INTRODUCTION

Autoimmune thyroid disease (AITD) is a common organ specific autoimmune disorder affecting mostly the middle aged women. About 2 to 4 percent of women and up to 1% of men are affected worldwide, and the prevalence rate increases with advancing age. (1)

AITD is a term that includes various clinical forms of autoimmune thyroiditis such as Graves' disease (GD), Hashimoto's (goitrous) thyroiditis, atrophic autoimmune hypothyroidism, postpartum thyroiditis (PPT) and thyroid associated orbitopathy (TAO), 2 other rare types of AITDs include silent thyroiditis and iatrogenic thyroiditis. (2)

Out of all these diseases, Hashimoto's thyroiditis (HT) and Graves' disease (GD) are the two commonest types and share many features immunologically. One form of the disease may change to the other as the course of the immune process progresses. (3)

Autoimmune hypothyroidism (AH) is the commonest type of AITD, it affects about 5 to 10% of middle aged and elderly women. Graves' disease (GD) is about one tenth as common as hypothyroidism affecting mostly the younger individuals (4). Many of these patients progress to hypothyroidism either spontaneously or after treatment with anti-thyroid drugs, post radioactive iodine therapy or post thyroidectomy. (5)

The hallmark of AITD is the production of antibodies to at least one of the main thyroid specific auto antigens such as thyroglobulin (TG), thyroid peroxidase (TPO), TSH receptor and the relatively newly discovered sodium iodide transporter Ab.(6)

Etiology:

The etiology of AITD is multifactorial. Susceptibility to the disease is determined by a combination of genetic, environmental and constitutional factors.

Numerous studies show a higher frequency of AITD in family members of patients with autoimmune hypothyroidism and Graves' disease (7). Both types of the disease cluster together in families which provide additional support that these conditions share common etiologic and pathogenic features. The autoimmune polyglandular syndrome type 2, involves the occurrence of autoimmune thyroid dysfunction with other autoimmune diseases which are Type 1 diabetes mellitus, Addison's disease, pernicious anemia & vitiligo. Shared genetic factors are likely in this group of autoimmune disorders. (8)

The most important susceptibility factor so far recognized is association of AITD with HLA-DR alleles. These MHC class-II genes play a critical role in the initiation of adaptive immune response. HLA-DR3 is the best-documented genetic factor for GD and HT in Caucasians (9), HLA-DR2, DR4 and DQ were also described.(10)

Some studies suggest an association between antecedent major life events and Graves' disease, but a causal role of stress in autoimmune process remains to be clearly established. (11)

Smoking is a minor risk factor for the development of thyroid ophthalmopathy. (12)

The female preponderance of thyroid autoimmunity is most likely due to the influence of sex steroids. Estrogen use and pregnancy are associated with a lower risk with postpartum flare up [13], and higher risk for developing hyperthyroidism. [14]

Pathology:

Hashimoto's thyroiditis is characterized by extensive infiltration of thyroid by lymphocytes, plasma cells and macrophages. The lymphoid aggregates often organifies themselves as follicle like structure containing germinal center and Langerhans cells. The thyroid follicular cells are destroyed to a variable extent, depending on the chronicity of the disease. During this process the remaining cell become hyperplastic and undergo oxyphilic metaplasia, which gives rise to the so-called Askanazy or Hurthle cells .[15]

In Graves' disease there is hypertrophy and hyperplasia of the thyroid follicles, the epithelium is columnar and the colloid shrinks. In addition a variable degree of lymphocytic infiltration is present, sometimes with germinal center formation, however the pathologic features are often obscured by prior treatment with anti-thyroid drugs .[16]

Intra thyroidal B-lymphocytes can synthesize TG, TPO and TSH-receptor Abs in vitro and this suggest that they are an important source of thyroid autoantibodies.[17]

Autoimmune features:

All forms of thyroid autoimmunity are associated with a lymhocytic infiltrate in the thyroid, and these lymphocytes are largely responsible for generating both T and B Cell-mediated auto reactivity. Other sites such as thyroid draining lymph nodes and bone marrow may also contain thyroid auto reactive lymphocytes in AITD, the initial autoimmune response by CD4+ T cells appears to up regulate the secretion of IFN-g resulting in the enhanced expression of MHC class II molecules on thyrocytes. This most likely triggers expansion of auto reactive T cells and gives rise to the characteristic inflammatory response and as the disease progresses; thyrocytes are targeted for apoptosis resulting in hypothyroidism. Another contributing factor to the observed hypothyroidism in Hashimoto's thyroiditis patients could be the circulating TSH inhibitory antibodies. [18]

Graves' disease on the other hand represents the other end of spectrum where in the patients suffer from hyperthyroidism. The activation of thyroid specific CD4+ T cells leads to the recruitment of auto reactive B cells as shown in (figure 1) and the mounting of thyroid stimulatory immune response via TSH-receptor stimulatory antibodies. [19]

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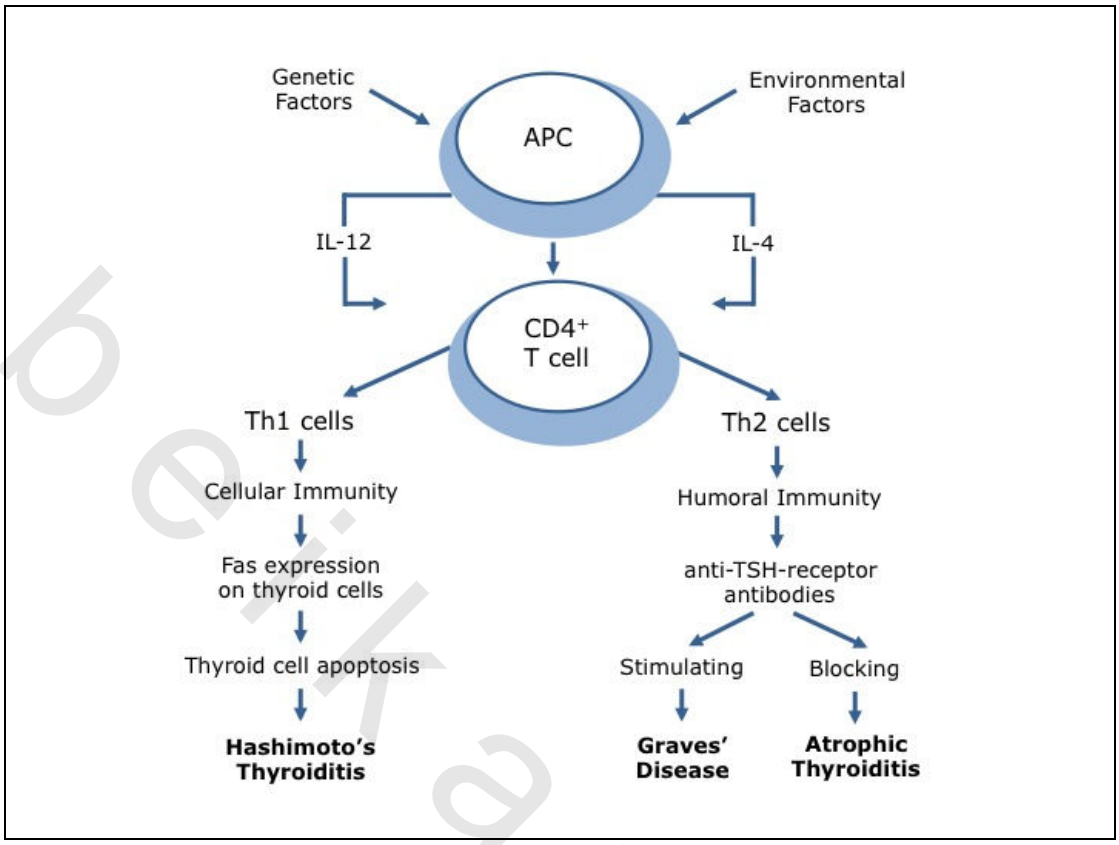

