteroidal anti-inflammatory drugs in patients with rheumatoid arthritis: a six-month randomised study. *Clin Drug Investig* 2004;24(2):89–101.
164. Kirwan JR, Hallgren R, Mielants H, Wollheim F, Bjorck E, Persson T, et al. A randomised placebo controlled 12 week trial of budesonide and prednisolone in rheumatoid arthritis. *Ann Rheum Dis* 2004;63(6):688–95.
165. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. *N Engl J Med* 1995;333(3):142–6.
166. Svensson B, Boonen A, Albertsson K, van der Heijde D, Keller C, Hafström I. Low-dose prednisolone in addition to the initial disease modifying anti-rheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: A two-year randomized trial. *Arthritis Rheum* 2005; 52(11):3360–70.
167. Van Everdingen AA, Jacobs JW, Siewertsz van Reesema DR. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. *Ann Intern Med* 2002;136(1):1–12.
168. Van Everdingen AA, Siewertsz van Reesema DR, Jacobs JW, Bijlsma JW. The clinical effect of glucocorticoids in patients with rheumatoid arthritis may be masked by decreased use of additional therapies. *Arthritis Rheum* 2004;51(2):233–8.
169. Wassenberg S, Rau R, Steinfeld P, Zeidler H. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: A multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005;52(11):3371–80.
170. Van Vliet-Daskalopoulou E, Jentjens T, Scheffer RTC. Intra-articular rimexolone in the rheumatoid knee: A placebo-controlled, double-blind, multicentre trial of three doses. *Br J Rheumatol* 1987;26(6):450–3.
171. Hansen M, Podenphant J, Florescu A, Stoltenberg M, Borch A, Kluger E, et al. A randomised trial of differentiated prednisolone treatment in active rheumatoid arthritis: clinical benefits and skeletal side effects. *Ann Rheum Dis* 1999; 58(11):713–8.
172. Corkill MM, Kirkham BW, Chikanza IC, Gibson T, Panayi GS. Intramuscular depot methylprednisolone induction of chrysotherapy in rheumatoid arthritis: a 24-week randomized controlled trial. *Br J Rheumatol* 1990;29(4):274–9.
173. Luqmani R, Hennell S, Estrach C, Birrell F, Bosworth A, Davenport G, et al. British Society for Rheumatology and british health professionals in Rheumatology guideline for the management of rheumatoid arthritis (the first two years). *Rheumatology (Oxford)* 2006;45(9):1167-9.
174. Nandi P, Kingsley GH, Scott DL. Disease-modifying anti-rheumatic drugs other than methotrexate in rheumatoid arthritis and seronegative arthritis. *Curr Opin Rheumatol* 2008; 20 (3): 251–6.

References

175. Allaart CF, Goekoop-Ruiterman YP, De Vries-Bouwstra JK, Breedveld FC, Dijkmans BA. Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. *Clin Exp Rheumatol* 2006;24(6 Suppl 43):1–77.
176. Goekoop-Ruiterman YP, de Vries BJK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007;146(6):406–15.
177. Goekoop-Ruiterman YP, De Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the best study): A randomized, controlled trial. *Arthritis Rheum* 2005;52(11):3381–90.
178. Van der Kooji SM, De Vries-Bouwstra JK, Goekoop-Ruiterman YP, et al. Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. *Ann Rheum Dis* 2007;66(10):1356–62.
179. Ferraccioli GF, Gremese E, Tomietto P, Favret G, Damato R, Di Poi E.. Analysis of improvements, full responses, remission and toxicity in rheumatoid patients treated with step-up combination therapy (methotrexate, cyclosporin A, sulphasalazine) or monotherapy for three years. *Rheumatology* 2002;41(8):892–8.
180. Furst DE. The risk of infections with biologic therapies for rheumatoid arthritis. *Semin Arthritis Rheum* 2010;39:327–46.
181. National Institute for Health and Clinical Excellence. Rituximab for the treatment of Rheumatoid Arthritis. (TA126). London: NICE; 2007.
182. National Institute for Health and Clinical Excellence. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. (TA130). London: NICE; 2007.
183. National Institute for Health and Clinical Excellence. Abatacept for the Treatment of Rheumatoid Arthritis. (TA141). London: NICE; 2008.
184. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003;48(1):35–45.
185. Klareskog L, Van Der HD, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004;363(9410):675–81.
186. Van der Heijde D, Klareskog L, Singh A, Tornero J, Melo-Gomes J, Codreanu C, et al. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. *Ann Rheum Dis* 2006;65(3):328–34.

