Endocrine Disorders in Autoimmune Rheumatism

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Autoimmune rheumatological diseases' incidence and prevalence have risen over the last decades and they are becoming increasingly important worldwide. Thyroid autoimmune diseases share with them an imbalance in the immune system that lead to a pro-inflammatory environment. Usually this is the result of a multi-factorial process. In fact, it includes not only a possible genetic predisposition, but also environmental causes like microbiota dysbiosis, diet rich in processed foods, exposure to toxicants and infections.

Keywords: rheumatological diseases ; thyroid diseases ; corticosteroids ; cushing's syndrome ; withdrawal syndrome

1. Introduction

Autoimmune rheumatological diseases include a wide and heterogeneous spectrum of disorders mainly affecting joints and the anatomical structures associated to them: muscles, bones, tendons, tendon sheaths, ligaments, tendon and ligament insertions, synovial bursa and fasciae [1][2]. They are chronic progressive conditions whose main symptoms include articular pain, stiffness, swelling, redness, warmness and mobility impairment.

Recent data show that both prevalence and incidence of rheumatological diseases have increased over the last decades worldwide and they have become a major public. health challenge [3]. In fact, they represent one of the most frequent causes of work absence, disability, morbidity and, as a result, consistent healthcare expenditures.

Common autoimmune disorders tend to coexist in the same subjects and to cluster in families. Rheumatoid arthritis (RA) is the most common of these diseases with a global prevalence of 0.3–1% and an annual incidence of 0.02–0.05% according to WHO data [4].

The association between RA and thyroid autoimmune diseases (AITDs) like Graves' disease and Hashimoto's thyroiditis is well-known but many aspects remain to be clarified [5].

These conditions share common immunopathogenic mechanisms and it has been reported a relevant influence of genetic susceptibility [6][7].

Moreover, patients affected by autoimmune rheumatological diseases are usually treated with corticosteroids and this therapy may last years with consistent cumulative doses. As a result, it is not uncommon to see among these patients cases of endocrine disorders caused by chronic glucocorticoids treatment like iatrogenic Cushing's syndrome or tertiary adrenal insufficiency after steroids' withdrawal.

In this review, we are going to deepen the common aspects of the pathogenicity of rheumatological and thyroid autoimmune diseases and the endocrine dysfunctions related to chronic glucocorticoids treatment.

2. Thyroid Diseases

The prevalence of AITDs, including Hashimoto's thyroiditis, Graves' disease and postpartum thyroiditis, is estimated to be as high as 5% of the general population (abnormal thyroid function varies within 7–9% in females and 1–2% in males across different populations) [8].

The pathogenesis of AITDs, like other autoimmune diseases, is multifactorial, combining genetic, immune, environmental and hormonal influences.

Hashimoto's thyroiditis (HT) is a typical T-cell-mediated autoimmune disease characterized by a diffuse goiter, the presence of anti-thyroid peroxidase (anti-TPO) and/or anti-thyroglobulin (anti-Tg) antibodies in serum (although it can be

seronegative too), varying degree of thyroid hypofunction, and intrathyroidal infiltration of B and T lymphocytes with CD4+ type 1 T helper (Th1) subtype predominance [9].

In Graves' disease, lymphocytic infiltration is mild and involves mainly CD4+ type 2 T helper (Th2) cells, which induce the production of antibodies to bind to the thyroid stimulating hormone (TSH) receptor [10].

Autoimmunity is crucial also for the development of rheumatological diseases, despite the pathogenicity process implies the production of systemic antibodies and not only organ-specific as seen in thyroid diseases. As a result, the diagnosis of these conditions is more challenging and there is a wide spectrum of non-disease specific antibodies associated with rheumatological diseases such as anti-nuclear antibodies (ANA), anti-double stranded DNA antibodies (Anti ds-DNA), anti-Smith (anti SM) antibodies or rheumatoid factor (RF).

The association of autoimmune thyroid diseases and a considerable number of autoimmune diseases including rheumatological diseases such as rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis, is called Autoimmune Polyendocrine Syndrome type 3 (APS 3).