Figure (1): pathogenesis of AITDs

Autoantibodies:

i. Thyroid Peroxidase (TPO) antibodies:

TPO is the key thyroid enzyme catalyzing both the iodination and coupling reaction for the synthesis of thyroid hormone. It is membrane bound and found in the cytoplasm and in high concentration on the apical microvillar surface of thyrocytes. It is of molecular weight between 100 to 105-kDa and previously was known as thyroid microsomal antigen. Multiple T & B Cell epitopes exists within the molecule and the antibody response to TPO is restricted at the level of the germ line heavy and light chain variable (V) region. [20]

Anti-TPO autoantibodies are found in over 90% of patients with autoimmune hypothyroidism and 75 % of Graves' disease. Together with Thyroglobulin antibodies these are the predominant antibodies in autoimmune hypothyroidism (AH). Anti-TPO antibodies are mainly of the IgG class with IgG 1 and IgG4 subclasses in excess.[21]

It was found to be not only a marker of HT but also a marker for other forms of AITD, It was also confirmed that the serum concentration containing autoantibodies TPO activity has a positive correlation to activity of chronic autoimmune thyroiditis. Therefore, auto antibody TPO is conceivably capable of being an important marker for diagnosis of AITD. [22]

About 10% of normal adults are having high serum anti-TPO antibody concentration and this prevalence increase up to 30 % in elderly, the concentrations are high in up to 20-30 % of patients with nodular goiter and thyroid carcinoma.[23]

ii. Thyroglobulin (TG) Antibodies:

TG is a 660-kDa glycoprotein composed of two identical subunits of 330 kDa each. It is secreted by the thyroid follicular cells into the follicular lumen and stored as colloid. They are polyclonal and mainly of IgG class with all four subclasses represented. TSH regulates the cell surface expression of TPO and TG altering the mRNA transcription of these two proteins, possibly at the gene promoter level. These effects are mimicked by auto antibodies (both blocking and stimulating) in the sera of the patients with GD. [24]

Thyroglobulin autoantibodies are found in 80-90 % of chronic autoimmune thyroiditis, and in 50-60 % of hyperthyroid Graves' disease, and the incidence is often higher in graves patients who develop hypothyroidism after radioiodine treatment, also it is about 25% in those with thyroid carcinoma and 10-15% in nodular goiter, but the incidence is very low in patients with sub-acute thyroiditis. [25]

Comparing anti-TPO Abs to Anti-TG Abs in the diagnosis of AITD it was found that the former (anti-TPO) is the predominant antibody in the autoimmune mechanism implicated in the pathogenesis of AITD which can directly damage thyroid cells compared to the later (anti-TG) [26,27] , however in a few patients with AITD normal levels of anti-TPO is observed with high concentrations of anti-TG.[28]

In normal population, the prevalence of thyroid antibodies to TG and TPO are common even in absence of significant thyroid disease. The tendency to secrete thyroid autoantibody is inherited in a Mendelian dominant manner where young women and relatives of patients with autoimmune thyroid disorders (AITD), have higher prevalence[29]. Also, it should be mentioned that patients with an increase TSH level and normal T4 level or subclinical hypothyroid patients will progress to overt thyroid failure at a rate of about 5% per year if the level of thyroid auto antibodies are elevated. [30]

iii. Thyroid Stimulating Hormone receptor Antibodies (TRAbs):

TSH-Receptor is the prime auto antigen in Graves' disease and atrophic thyroiditis. It is located primarily on the basal surface of thyroid follicular cells in addition to the adipocytes, fibroblasts, bone cells and a variety of additional sites. [31]

In Graves' disease thyroid stimulating antibodies (TSAbs) bind to the receptor and stimulate the thyroid cell to produce excessive amount of thyroid hormones resulting in hyperthyroidism. In patients with atrophic thyroiditis the major antibody is the TSH-R blocking antibody. After binding to the receptor this antibody blocks the binding of TSH to its receptor, thus preventing stimulation of thyroid cell. This results in diminished thyroid hormone output, atrophy of thyroid gland and the clinical state of hypothyroidism. [32]

The performance of TSH receptor antibodies is excellent in the differential diagnosis of types of overt hyperthyroidism with high sensitivity and specificity up to 95% in cases of Graves' disease [33], also it can be used for prognosis of remission. [34]

Second-generation TRAb assays with high clinical sensitivity and specificity are the method of choice as they are widely available in Europe [35]. They have 95–99% sensitivity for the detection of GD, with close to 100% specificity. The use of these assays in clinical routine is helpful in the differential diagnosis of hyperthyroidism such as : toxic multinodular goitre, solitary hyperfunctioning nodule, painless thyroiditis, iodine-induced hyperthyroidism or exogenous ingestion of thyroid hormones, since the presence of autoantibodies confirms GD, whilst their absence indicates a non-autoimmune origin of hyperthyroidism[36] .Also its titer can be used as a prognostic factor and in predicting neonatal thyrotoxicosis if measured in maternal serum in the last trimester. [37]

Recent studies have shown that TRAbs can be detected in patients with graves' ophthalmopathy based on the fact of the presence of TSH receptors in the fibroblasts of the retro orbital tissue and its titer can be used as a monitor for treatment [38,39]. Also it was found to be present in other tissues as lymphocytes, adipocytes, neuronal cells, and astrocytes. [40,41]

iv. Others:

Antibodies against the sodium/iodide symporter (NIS) were also demonstrated in the majority of Graves', it was recently found that one third of Graves' disease sera and 15% of hashimoto's contain antibodies capable of blocking NIS mediated iodide uptake in cells transfected with the human NIS but the relevance of this to thyroid function is unclear. [42]

Clinical Features:

Regarding the clinical features of hashimoto's thyroiditis or what is called goitrous autoimmune thyroiditis ,it can range from being completely asymptomatic (sub clinical form) to the full blown picture of hypothyroidism (clinical form), In a study performed in the USA, the prevalence of subclinical and clinical hypothyroidism was 4.6% and 0.3% respectively. [43]