References

187. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004; 50 (5):1400–11.
188. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, et al. Adalimumab, a fully human anti tumor necrosis factor alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (safety trial of adalimumab in rheumatoid arthritis). *J Rheumatol* 2003;30(12):2563–71.
189. Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. *Ann Rheum Dis* 2006;65(10):1357–62.
190. Westhovens R, Cole JC, Li T, Martin M, Maclean R, Lin P, et al. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. *Rheumatology*. 2006;45(10):1238–46.
191. Van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* 2006;54(4): 1063–74.
192. Strand V, Balbir GA, Pavelka K, Emery P, Li N, Yin M, et al. Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years. *Rheumatology* 2006; 45(12):1505–13.
193. Bresnihan B, Newmark R, Robbins S, Genant HK. Effects of anakinra monotherapy on joint damage in patients with rheumatoid arthritis. Extension of a 24-week randomized, placebo-controlled trial. *J Rheumatol* 2004;31(6):1103–11.
194. Nuki G, Bresnihan B, Bear MB, McCabe D. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002;46(11):2838–46.
195. Smolen J. On behalf of the EULAR Task Force. Session 10: update of EULAR rheumatoid arthritis management recommendations. Presented at: EULAR 2013, the Annual Congress of the European League Against Rheumatism; Madrid, Spain; June 15, 2013.
196. Fransen J, Moens HB, Speyer I, van Riel PL. Effectiveness of systematic monitoring of rheumatoid arthritis disease activity in daily practice: a multicentre, cluster randomised controlled trial. *Ann Rheum Dis* 2005;64(9):1294–8.

References

197. Verstappen SM, Jacobs JW, Van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis* 2007;66(11):1443–9.
198. Alderman AK, Ubel PA, Kim HM, Fox DA, Chung KC. Surgical management of the rheumatoid hand: consensus and controversy among rheumatologists and hand surgeons. *J Rheumatol* 2003; 30(7):1464–72.
199. Alderman AK, Arora AS, Kuhn L, Wei Y, Chung KC. An analysis of women's and men's surgical priorities and willingness to have rheumatoid hand surgery. *J Hand Surg Am* 2006; 31(9):1447–53.
200. Anaya JM, Shoenfeld Y, Correa PA, García-Carrasco M, Cervera R. Autoinmunidad y enfermedad autoinmune,corporación para investigaciones biológicas. 1sted. Colombia: Medellin; 2005.
201. Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases:improved estimates and clustering of diseases. *J Autoimmune* 2009;33:197-207.
202. Goris A, Liston A. The immunogenetic architecture of autoimmune disease. *Cold Spring Harb Perspect Biol* 2012;4(3): 1-14.
203. Anaya JM. The autoimmune tautology. *Arthritis Res Ther* 2010;12(6):147.
204. Anaya JM, Corena R, Castiblanco J, Rojas-Villarraga A, Shoenfeld Y. The kaleidoscope of autoimmunity: multiple autoimmune syndromes and familial autoimmunity. *Expert Rev Clin Immunol* 2007;3(4):623-35.
205. Gutierrez-Achury J, Coutinho de Almeida R, Wijmenga C. Shared genetics in coeliac disease and other immune mediated diseases. *J Intern Med* 2011; 269(6):591-603.
206. Anaya JM, Shoenfeld Y, Correa PA, García-Carrasco M, Cervera R. Autoinmunidad y enfermedad autoinmune,corporación para investigaciones biológicas. 1sted. Colombia: Medellin; 2005.
207. Cotsapas C, Voight BF, Rossinetal E, Lage K, Neale BM, Wallace C, et al. Pervasive sharing of genetic effects in autoimmune disease. *PLoS Genetics* 2011; 7(8): 1-8.
208. Barker JM. Clinical review: type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. *J Clin Endocrinol Metab* 2006;91:1210-7.
209. Tait KF, Marshall T, Berman J, Carr-Smith J, Rowe B, Todd JA, et al. Clustering of autoimmune disease in parents of siblings from the type 1 diabetes Warren repository. *Diabet Med* 2004;21: 358-62.
210. Laberge G, Mailloux CM, Gowan K, Holland P, Bennett DC, Fain PR, et al. Early disease onset and increased risk of other autoimmune diseases in familial generalized vitiligo. *Pigment Cell Res* 2005; 18: 300-5.