The correlation between thyroid and rheumatological diseases is that they share in their pathological process both genetic and environmental factors. This is due to both pre-existing and environmental factors. In fact, the onset of autoimmune diseases commonly is in late childhood or late adulthood confirming the fact that phenotype depends not only from genetic factors but also from non-genetic processes like antibody production, epigenetic programming as well as environmental factors like tobacco smoking and the intestinal microbiota [11].

2.1. Genetic Factors

Many genome-wide association studies (GWAS) showed that there are several genetic loci associated with the likelihood of developing both thyroid and rheumatological diseases.

The strongest correlation is with human leukocyte antigen (HLA), the locus of the genes that encode proteins found on cell surface responsible for the regulation of the adaptive immune system. HLAs corresponding to major histocompatibility complex II (MHC II) present antigens from outside the cell to T-helper lymphocytes (or CD4 positive T cells) [12].

Among those HLAs there are autoimmunity-prone haplotypes like HLA-DQ8/DR4 that favour a strong Th-1 and Th-17 pro-inflammatory response to self-antigens and they are usually found in patients affected by some autoimmune rheumatological diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and in autoimmune thyroid disease [13][14][15].

A polymorphism of a gene coding protein tyrosine phosphatase non-receptor type (PTPN22) involved in several signaling pathways associated with the immune response was found in other autoimmune disorders like juvenile rheumatoid arthritis, and Graves' disease [16]. However, a Russian study did not found any correlation between the above-mentioned polymorphism and rheumatoid arthritis probably because the prevalence of the former varies in different ethnic groups as reported in previous studies [17][18].

The cell surface co-receptor cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a critical attenuator of T-cell activation and it is a component of the regulatory systems of peripheral tolerance [19]. Genome wide association studies elucidated that CTLA-4 polymorphisms represent a locus of susceptibility for autoimmune thyroid diseases and rheumatoid arthritis [20][21][22].

A proof of that is the possible development of Hashimoto's thyroiditis, Graves' disease, arthritis and polymyalgia rheumatica or the flaring up of pre-existing rheumatological conditions like rheumatoid arthritis during treatment with ipilimumab, an immune checkpoint inhibitor drug targeting CTLA-4 [23][24][25][26].

Moreover, rare heterozygous CTLA4 mutations can lead to common variable immunodeficiency (CVID) with non-functional FoxP3+ regulatory T cells (Treg cells) resulting in systemic autoimmunity associated with defective response to infections [27][28][29].

Polymorphisms of interleukin 2 receptor alfa (IL-2 RA or CD 25) that also cause a dysfunction of regulatory T cells are linked to a wide spectrum of rheumatological autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis [30].

There are also other promising susceptibility loci linked to the development of autoimmune diseases like IL23R, TYK2 and A20 that are currently being studied [31][32].

2.2. Environmental Factors

Autoimmune thyroid and rheumatological diseases can be associated with several environmental factors including intestinal microbiota, diet components, vitamin D, chemicals including endocrine disruptors, cigarette smoke and infections.

Bacteria that form intestinal microbiota are involved in maintaining the homeostasis of the immune system by the secretion of metabolites. Some of them are short-chain fatty acids (SCAs) like acetate, propionate and butyrate and they are produced through the fermentation of non-digestible carbohydrates.

Their function is to regulate T cells differentiation, stimulate the production of anti-inflammatory or anti-microbial mediators and they are crucial for epithelial barrier function as they prevent a condition characterized by an altered intestine permeability known as the “leaky gut” [33][34][35].

In fact, an abnormal composition of intestinal microbiota, also called gut dysbiosis, alters the expression level of Toll-like receptors (TLRs) of antigen presenting cells, causing an imbalance between Th17 and Treg (Regulatory T cells) and has a major impact of antibodies production [36].

All this process may lead to an increasing number of autoantigens targeted by T cells and to the activation of autoreactive B cells that produce autoantibodies versus a large number of autoantigens leading to autoimmunity [37][38].

A study by Shor et al. found that gastrointestinal-related antibodies are associated to a wide spectrum of autoimmune diseases including thyroid and rheumatological diseases. For instance the titer of antibodies anti Saccharomyces cerevisae (ASCA), which is a yeast usually found in human microbiota, was found to be significantly higher in patients affected by Graves’ disease or by systemic lupus erythematosus than in the general population [39].