Subclinical hypothyroidism is characterized by an increase in serum thyrotropin (TSH) whilst serum levels of thyroxin (T4) and triiodothyronine (T3) remain normal. Although it may be completely asymptomatic some patients may complain of feeling of tightness or neck fullness, however neck pain and tenderness are rare [44].It is present in a significant proportion of population (8% of females and 3% of males) [30], but the risk of developing overt hypothyroidism is four times higher than normal population. [45]

The overt disease is defined by the dramatic loss of thyroid follicular cells (thyrocytes), hypothyroidism(which is mostly presented by weight gain, easy fatigability, lethargy, cold intolerance, hair fall, depression , constipation and others and is present in about 20 % of patients at presentation), goiter(which is usually firm, non-tender and irregular). Hashimoto's thyroiditis can be also associated with other autoimmune disorder such as: type 1diabetes, vitiligo, coeliac disease, multiple sclerosis and others. [46,47]

Hypothyroidism affects the central nervous system and the peripheral nervous system at multiple levels, resulting in a diverse set of neurologic symptoms and signs which include depression, dementia, headache, cranial nerve abnormalities example: sensorineural hearing loss, vertigo, increase susceptibility for developing strokes and memory problems. [48]

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Hypothyroidism can also alter the cardiac functions by decreasing cardiac output and cardiac contractility, a reduction in heart rate, and an increase in peripheral vascular resistance. There are also significant changes in modifiable atherosclerotic risk factors, including hypercholesterolemia, diastolic hypertension, carotid intimal media thickness, and endothelial derived relaxation factor (nitric oxide), which accompany overt hypothyroidism and presented clinically by dyspnea, orthopnea, edema, alteration in heart rate, rhythm and blood pressure. [49-51]

Other systemic manifestations of hypothyroidism include: [52]

Dermatologic:

Dry coarse skin, brittle hair, hair loss, non-pitting peripheral edema.

Ears, eyes, throat:

Hearing loss, hoarse voice, peri-orbital edema, facial puffiness.

Pulmonary:

Dyspnea, pleural effusions, hypoventilation, sleep apnea.

Gastrointestinal:

Anorexia, constipation.

Genitourinary:

Menstrual disorders, decreased libido, impotence, infertility.

Psychiatric:

Depression, psychomotor retardation, coma.

In Graves' disease, patients usually present with the classical triad of hyperthyroidism, ophthalmopathy and dermopathy. Typical manifestations of hyperthyroidism is present in about 90 % of patients which is mainly characterized by excessive sympathetic activity in the form of tachycardia, excessive sweating, nervousness, hyper defecation, heat intolerance, menstrual irregularities in females, weight loss, myopathy and others. [53]

It was found that many patients may present with atypical manifestations such as anemia which may be iron deficiency, pernicious or autoimmune hemolytic anemia [54], in addition to jaundice, vomiting and right heart failure. [55-57]

Ophthalmopathy is a hallmark of Graves' disease, it may precede, coincide or follow the onset of the hyperthyroid state. Approximately 35-40% of patients with Graves' disease have clinical evidence of Graves's ophthalmopathy. Progression from mild to moderate/severe ophthalmopathy occurs in about 3% of cases. [58]

Signs and symptoms may vary and depend on the stage that the patient is experiencing. Initially, an acute or sub-acute stage of active inflammation occurs where the patient usually complain of dry eyes, protrusion of the globe, field loss, limitation of eye

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movement, diplopia ,puffy eye lids or even it may progress to sight loss. Later, the patient progresses to a more quiescent stage, which is characterized by fibrosis. [59]

Dermopathy (pretibial myxedema) is present in about 4 % of patients while acropathy (clubbing of fingers and toes with soft tissue swelling) is quite rare (1% of patients). [60]

Diagnosis of AITD:

Diagnosis of AITD is based upon clinical features, laboratory investigations and imaging.

Clinical features:

History taking and good physical examination can differentiate different types of autoimmune thyroid disorders as previously mentioned.

Thyroid function tests:

Serum TSH measurement is the most reliable test to diagnose all common forms of hypothyroidism and hyperthyroidism, an elevated serum TSH concentration (more than 2.5 mu/L) is present in both overt and mild hypothyroidism(subclinical).[61] TSH follow up is used also to monitor response to treatment and progression of the disease. In the subclinical form, the serum FT4 concentration is, by definition, normal while in overt form it will be low. In hyperthyroidism, serum TSH concentrations is typically less than 0.1 mIU/L. [62].If Graves' disease is suspected based on low TSH and high free T4, radioiodine thyroid scanning is recommended to be done which will show diffuse uptake [63].However this is not the case with thyroiditis where the uptake is low as in the early thyrotoxic phase which can be diagnosed by short history of hyperthyroidism.[64]

Antibodies:

As discussed before, the role of thyroid autoantibodies in diagnosis of AITD and monitor of therapy and relapse as for example in Hashimoto thyroiditis Anti-TPO antibodies and Anti-TG antibodies are high in about 80-90% of cases and they can be considered a good sensitive marker of the disease. In subclinical hypothyroidism their presence in the sera of patients may indicate tendency to revert later to overt form. However in Graves' disease TSH-receptor antibodies are high in more than 95% of cases and can be used as prognostic factor and predictor of relapse. [65]

Role of ultrasonography (USG):

Ultrasound is a quick technique which allows accurate assessment of the solid or cystic nature of the thyroid lesion. It has a unique and valuable role in imaging the thyroid gland. It extends the palpating fingers of the clinician to provide excellent and reproducible anatomic images, it is safe comfortable for the patients with moderate cost, noninvasive with no morbidity or mortality. It does not involve any radioactivity, and so is safe for children and pregnant women. It requires only a standard ultrasound machine, and an expert ultra- sonographer. [66]

On gray-scale USG of Graves' disease, thyroid gland is diffusely enlarged (2-3 times its normal size), hypo echoic and heterogeneous. Color flow imaging reveals a spectacular

pattern "thyroid inferno" with marked hyper vascularity as shown in (figure 2). This pattern demonstrates extensive intra-thyroid flow both in systole and diastole [67]. In contrast to Hashimoto's thyroiditis, the characteristic USG appearance is focal or diffuse as shown in (figure 3) glandular enlargement with coarse, heterogeneous and hypo echoic parenchymal echo pattern. Presence of multiple discrete hypo echoic micro nodules (1-6 mm size) is strongly suggestive of chronic thyroiditis. Fine echogenic fibrous septae may produce a pseudo lobulated appearance of the parenchyma. Color Doppler may demonstrate slight to markedly increased vascularity of the thyroid parenchyma, however it is difficult to differentiate between the two conditions on ultrasound basis. [68,69]

Also it should be mentioned that ultrasound is unable to diagnose the etiology of thyroiditis. [44]