References

211. Kasperlik-Zaluska A, Czarnocka B, Czech W. High prevalence of thyroid autoimmunity in idiopathic Addison's disease. *Autoimmunity* 1994;18:213-6.
212. Barcellos LF, Kamdar BB, Ramsay PP, DeLoa C, Lincoln RR, Caillier S, et al. Clustering of autoimmune diseases in families with a high-risk for multiple sclerosis: a descriptive study. *Lancet Neurol* 2006;5:924-31.
213. Broadley SA, Deans J, Sawcer SJ, Clayton D, Compston DA. Autoimmune disease in first-degree relatives of patients with multiple sclerosis. A UK survey. *Brain* 2000; 123(Pt 6):1102-11.
214. Kumar V, Rajadhyaksha M, Wortman J. Celiac disease-associated autoimmune endocrinopathies. *Clin Diagn Lab Immunol* 2001; 8:678-85.
215. Pagana KD, Pagana TJ. *Mosby's manual of diagnostic and laboratory tests*. 4th ed. St. Louis: Mosby Elsevier; 2010.
216. Linker JB, Williams RC Jr. Tests for detection of rheumatoid factors. In: Rose R, Friedman H, Fahey JC (ed). *Manual of clinical laboratory immunology*. 3rd ed. Washington: American Society for Microbiology; 1985.
217. Pruijn GJ, Wiik A, van Venrooij WJ. The use of citrullinated peptides and proteins for the diagnosis of rheumatoid arthritis. *Arthritis Res Ther* 2010; 12 (1):203.
218. Engall E. Enzyme immunoassay ELISA and EMIT. In: van Vunakis H, Langone JJ (eds). *Methods in enzymology*. New York: Academic Press; 1980. 419-39.
219. Uotila M, Ruoslahti E, Engvall E. Two-site sandwich enzyme immunoassay with monoclonal antibodies to human alpha-fetoprotein. *J Immunol Methods* 1981;42(1):11-5.
220. Spencer CA, Takeuchi M, Kazarosyan M, MacKenzie F, Beckett GJ, Wilkinson E. Interlaboratory/Intermethod differences in Functional Sensitivity of Immunometric Assays of Thyrotropin (TSH) and impact on reliability of measurement of subnormal concentrations of TSH. *Clin Chem* 1995; 41, 367-74.
221. Jensen E, Hyltoft Petersen P, Blaabjerg O, Hansen PS, Brix TH, Kyvik KO, et al. Establishment of a serum thyroid stimulating hormone (TSH) reference interval in healthy adults. The importance of environmental factors, including thyroid antibodies. *Clin Chem Lab Med* 2004;42(7):824-32.
222. Hamilton TE, Davis S, Onstad L, Kopecky KJ. Thyrotropin levels in a population with no clinical, autoantibody, or ultrasonographic evidence of thyroid disease: implications for the diagnosis of subclinical hypothyroidism. *J Clin Endocrinol Metab* 2008;93(4):1224-30.
223. Barker SB. Determination of protein bound Iodine. *J Biol Chem* 1984;173:715-24.
224. Chopra IJ, Solomon DH, HO RS. A Radioimmunoassay of triiodothyronine. *J Clin Endocrinol Metab* 1971; 33:865-8.