Therefore, recent and ongoing studies are focusing on the possibility of using probiotics and fecal transplantation as a treatment of autoimmune disease with promising results [40][41][42].

Lately, studies have suggested that low vitamin D concentrations and other conditions which may result in reduced vitamin D function (e.g., certain Vitamin D receptor gene polymorphisms, pathologies of vitamin D gene and its binding protein) may increase the risk of AITDs [43][44]. Vitamin D is known to regulate the adaptive immunity and its deficiency has been linked to the development of Hashimoto’s thyroiditis, Graves’ disease, rheumatoid arthritis and systemic lupus erythematosus [45][46][47]. In fact, it has been described that the lack of this crucial hormone may cause gut dysbiosis and, a result, a pro-inflammatory environment [48]. The supplementation with the inactive form of vitamin D, cholecalciferol, in animal studies led to the improvement of gut microbiota and intestinal inflammation [49][50]. Moreover, it has been demonstrated that cholecalciferol has beneficial effects on AITDs and on rheumatological manifestations, and these results may be related to a change towards a more favourable microbiota composition [45][51].

Diet is crucial for a healthy and functional microbiota and the change in human nutrition that has occurred since the mid 20th century probably has played a relevant role in the increase of autoimmune diseases’ prevalence and incidence. In fact, the need of long-lasting food led to its industrial processing and the adding of compounds like preservatives, artificial sweeteners and emulsifiers that alter the microbiota composition [52][53][54].

However, the consumption of processed food does not affect only microbiota. Usually this type of food has a high content of sodium that causes an increase in hypertonicity that recent studies have linked to an enhancement of Th17 immune response. This causes an imbalance between pro-inflammatory and anti-inflammatory mediators [55][56][57]. A study by Salgado E. et al. with 18,555 partecipants found a significantly higher proportion of patients affected by rheumatoid arthritis between high-salt consumers with a dose dependent relationship [58]. This report was later confirmed in subsequent studies [59][60].

Among chemicals, several toxicants have been described to induce both systemic and organ-specific autoimmune diseases, including rheumatological and thyroid ones.

For instance, exposure to silica and asbestos was found to be associated with the developing of systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis and vasculitis. The phagocytosis of asbestos and silica crystals

leads to inflammasome activation causing an increase in pro-inflammatory cytokine expression, the generation of reactive oxygen and nitrogen species and the induction of aberrant cell death [61][62][63][64].

Excess iodine ingestion is known to be a contributing factor to the development and the exacerbation of autoimmune thyroiditis. In fact, studies showed that iodine excess can lead to increased thyroid lesions and to the increase in thyroid-specific antibodies [65][66][67].

Chemicals that cause an impairment to the endocrine function of one or more glands are called “endocrine disruptors” and they may contribute to the development of rheumatological and thyroid autoimmune diseases.

Indeed, the increase in the consumption of plasticizers, nitrate and mercury has been linked to the rising number of patients affected by autoimmune thyroid diseases, rheumatoid arthritis and systemic lupus erythematosus [68][69][70][71].

Moreover, it has been deeply studied that the toxicants contained in cigarette smoke can cause a relevant genetic damage by increasing the oxidative stress and an imbalance between pro-inflammatory and anti-inflammatory immune response [72][73][74]. As a result, in smokers autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus and Graves’ disease are more frequent and severe [75][76][77][78][79][80][81][82][83].

To conclude, many studies highlighted a pivotal role for infections in autoimmune diseases. In particular, a strong relationship between autoimmune rheumatological diseases and hepatitis C virus, hepatitis B virus, Herpesviridae, Staphilococcus aureus was found [84][85][86].

For autoimmune thyroid diseases a causative role for infectious agents in humans still has to be established [87][88].

The main mechanisms by which infections can participate in autoimmune diseases’ development are molecular mimicry, bystander activation, epitope spreading and polyclonal activation of B cells.