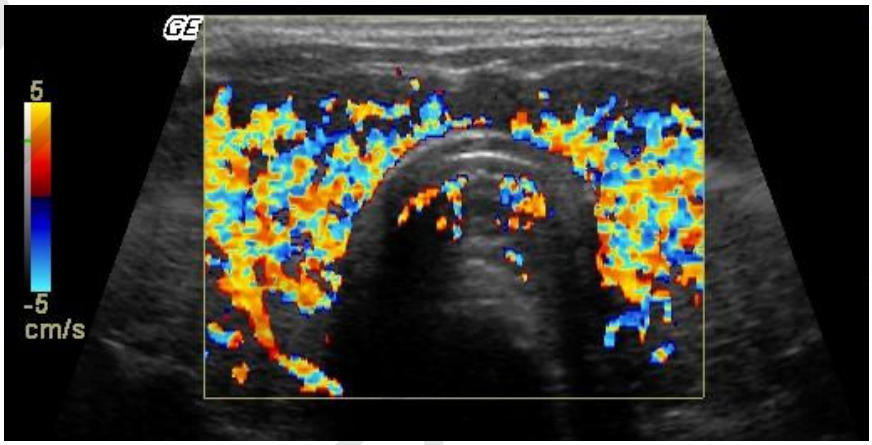

Figure 2: Ultrasound picture of Graves' disease showing marked hyper vascularity (thyroid inferno sign)

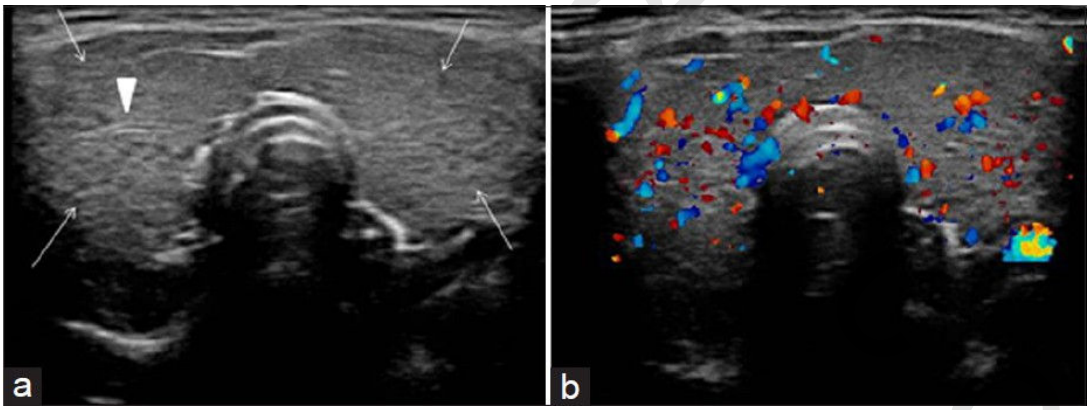

Figure 3: Diffuse Hashimoto's thyroiditis in a 35-year-old female patient, who presented with features of hypothyroidism and had anti-thyroid antibodies positive for the disease. Transverse gray-scale ultrasound neck (a) demonstrates diffuse enlargement of thyroid gland with heterogeneous echo texture. Multiple tiny and discrete hypo echoic nodules (micro nodules, arrows) and few linear echogenic septae (arrowhead) are also noted. Color Doppler sonogram (b) demonstrates mildly increased parenchymal vascularity.

We previously described the two most common forms of autoimmune thyroid disorders (Graves' disease and hashimoto's thyroiditis), however other less common types are to be mentioned briefly:

1-Atrophic thyroiditis:

Atrophic thyroiditis is an organ-specific autoimmune disease characterized by thyroid autoantibodies, functional hypothyroidism, and absence of goiter. Atrophic thyroiditis is a rare entity, it is considered to be the end stage of hashimotos' [(70)], which occurs between the ages of 40–60 years especially in elderly women.[(71)] The clinical presentation varies from asymptomatic AT, overt hypothyroidism, and myxedema. The pathological features are atrophic thyroid gland with lymphocytic infiltration and fibrous tissue replacing normal thyroid parenchyma. There are no current diagnostic criteria for AT. Diagnosis is usually based on clinical or sub clinical hypothyroidism, positive thyroid blocking antibodies and thyroid ultrasound with diffuse low thyroid echogenicity associated with a reduced thyroid volume. [(72,73)]

2-Postpartum thyroiditis:

Postpartum thyroiditis represents 29-50% of all case of thyroiditis[(44)],A family history of autoimmune thyroid disease is found in 50 percent of patients with the postpartum form of thyroiditis, it usually starts with a thyrotoxic phase in the first 3 months following delivery and lasts for one or two months, the majority of patients usually present with signs of the hypothyroid stage although few of them can also describe the acute symptoms of hyperthyroidism, such as tachycardia, palpitations, heat intolerance, nervousness and weight loss. A small painless goiter is present in 50 percent of patients.[(74,75)] The ESR and white blood cell count are normal. T_4 and triiodothyronine (T_3) levels are initially elevated, Anti microsomal antibodies are present in 50 to 80 percent of patients, while anti thyroid peroxidase antibodies are present in nearly all patients. RAIU is decreased in the hyperthyroid phase of the disease, however it is contraindicated to be done if the patient is lactating and so lactation is recommended to be stopped 48 hours pre and post radiation [(76)]. After this phase the patient returns to a euthyroid state or hyperthyroidism ensues for several months. [(77)] Patients with an initial episode of postpartum sub-acute lymphocytic thyroiditis have a notably high risk of recurrence in subsequent pregnancies. [(78)]

3-Thyroid associated orbitopathy:

Thyroid-associated orbitopathy (TAO), frequently termed Graves ophthalmopathy, is part of an autoimmune process that can affect the orbital and periorbital tissue; Thyroid-associated orbitopathy may precede, coincide, or follow the systemic complications of dysthyroidism. Although Graves' disease is the most common cause, Hashimoto thyroiditis has also been implicated. The ocular manifestations of thyroid-associated orbitopathy include eyelid retraction, proptosis, chemosis, periorbital edema, and altered ocular motility with significant functional, social, and cosmetic consequences. Although most cases of thyroid-associated orbitopathy do not result in visual loss, this condition can cause vision-threatening exposure keratopathy, troublesome diplopia, and compressive optic neuropathy. Therefore, although the prognosis is generally favorable for patients with this condition and most patients do not require surgical intervention. [(79,80)]

If the diagnosis of thyroid-associated orbitopathy (TAO) can be established clinically, then it is not necessary to routinely order a computed tomography (CT) scan or a magnetic resonance image (MRI).–MRI is more sensitive for showing optic nerve compression, whereas CT scanning is performed before bony decompression, because it shows better bony architecture, it usually reveals thick muscles with tendon sparing. The inferior rectus muscle and the medial rectus muscle are usually involved. Bilateral muscle enlargement is the norm; unilateral cases usually represent asymmetric involvement rather than normality of the less involved side. (81)

4-Iatrogenic thyroiditis:

Iatrogenic hypothyroidism may be induced by over dose of anti-thyroid drugs or following RAIU, on the other hand iatrogenic thyrotoxicosis may be caused by excessive ingestion of thyroid hormones ("thyrotoxicosis factitia"); iodine-induced hyperthyroidism (radiologic contrast agents, topical antiseptics, other medications) or induced by the iodine overload and cytotoxicity associated with amiodarone represents a significant challenge.(82)