References

225. Walker WHC. Introduction: an Approach to immunoassay. *Clin Chem* 1977; 23 (2): 384.
226. Schuurs AH, Van Weemen BK. Review, enzyme – immunoassay. *Clin Chem Acta* 1977; 81 (5): 1.
227. Terunori Mitsuma, Noriyuki Nihei, Marvin C. Gershengorn, and Charles S. Hollander. Serum triiodothyronine: measurements in human serum by radioimmunoassay with corroboration by gas-liquid chromatography. *J Clin Invest.* 1971; 50(12): 2679–88.
228. Skelley DS, Brown LP, Besch PK. Radioimmunoassay. *Clin Chem* 1973;19(2):146-86.
229. Ruf J, Toubert ME, Czarnocka B, Durand-Gorde JM, Ferrand M, Carayon P. Relationship between immunological structure and biochemical properties of human thyroid peroxidase. *Endocrinology* 1989;125(3):1211-8.
230. Mckenzie JM, Zakarija M, Sato A. Humoral immunity in graves' disease. *Clin Endocrinol Metab* 1978;7:31-45.
231. Bolton J. Measurement of thyroid stimulating hormone receptor autoantibodies by ELISA. *Clin Chem* 1999;45:2285-7.
232. Kamijo K. TSH receptor antibody measurement in patients with various thyrotoxicosis and hashimoto's thyroiditis:a comparison of two-step assays, coated plate ELISA using porcine TSH receptor and coated tube radioassay using human recombinant TSH receptor. *J Endocrinol* 2003; 50:113-6.
233. Tahir A, Ahidjo A, Yusuph H.Ultrasonic assessment of thyroid gland. *J Thyroid Res* 2011;3:26-31.
234. Vaz C. Thyroid ultrasound 101:what is it? and what can i expect?. *Thyroid* 2009;19(11):1167-214.
235. Vaz C. Thyroid ultrasound 101:what is it? and what can i expect?. *J Endocrinol Invest* 2010; 33(5 Suppl):51-6.
236. Dvorakova M, Bilek R, Cerovska J, Hill M, Novák Z, Vavrejnová V, et al. The volumes of the thyroid gland in adults aged years in the Czech Republic--determination of the norms. *Vnitr Lek* 2006; (5): 18-65.
237. Scarpa V, Kappaousta E, Tertipi A, Anyfandakis K, Vakaki M, Dolianiti M, et al. Epidemiological characteristics of children with autoimmune thyroid disease. *Hormones (Athens)* 2011; 10 (3):207-14.
238. Scarpa V, Kousta E, Tertipi A, Vakaki M, Fotinou A, Petrou V, et al. Treatment with thyroxine reduces thyroid volume in euthyroid children and adolescents with chronic autoimmune thyroiditis. *Horm Res Paediatr* 2010; 73(1): 61-7.
239. Kotz S, Balakrishnan N, Read CB. *Encyclopedia of statistical sciences*. 2nded. Hoboken, New Jersey: Wiley-Interscience; 2006.

References

240. Kirkpatrick LA, Feeney BC. A simple guide to IBM SPSS statistics for version 20.0. Student ed. Belmont, Calif.: Wadsworth, Cengage Learning; 2013.
241. Eschler DC, Hasham A, Tomer Y. Cutting edge: the etiology of autoimmune thyroid diseases. *Clin Rev Allergy Immunol* 2011; 41(2):190–7.
242. Tomer Y, Huber A. The etiology of autoimmune thyroid disease: a story of genes and environment. *J Autoimmun* 2009; 32(3-4): 231–9.
243. Shin JI, Kim MJ, Lee JS. Graves' disease, rheumatoid arthritis, and anti-tumor necrosis factor-alpha therapy. *J Rheumatol* 2009;36(2):449-50.
244. Kerimović-Morina D. Autoimmune thyroid disease and associated rheumatic disorders. *Srp Arh Celok Lek* 2005; 133 (Suppl 1): 55-60.
245. Shiroky JB, Cohen M, Ballachey ML, Neville C. Thyroid dysfunction in rheumatoid arthritis: a controlled prospective survey. *Ann Rheum Dis* 1993; 52: 454-6.
246. Kvien TK, Uhlig T, Ødegård S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis: the sex ratio. *Ann N Y Acad Sci* 2006; 1069:212-22.
247. del Rincon I, Battafarano DF, Arroyo RA, Murphy FT, Escalante A. Heterogeneity between men and women in the influence of the HLA-DRB1 shared epitope on the clinical expression of rheumatoid arthritis. *Arthritis Rheum* 2002;46(6):1480-8.
248. Cardenas Roldan J, Amaya-Amaya J, Castellanos-de la Hoz J, Giraldo-Villamil J, Montoya-Ortiz G, Cruz-Tapias P, et al. Autoimmune thyroid disease in rheumatoid arthritis: a global perspective. *Arthritis* 2012;2012:1-15.
249. Charles PJ, Plant D, Chowdhury M, Worthington J, Venables P. Antibodies to thyroglobulin and thyroid peroxidase in rheumatoid arthritis: environmental and genetic associations. *Ann Rheum Dis* 2011;70(Suppl 2):A88-A9.
250. Cojocaru-Gofita IR, Ciurea P, Rosu A, Musetescu AE, Vreju F, Barbulescu A. Hypothyroidism—risk factor for treatment resistant, aggressive rheumatoid arthritis onset. *Scandinavian J Rheumatol* 2010; 39:29.
251. Yildirim K, Karatay S, Melikoglu MA, Gureser G, Ugur M, Senel K. Associations between Acute Phase Reactant Levels and Disease Activity Score (DAS28) in Patients with Rheumatoid Arthritis. *Annals of Clinical & Laboratory Science* 2004;34(4):423-6.
252. Wolfe F, Michaud K. One clinical and research significance of the erythrocyte sedimentation rate. *J Rheumatol* 1994; 21:1227-37.
253. Geng Y, Zhou W, Zhang ZL. A comparative study on the diversity of clinical features between the sero-negative and sero-positive rheumatoid arthritis patients. *Rheumatol Int* 2012; 32: 3897-901.
254. Westwood OM, Nelson PN, Hay FC. Rheumatoid factors: what's new? *Rheumatology (Oxford)* 2006; 45: 379-85.

References

255. Kastbom A, Strandberg G, Lindroos A, Skogh T. Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedish TIRA project). *Ann Rheum Dis* 2004;63:1085-9.
256. Binesh F, Salehabadi HS, Behniafard N, Ranginkaman K, Behniafard N. A comparative assessment of the diagnostic value of anti-cyclic citrullinated peptide antibodies and rheumatoid factor in rheumatoid arthritis. *J Clin Exp Pathol* 2014; 4:158
257. El-Sherif WT, El Gendi SS, Ashmawy MM, Ahmed HM, Salama MM. Thyroid disorders and autoantibodies in systemic lupus erythematosus and rheumatoid arthritis patients. *Egypt J Immunol* 2004; 11(2):81–90.
258. Silman AJ, Ollier WE, Bubel MA. Autoimmune thyroid disease and thyroid autoantibodies in rheumatoid arthritis patients and their families. *Br J Rheumatol* 1989; 28(1):18–21.
259. Porkodi R, Ramesh S, Mahesh A, Kanakarani P, Rukmangathrajan S, Rajendran PC. Thyroid dysfunction in systemic lupus erythematosus and rheumatoid arthritis . *J Indian Rheumatol Assoc* 2004; 12: 88-90.
260. Singh B, Mittal BR, Bhattacharya A, Deodhar SD. A cross sectional evaluation of circulating thyroid hormonal profile in patients with rheumatoid arthritis. *IJNM* 2002; 17(2 &3): 68-72.
261. Wellby ML, Kennedy JA, Pile K, True BS, Barreau P. Serum interleukin-6 and thyroid hormones in rheumatoid arthritis. *Metabolism - Clinical and Experimental* 2001; 50(4):463-7.
262. Elattar EA, Younes TB, Mobasher SA. Hypothyroidism in patients with rheumatoid arthritis and its relation to disease activity. *Egypt Rheumatol Rehabil* 2014;41:58-65.
263. van Halm V, Peters MJ, Voskuyl AE, Boers M, Lems WF, Visser M, et al. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. *Ann Rheum Dis* 2009; 68(9):1395-400.
264. Magnus JH, Birketvedt T, Haga HJ. A prospective evaluation of antithyroid antibody prevalence in 100 patients with rheumatoid arthritis. *Scand J Rheumatol* 1995; 24(3):180–2.
265. Innocencio RM, Romaldini JH, Ward LS. High prevalence of thyroid autoantibodies in systemic sclerosis and rheumatoid arthritis but not in the antiphospholipid syndrome. *Clin Rheumatol* 2003; 22(6):494.
266. Başkan BM, Filiz S, Aktekin LA, Yurdakul FG, Çınar NK, Hatice B. Relationship between thyroid autoimmunity and depression, quality of life, and disease symptoms in patients with fibromyalgia and rheumatoid arthritis. *Turk J Rheumatol* 2010; 25: 130-6.