Amiodarone-induced thyrotoxicosis (AIT) develops in 3% of amiodarone-treated patients in North America. AIT is classified as type 1 or type 2. Type 1 AIT occurs in patients with underlying thyroid pathology such as autonomous nodular goiter or Graves' disease. Type 2 AIT is a result of amiodarone causing a subacute thyroiditis with release of preformed thyroid hormones into the circulation. (83)

5-Silent thyroiditis:

Silent or Painless thyroiditis is considered a variant form of chronic autoimmune thyroiditis (Hashimoto's thyroiditis), suggesting that it is part of the spectrum of thyroid autoimmune disease. It is characterized by transient hyperthyroidism, followed sometimes by hypothyroidism, and then recovery .Patients usually have high serum concentrations of anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG) antibodies, many have a family history of thyroid autoimmune disease, and some develop overt chronic autoimmune thyroiditis several years later.(84)

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Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality. [85-89]

Given the presence of autoantibodies, such as rheumatoid factor (RF) and anti–cyclic citrullinated peptide [anti-CCP]), which can precede the clinical manifestation of RA by many years [90-93], RA is considered an autoimmune disease.[94,95] Autoimmunity and the overall systemic and articular inflammatory load drive the destructive progression of the disease. However, although structural changes, which can be visualized by conventional radiography or other imaging techniques, best distinguish RA from other arthritic disorders[96], joint damage is rarely apparent in the very early stages of disease, but rather accumulates consistently over time. [97-100]

Over the last decade, the optimal use of disease modifying anti-rheumatic drugs (DMARDs), in particular the anchor DMARD methotrexate (MTX) [101-103], and the availability of new biologic agents [104], have dramatically enhanced the success of RA management. Moreover, it has been recognized that early therapeutic intervention improves clinical outcomes and reduces joint damage and disability. [105-107]

Undoubtedly, treating patients at a stage at which evolution of joint destruction can still be prevented would be ideal, however, at present, clinical trials of RA treatments are hampered by lack of criteria allowing for study enrollment of patients at early stages of disease. Thus, to date it has not been possible to effectively investigate the efficacy of early interventions in terms of their ability to prevent later-stage RA, since there are no validated or accepted uniform criteria to classify such individuals with early disease. [108]

The standard and accepted means of defining RA is by use of classification criteria. Classification criteria enable the stratification of groups of individuals into those with and those without RA in order to standardize recruitment into clinical trials and related studies, and provide the basis for a common approach to disease definition that can be used to compare across studies and centers. The classification criteria set that is in widespread international use to define RA is the 1987 American College of Rheumatology (ACR; formerly the American Rheumatism Association) criteria.

These criteria are well accepted as providing the benchmark for disease definition, but have a significant limitation in that they were derived by trying to discriminate patients with established RA from those with a combination of other definite rheumatologic diagnoses. They are therefore not helpful in achieving the goal of identifying patients who would benefit from early effective intervention, as discussed above. Indeed, with modern therapies, the goal is to prevent individuals from reaching the chronic, erosive disease state that is exemplified in the 1987 criteria for RA. [109]

Summary of 1987 ACR classification criteria for rheumatoid Arthritis: [110]

Patients must have four of the seven criteria:

- Morning stiffness lasting at least 1 hour*

- Swelling in three or more joints*(The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints)
- Swelling in hand joints*(as defined above in a wrist, MCP, or PIP joint)
- Symmetric joint swelling*(Simultaneous involvement of the same joint areas (as defined above) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
- Erosions or decalcification on x-ray of hand
- Rheumatoid nodules
- Abnormal serum rheumatoid factor.

*Must be present at least six weeks.

A joint working group of the ACR and the European League against Rheumatism (EULAR) was therefore formed to develop a new approach for classification of RA. While classification criteria are potentially adopted for use as aids for diagnosis, the focus was not on developing diagnostic criteria or providing a referral tool for primary care physicians, rather to facilitate the study of patients at an earlier stage so the working group developed the 2010 ACR/EULAR classification criteria. [111]

The 2010 ACR/EULAR classification criteria for RA: [112]

A score of ≥6/10 is needed for classification

A. joint involvement:

1 large joint	0
2-10 large joints	1
1-3 small joints with or without large joints affection)	2
4-10 small joints (with or without large joints affection)	3
>10 joints (at least one small joint)	5

B. Serology (at least 1 test result is needed for classification)

Negative RF and negative ACPA	0
Low-positive RF or low positive ACPA	2
High positive RF or high positive ACPA	3

C. Acute phase reactants (at least 1 test result is needed for classification)

Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1

D. Duration of symptoms:

<6 weeks	0

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≥ 6 weeks	1

It is important to clarify some definitions used by the ACR/EULAR classification for example:

Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis .Distal inter phalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement. "Large joints" refers to shoulders, elbows, hips, knees, and ankles. "Small joints" refers to the metacarpophalangeal joints, proximal inter phalangeal joints, second through fifth metatarsophalangeal joints, thumb, inter phalangeal joints, and wrists. Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.[113-115]

Pathophysiology:

The earliest event in RA pathogenesis is activation of the innate immune response, which includes the activation of dendritic cells by exogenous material and autologous antigens. Antigen-presenting cells, including dendritic cells, macrophages and activated B cells, present arthritis-associated antigens to T cells as shown in (figure 4). Concurrently, CD4+ T cells that secrete IL-2 and IFN-g infiltrate the synovial membrane. [116]

B cells contribute to RA pathogenesis not only through antigen presentation, but also through the production of antibodies, autoantibodies and cytokines. RF and anti-CCP autoantibodies are common in patients with RA. B lymphocytes express cell surface proteins, including immunoglobulin and differentiation antigens such as CD20 and CD22. Autoantibodies can form larger immune complexes that can further stimulate the production of pro-inflammatory cytokines, including TNF-a, through complement and Fc-receptor activation. [117]

T- and B-cell activation result in increased production of cytokines and chemokines, leading to a feedback loop for additional T-cell, macrophage and B-cell interactions. In addition to antigen presentation, macrophages are involved in osteoclastogenesis and are a major source of cytokines, including TNF-a, IL-1 and IL-6 which are the main cytokines involved in the inflammatory response resulting in tissue degradation also Within the synovial membrane there is a great increase in activated fibroblast-like synoviocytes, which also produce inflammatory cytokines, PGs and MMPs . Synoviocytes contribute to the destruction of cartilage and bone by secreting MMPs into the SF and by direct invasion into these tissues. [118-120]