References

267. Koszarny A, Majdan M, Suszek D, Wielosz E, Dryglewska M. Relationship between rheumatoid arthritis activity and antithyroid antibodies. *Pol Arch Med Wewn* 2013;123(7-8):394-400.
268. Andonopoulos AP, Siambi V, Makri M, Christofidou M, Markou C, Vagenakis AG. Thyroid function and immune profile in rheumatoid arthritis. A controlled study. *Clin Rheumatol* 1996;15(6):599-603.
269. Koga Y, Kuromaru R, Takada H, Hara T. Juvenile idiopathic arthritis associated with autoimmune thyroid disorders and autoimmune cholangitis. *Rheumatology (Oxford)* 2001; 40(8):942-3.
270. Yavasoglu I, Senturk T, Coskun A, Bolaman Z. Rheumatoid arthritis and anti-thyroid antibodies. *Autoimmunity* 2009; 42(2): 168–9.
271. Raterman HG, van Halm VP, Voskuyl AE, Simsek S, Dijkmans BA, Nurmohamed MT. Thyroid peroxidase antibodies in rheumatoid Arthritis. *Ann Rheum Dis* 2008; 67(2):229-32.
272. Przygodzka M, Filipowicz-Sosnowska A. Prevalence of thyroid diseases and anti thyroid antibodies in women with rheumatoid arthritis. *Pol Arch Med Wewn* 2009; 119 (1-2): 39-44.
273. Lee YA, Song SH, Ran SHIY. Higher prevalence of coexisting papillary thyroid cancer as well as autoimmune thyroid diseases in patients with rheumatoid arthritis. [abstract]. *Arthritis Rheum* 2010; 62 (Suppl 10):1038

المُلخَص العَرَبِي

ان الامراض المناعية او كما يطلق عليها امراض المناعة الذاتية هي تلك الامراض التي تحدث للانسان حينما يقوم جسمه بتكوين اجساما مضاده تهاجم خلاياه و انسجته، و يحدث ذلك مؤثرا اما على عضو واحد او على الجسم بأكمله.

تعتبر امراض الغده الدرقيه المناعية خير مثال على ذلك والتي تشتمل على العديد من الامراض من اشهرها مرض جريفز و التهاب الغده الدرقيه هاشيموتو(مرض هاشيموتو) والذان يتميزان بوجود الاجسام المضاده لانزيم thyroglobulin و thyroid peroxidase.

يعتبر الروماتويد المفصلي مرض مناعي يصاحبه التهاب مزمن في المفاصل الزلاليه مما يؤدي الى خلل في تكوينها والذي بدوره يسبب عدم قدرتها على القيام بوظيفتها. يصاحب هذا المرض ايضا وجود الاجسام المضاده : عامل الروماتويد والاجسام المضاده لل CCP، والتي عن طريقها يتم تقسيم المرض الى نوعين و هما الروماتويد المفصلي المصلي الايجابي(موجب لاحدهما او كلاهما) و الروماتويد المفصلي المصلي السلبي(سالب لكلاهما).

اعتمادا على التقنيه المناعية السابق ذكرها في حوث الامراض المناعية والتي تفترض وجود خلفيه جينييه واكينيكيه مشتركه فانه يجدر بنا الاشاره الى ان الامراض المناعية غالبا ما تأتي معا.و من هذا المنطلق تم اجراء العديد من الابحاث لدراسه العلاقه بين امراض الغده الدرقيه المناعية و الروماتويد المفصلي وبالرغم من عدم وضوح التقنيه المشتركه لحدوث كلا منهما، الا انه وجد زياده انتشار امراض الغده الدرقيه المناعية بين مرضى الروماتويد المفصلي عن الاصحاء.

الهدف من هذا البحث هو دراسه العلاقه بين اضطرابات الغده الدرقيه(زياده او نقص افرازها) و الروماتويد المفصلي المصلي الايجابي و السلبي و ايضا دراسه وجود الدلالات المناعية لامراض الغده الدرقيه (الاجسام المضاده لانزيم thyroglobulin و thyroid peroxidase و مستقبلات ال TSH) و علاقتها بخلل وظائف الغده الدرقيه والاجسام المضاده عامل الروماتويد والاجسام المضاده لل CCP.

لقد اجريت هذه الدراسه على عدد ٧٠ مريض (سبعون مريضا) يعانون من الروماتويد المفصلي في المستشفى الرئيسي الجامعي بالاسكندريه و عياده امراض الروماتيزم و المناعه.

لقد تم تقسيم المرضى الى مجموعتين: المجموعه الاولى شملت عدد ٣٥ مريض (خمسه و ثلاثون مريضا) بالروماتويد المفصلي المصلي الايجابي و المجموعه الثانيه شملت عدد ٣٥ مريض(خمسه و ثلاثون مريضا) بالروماتويد المفصلي المصلي السلبي بالاضافه الى عدد ٢٠ شخص (عشرون شخصا) من الاصحاء من نفس الفئه العمريه للمقارنه.

لقد تم قياس درجه نشاط المرض باستخدام طريقه DAS 28 بالاضافه الى عد دم كامل،بولينا ،كرياتينين،انزيمات الكبد،سرعه ترسيب، معامل C التفاعلي، عامل الروماتويد، والاجسام المضاده لل CCP، T4،T3،TSH، الاجسام المضاده لانزيم thyroglobulin و thyroid peroxidase و مستقبلات ال TSH و موجات فوق الصوتيه للغده الدرقيه.

لقد وجد ان سرعه الترسيب ، معامل C التفاعلي ، عامل الروماتويد والاجسام المضاده لل CCP اعلى في مرضى الروماتويد المفصلي مقارنه بالاصحاء و خاصه في النوع المصلي الايجابي عن السلبي، كما تبين انه يوجد خلل في وظائف الغده الدرقيه و خاصه نقص افرازها في المرضى المصابين بالروماتويد المفصلي عن الاصحاء.

اما عن الاجسام المضاده فقد لوحظ ان الاجسام المضاده لانزيم thyroglobulin و thyroid peroxidase كانت اعلى في مرضى الروماتويد المفصلي مقارنه بالاصحاء و خاصه في النوع المصلي الايجابي عن السلبي و هو ما يؤكد نظريه التقنيه المناعية المشتركه بين كلا المرضين، ولكن الاجسام المضاده لمستقبلات ال TSH وجدت في نسبه قليله من المرضى.

ايضا باستخدام اشعه الموجات فوق الصوتيه لايضاح العلامات المميزه لالتهاب الغده الدرقيه المناعى وجد توافر هذه العلامات في مرضى الروماتويد المفصلي عن الاصحاء.

و اخيرا كانت هناك علاقه احصائيه ايجابيه بين الاجسام المضاده لمرض الروماتويد المفصلى (عامل الروماتويد و الاجسام المضاده لل CCP) و الاجسام المضاده للغده الدرقيه خاصه الاجسام المضاده لانزيم thyroid peroxidase و الاجسام المضاده لمستقبلات ال TSH.

من هنا نستنتج ان امراض الغده الدرقيه المناعيه اكثر انتشارا بين مرضى الروماتويد المفصلى عن الاصحاء و خاصه النوع المصلى الإيجابي عن السلبى.



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كلية الطب
قسم الأمراض الباطنة

دراسة العلاقة بين امراض الغده الدرقيه المناعيه والروماتويد المفصلى المصلى الإيجابى والسلبى

رسالة مقدمة

لقسم الأمراض الباطنة - كلية الطب - جامعة الإسكندرية
ضمن متطلبات درجة

الماجستير

فى

الأمراض الباطنة

من

شاهنده عبده نعمان أحمد المعداوى

بكالوريوس الطب والجراحة ، ٢٠٠٩

كلية الطب، جامعة الإسكندرية

[٢٠١٥ / ٢]



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رسالة مقدمة من

شاهنده عبده نعمان أحمد المعداوى

للحصول على درجة

الماجستير

فى

الأمراض الباطنة

التوقيع

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لجنة المناقشة والحكم على الرسالة

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موافقون

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المشرف المشارك

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