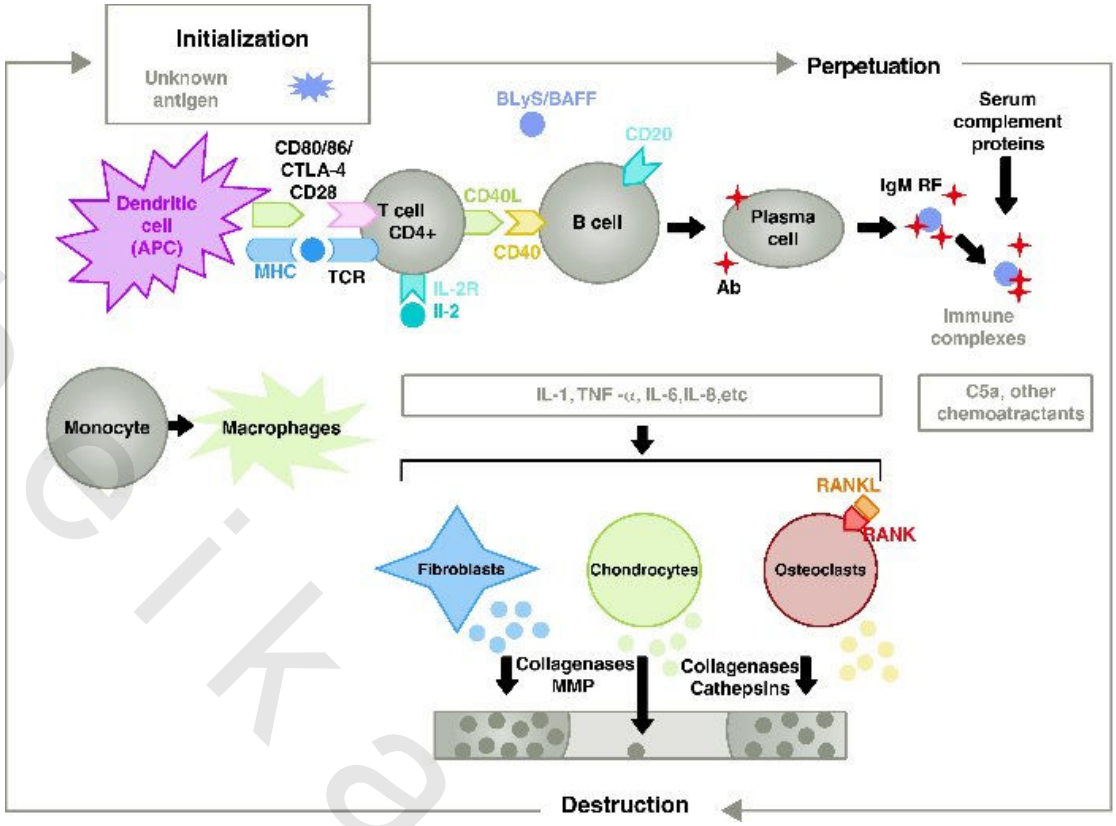

Figure (4): Pathophysiology of Rheumatoid arthritis

Clinical picture:

Rheumatoid arthritis primarily is a clinical diagnosis. Patients commonly present with pain and stiffness in multiple joints, although one third of patients initially experience symptoms at just one location or a few scattered sites. In most patients, symptoms emerge over weeks to months, starting with one joint and often accompanied by prodromal symptoms of anorexia, weakness, or fatigue. In approximately 15 percent of patients, onset occurs more rapidly over days to weeks. In 8 to 15 percent of patients, symptoms begin within a few days of a specific inciting event, such as an infectious illness. (121)

Joints most commonly affected are those with the highest ratio of synovium to articular cartilage. The wrists are nearly always involved, as are the proximal inter phalangeal and metacarpophalangeal joints. The distal inter phalangeal joints and sacroiliac joints tend not to be affected. Rheumatoid joints typically are boggy, tender to the touch, and warm, but they usually are not erythematous. Some patients complain of "puffy" hands secondary to increased blood flow to inflamed areas. Prominent epitrochlear, axillary, and cervical lymph nodes may be noted. Muscles near inflamed joints often atrophy. Subcutaneous skin nodules are also found mainly on the olecranon, calcaneal tuberosity and metacarpophalangeal joints. Weakness is commonly out of proportion to pain on examination. Morning stiffness lasting at least 45 minutes after initiating movement is common. Patients often hold joints in flexion to minimize painful distension of joint capsules. Low-grade fever, fatigue, malaise, and other systemic complaints may arise, especially in an acute presentation. (122)

The fingers may suffer from almost any deformity depending on which joints are most involved. Specific deformities, which also occur in osteoarthritis, include ulnar deviation, boutonniere deformity, swan neck deformity and "Z-thumb." "Z-thumb" or "Z-deformity" consists of hyperextension of the inter phalangeal joint, fixed flexion and subluxation of the metacarpophalangeal joint and gives a "Z" appearance to the thumb. The hammer toe deformity may be seen. In the worst case, joints are known as arthritis mutilans due to the mutilating nature of the deformities. [123]

Systemic manifestations of Rheumatoid arthritis include:

Lungs:

Fibrosis of the lungs is a recognized response to rheumatoid disease. Caplan's syndrome describes lung nodules in individuals with RA and additional exposure to coal dust. Pleural effusions are also associated with RA. Another complication of RA is Rheumatoid Lung Disease. It is estimated that about one quarter of Americans with RA develop Rheumatoid Lung Disease. [124]

Kidneys:

Renal amyloidosis can occur as a consequence of chronic inflammation. RA may affect the kidney glomerulus directly through a vasculopathy or a mesangial infiltrate . Treatment with Penicillamine and gold salts are recognized causes of membranous nephropathy. [125]

Heart and blood vessels:

People with RA are more prone to atherosclerosis, and risk of myocardial infarction (heart attack) and stroke is markedly increased.[126] Other possible complications that may arise include: pericarditis, endocarditis, left ventricular failure, valvulitis and fibrosis. [127]

Others:

Episcleritis, scleromalacia, keratoconjunctivitis sicca , anemia(due to chronic illness or autoimmune hemolytic anemia)[128] .A low white blood cell count (neutropenia) usually only occurs in patients with Felty's syndrome with an enlarged liver and spleen.[129], peripheral neuropathy, osteoporosis and unfortunately lymphoma may also occur although uncommon. [130]

Diagnosis:

Clinical:

History taking and good physical examination as previously mentioned in addition to the disease activity score in 28 joints(DAS 28) as shown in figure (5) which is an assessment used by clinicians to measure rheumatoid arthritis (RA) disease activity, to determine whether the signs and symptoms have reduced or stopped, and if treatment needs to be adjusted. It is calculated using a formula that includes counts for tender and swollen joints, an evaluation of general health by the patient (on a scale of 0 to 100), and a measure of circulating inflammatory markers.[131]

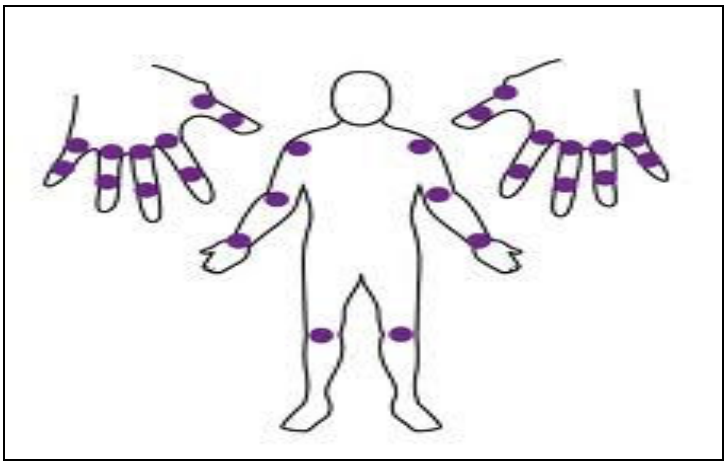

Figure (5): Joints to be assessed in DAS calculation:

Right and left (5 metacarpophalangeal joints, 5 proximal interphalangeal joints, knee, shoulder, elbow, wrist)

After assessment the results are interpreted as follows:

Remission (<2.6)
Low Activity (2.6-3.2)
Moderate Activity (>3.2 - 5.1)
Severe Activity (>5.1)

Figure (6): Interpretation of DAS results

Laboratory:

The identification of persistent synovitis is largely a clinical skill. However, there are investigations that help to demonstrate that there are abnormalities that require intervention. Some of them are non-specific while others are specific pointing towards the diagnosis as follow:

Routine:

Nonspecific tests for example complete blood count may reveal anemia(of chronic illness or autoimmune hemolytic anemia), neutropenia or thrombocytosis, tests of liver and kidney function, serum uric acid (hyperuricemia may be mistaken for RA), and a urinalysis. [(132)]

Erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) levels – Both the ESR and CRP are typically elevated in RA, The degree of elevation of these acute phase reactants varies with the severity of inflammation, Although increased levels of acute phase reactants are not specific for RA, they are often useful for distinguishing

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inflammatory conditions from non-inflammatory disorders that present with musculoskeletal symptoms (eg, osteoarthritis or fibromyalgia). [133]

Serology:

RF and anti-CCP antibodies are initially performed in evaluating a patient with suspected RA. The results of both tests are informative, since a positive result for either test increases overall diagnostic sensitivity, while the specificity is increased when both tests are positive. Despite this, both tests are negative on presentation in up to 50 percent of patients and remain negative during follow-up in 20 percent of patients with RA, RFs occur in 70 to 80 percent of patients with RA. Their diagnostic utility is limited by their relatively poor specificity, since they are found in 5 to 10 percent of healthy individuals, 20 to 30 percent of people with Sjogren syndrome, SLE, all patients with mixed Cryoglobulinemia (usually caused by hepatitis C virus [HCV] infections), and in those with many other inflammatory conditions. Higher titers of RF (at least three times the upper limit of normal) have somewhat greater specificity for RA. The prevalence of RF positivity in healthy individuals rises with age.[134]

Antibodies to citrullinated peptides/proteins are usually measured by enzyme-linked immunosorbent assays (ELISAs) using CCPs as antigen. Anti-CCP antibodies have a similar sensitivity to RF for RA but have a much higher specificity (95 to 98 percent)[135,136]. The specificity is greater in patients with higher titers of anti-CCP antibodies (at least three times the upper limit of normal). [137]

It was found that there is a strong correlation between anti-CCP titer and disease activity and also in predicting disease damage [138], in addition to its prognostic value following treatment with falling of its titer on serial measurments. [139]

It should be mentioned that patients can be classified according to their RF and anti-CCP antibodies (ACPA) assay into seropositive (positive to one or both of them) and seronegative (negative to both) the latter is usually diagnosed on clinical basis and it is less aggressive that the seropositive variety but later the patient may revert to seropositive and the antibodies are detected in the sera however it was found that 15 % of patients remain negative after 2 years of the disease. [140]

Seronegative RA should be differentiated from other seronegative spondyloarthropathies (previously known as rheumatoid variants) including Ankylosing spondylitis, reactive arthritis, psoriatic arthropathy, inflammatory bowel disease (IBD) associated arthropathies and undifferentiated spondyloarthropathies which are RF negative arthropathies and HLA-B27 strongly associated. [141]

Antinuclear antibody (ANA) testing – A negative ANA helps exclude SLE and other systemic rheumatic diseases; the ANA may be positive in up to one-third of patients with RA. [142]

Imaging:

Plain x-ray hands and feet:

X-ray can visualize bone erosions, joint space narrowing as an indirect sign of cartilage thinning, juxta-articular osteoporosis, cysts and, in severe cases, joint

subluxations, mal-alignment and/or ankylosis [143].X-ray can be helpful in the differentiation of RA from other joint conditions including osteoarthritis, psoriatic arthritis and neoplasms.[144], early progression in X-ray erosions is related to future impairment in physical function. [145]

Computed tomography:

CT is a tomographic radiographic imaging method that visualizes calcified tissue with high resolution. It can be considered a standard reference for detecting destructions of calcified tissues, however, in comparison with MRI and US, CT visualizes soft tissue changes inadequately. [146]

Magnetic resonance imaging:

MRI can be considered a good diagnostic modality without the use of ionizing radiation, and allows assessment of all the structures involved in arthritic disease, i.e. synovial membrane, intra- and extra-articular fluid collections, cartilage, bone, ligaments, tendons and tendon sheaths, it has been proven to be more sensitive than x-ray and CT in demonstration of the joint changes specially knees, wrist and fingers. [147]

Ultrasonography:

US can visualize inflammatory as well as destructive RA changes, It allows assessment of synovitis by detection of thickening of the synovial membrane of inflamed joints, bursa or tendon sheaths by grey-scale (B-mode) US [148], and by revealing and potentially quantifying increased synovial blood flow using Doppler techniques.[149,150] , US can also detect fluid in joints, bursa and tendon sheaths[151], and may be used to evaluate the integrity of tendons and ligaments, as well as imaging entheseal inflammation.[152,153]

Prognosis:

Bad prognostic factors include:

Older age [154], female gender, longer disease duration, acute phase markers with high titer [155], Presence of rheumatoid nodules, baseline radiological score. [156]

RF titer stands out as repeatedly being a good predictor of prognosis (both for radiology and function) in most studies. [157]

Anti-CCP positivity is a predictor of prognosis. Interactions with RF occur, so that the worst prognosis is seen for patients positive for both RF and anti-CCP, the best prognosis in those patients negative for both antibodies, and intermediate prognoses for those positive for one antibody only. [158]

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Treatment:

• Symptom relief:

A variety of analgesics provide symptomatic benefit in RA (eg: decreased pain, better sleep, improved activities of daily living, improved social activities, satisfaction with medication). [159,160]

Amitriptyline (in quite high doses) has been shown to be successful in reducing joint swelling, and help to lift a low mood and chronic fatigue. [161]

50 mg indomethacin or 50 mg diclophenac are beneficial. Also the addition of Paracetamol to Naproxen improved pain control. [162]

NSAIDs (for example: ibuprofen, diclofenac, naproxen) and COX2 inhibitor drugs (for example, rofecoxib, celecoxib and etoricoxib) have anti-inflammatory and analgesic properties, and many people with RA can testify to their effectiveness in controlling their symptoms.

Indeed the quality of life of many would be diminished for many people by not allowing continuing treatment with NSAIDs that they may need to take in significant doses over many years. There is no evidence to suggest that NSAIDs modify the course of RA, and they are purely for symptomatic benefit. [163]

• Role of steroids:

In recent-onset RA, low dose oral steroid regimes give symptomatic and quality of life benefit for up to 3 months. [164]

The majority of the trials suggest that steroids are disease modifying in slowing radiological damage over 2 years. [165-169]

In established RA, Knee joint injections of steroid give sustained benefit from a symptomatic and functional viewpoint [170]. Using oral steroids in variable doses to control symptoms may improve function over 1 year. [171]

The evidence that the use of steroids in established RA may be disease modifying is conflicting, some trials probably underpowered showed no significant effect. This evidence base is not as strong as the evidence base for recent-onset RA.[172]

• Disease-modifying anti rheumatic drugs (DMARDs):

Therapy with disease-modifying anti rheumatic drugs (DMARDs) should be started as soon as the diagnosis of rheumatoid arthritis (RA) is made. The early use of DMARDs has been recommended in recent years to reduce disease progression and long-term disability. The need for early use of DMARDs is incorporated in new National Institute for Health and Care Excellence (NICE) guidance. [173]

This group includes: [174]

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1. Hydroxychloroquine (Plaquenil).
2. Leflunomide (Arava).
3. Cyclosporine (Neoral).
4. Sulfasalzine (Azulfidine).
5. Methotrexate (Rheumatrex, Trexall).
6. Azathioprine (Imuran).
7. Cyclophosphamide (Cytoxan).

For many patients, mono therapies such as methotrexate work well [175-178]. Studies comparing Sulphasalazine with Methotrexate and Cyclosporin in combination therapies suggest that the latter two are superior for some outcomes to the former.[179]

If a patient fails on methotrexate monotherapy, the chances they will have a good response to other conventional DMARDs are less.

- **Biological drugs:**

Biological therapies specifically inhibiting targeted molecules of the immune system allow far better disease control. [180]

Some biological drugs have already been studied and approved such as Rituximab, a B-lymphocyte depletory [181], and the anti-TNF drugs (Adalimumab, Etanercept and Infliximab) [182]. Abatacept (a co-stimulation inhibitor preventing T-lymphocyte activation) has recently been appraised and deemed not to be cost-effective for use. [183]

In patients with established active disease despite conventional disease modifying drugs, the addition of a biological drug generally adds significant benefits for symptom control, function and quality of life [184-188], the combination of anti-TNF with methotrexate was superior to anti-TNF drug alone for symptomatic benefit, and in studies that measured them, functional outcomes, quality of life and joint damage.[189,190]

The only studies to compare biological therapy directly with conventional disease modifying drug in established RA suggest that Etanercept is superior to sulphasalazine, and Rituximab is superior to Methotrexate, for symptom control and functional benefit.[191,192]

Anakinra is a recombinant form of human IL-1 receptor antagonist that inhibits the activity ofIL-1, thus theoretically protecting both cartilage and bone. It is licensed for use in combination with methotrexate in patients who have had an inadequate response to methotrexate alone. Anakinra in different doses works well in an extension study in patients previously randomized to placebo for a variety of disease activity measures, radiological and functional outcomes. [193,194]

Highlights from the EULAR stepwise approach on 2012 include the following :[195]

- Patients with active disease should be monitored every 3 months, and treatment should be adjusted if there is no improvement at 6 months.
- Methotrexate (MTX) is recommended as first-line therapy; sulfasalazine (SSZ) or leflunomide can be substituted if there are contraindications to MTX.

- Anti-tumor necrosis factor (TNF) agents are no longer the only biologics recommended for patients with an insufficient response to MTX; all biologics are considered to be similarly effective.
- Biologics should be combined with disease-modifying anti rheumatic drugs (DMARDs).

It was shown that intensive treatment strategies with the aim of keeping the Disease Activity Score to low levels of activity resulted in substantially better outcomes. [196,197]

- **Surgical treatment:**

The amount of evidence to address the timing of surgical referral is scanty and of limited quality. A survey of hand surgeons and rheumatologists agreed on stage 3 MCP joint disease being the most appropriate time for surgery, and 3–6 months of resistant synovitis for extensor tenosynovectomy. [198,199]

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Autoimmune diseases (ADs) are chronic conditions initiated by the loss of immunological tolerance to self-antigens; they represent a heterogeneous group of disorders that afflict specific target organs or multiple organ systems. The chronic nature of these diseases places a significant burden on the utilization of medical care, increases direct and indirect economic costs, and diminishes quality of life. [200]

Autoimmune diseases affect a significant proportion of the population with >4 % of the European population suffering from one or more of these diseases ,although all autoimmune diseases share similarities in the basic immunological mechanisms ,in other aspects as clinical manifestations and age of onset, individuals vary widely. Most of autoimmune diseases are however multifactorial in nature with susceptibility controlled by multiple genetic and environmental factors. [201,202]

Many of the gene variants associated with risk in one autoimmune disease have shown to also have an association with the development of additional autoimmune diseases. This shared association, and the observation that multiple autoimmune diseases tackle in same patients and the same families has led to the model of a cluster of gene variants that decreases immunological tolerance. A large number of genes fall into the category of general autoimmune risk variants, just as genetic data have been used to further understand the biology of autoimmunity, immunological data can be used to further understand the genetics of autoimmunity.[202]

There are clinical and genetic grounds for assuming similar immune genetic mechanisms in autoimmune diseases (AIDs). Clinical evidence highlights the co-occurrence of distinct AIDs within members of a nuclear family and within an individual [203]. Individuals with a multiple autoimmune syndrome (MAS) have been grouped into three basic groups in which various AIDs cluster around one of three "main" AIDs, namely, systemic lupus erythematosus (SLE), autoimmune thyroid disease (AITD), and primary Sjogren's syndrome (SS). These three might be considered the "chaperones" of the other AID [204]. Along the same line of clinical evidence, there are therapies such as tumor necrosis factor inhibitors, rituximab, or a gluten-free diet that are already proving effective for more than one AID. [205,206]

With regards to genetic evidence, it has also been stated that around 44% of the single nucleotide polymorphisms (SNPs), which were found in genome-wide association studies (GWAS) on AIDs, are shared by two or more of the following diseases: celiac disease, Crohn's disease, psoriasis, multiple sclerosis (MS), rheumatoid arthritis (RA), type 1 diabetes (T1D), and SLE. [207]

Based on the previously mentioned immune genetic theory, it was found that AITD can be associated with other autoimmune diseases including type 1 diabetes[208,209] vitiligo[210] ,Addison's disease,[211] and multiple sclerosis.[212,213]

On the other hand RA as an autoimmune disease can also cluster together with other autoimmune diseases as myasthenia graves, vitiligo, type 1 diabetes and coeliac disease.[214]

And thus, an important question to be raised concerning the clustering of autoimmune diseases together represented as autoimmune thyroid diseases and rheumatoid arthritis particularly seropositive versus seronegative subtypes and hence the aim of our study.