Molecular mimicry is probably the most important of them and it occurs because of the cross-reactivity of microbial and self-antigens. As a consequence, autoreactive T-cells are activated and they trigger an autoimmune reaction.

Bystander activation is the process typical of the chronic inflammation state by which antigen-presenting cells stimulate the proliferation of T and B cells by presenting them self-epitopes of the damaged tissues.

Epitope spreading occurs when the proliferation of T and B cells of bystander activation is directed against a different part of the same protein or against a different protein.

To conclude, the polyclonal activation of B cells is the consequence of the constant activation of immunity that leads to the formation of immune-complexes that cause tissue damage [89][90][91].

3. Effects of Chronic Glucocorticoid Treatment

As seen in the previous chapter, an over-activated immune system is crucial for the pathogenesis of rheumatological autoimmune systemic diseases and glucocorticoids (GCs), along with other immunosuppressant drugs, still represent a leading treatment. In fact, they are anti-inflammatory drugs that strongly suppress the immune system.

First, they stimulate the transcription factors coding for anti-inflammatory gene products such as interleukin-1 receptor type II (IL-1R2) and interleukin 10 (IL-10). GCs also inhibit the synthesis of almost all known inflammatory cytokines blocking transcription factors that are essential for the pro-inflammatory response: nuclear factor-kappa-B (NF-kB) and activator-protein 1 (AP-1) [92][93]. Moreover, their activity is also against the secretion of pro-inflammatory cytokines affecting post-translational events [94].

It is estimated that approximately 1% of the Western world receives prolonged therapy with synthetic GCs, resulting in a supraphysiological exposure causing several effects [95]. They can be organ-specific, ranging from adrenal glands to thyroid dysfunction. GC-induced impairment of HPA axis will be discussed later. Although thyrocytes express GC receptors that play an important role in differentiation of thyroid cells, an exposure to high doses of GC can cause thyroid function impairment [96]. In fact, glucocorticoids decrease serum TSH, reduce TSH response to TRH and impair peripheral conversion of T4 to T3 [97][98]. This effect of reducing T3 serum levels is the reason of GC administration during thyroid storm [99]. Chronic GC treatment can also cause multi-systemic effects known as Cushing’s syndrome [95].

3.1. Cushing’s Syndrome

Glucocorticoids are drugs with different properties and some of them are considered as adverse effects of GCs.

A long-lasting treatment with GCs may lead to a severe adverse event, the so-called iatrogenic Cushing's syndrome [100].

All available forms of GCs are capable of producing Cushing's syndrome with signs and symptoms that are generally related to the dose and the duration of treatment. Although supra-physiological doses (>7.5 mg/d of prednisone) usually are required before patients manifest significant Cushingoid effects, some patients can develop Cushingoid appearance with chronic administration of lower doses (5 mg/d of prednisone) [100][101].

Iatrogenic Cushing's syndrome is considered as the most common cause of hypercortisolism.

Its clinical presentation is similar to that of the endogenous form and includes plethora, striae rubrae, thin skin and proximal muscles' hypotrophy. These patients are usually obese with a redistribution of body fat to truncal areas, buffalo hump, enlarged dorsocervical and supraclavicular fat pads and the classic moon face.

Moreover, like in the endogenous form, iatrogenic Cushing's syndrome can be linked with systemic diseases and comorbidities [100][101][102].

Among metabolic alterations, GCs increase insulin resistance leading to hyperglycemia, impaired glucose tolerance and eventually diabetes mellitus especially in predisposed patients [100][102][103]. Moreover, the resulting hyperinsulinism, along with hyperphagia related to GCs therapy, contributes to weight gain and obesity.

Dyslipidemia seems to be less frequent than other metabolic comorbidities in human Cushing's syndrome. Nevertheless, it plays an important role in determining the global cardiovascular risk in overt and subclinical Cushing's syndrome. In particular, it is reported an increase of triglycerides and total cholesterol levels whereas HDL levels can vary [104].

Despite their limited mineralocorticoid activity, treatment with high doses of GCs leads to an increased excretion of potassium and sodium absorption resulting in higher blood pressure. Moreover, it has been described that cortisol excess increases levels of clotting factors and impairs fibrinolytic capacity rising the overall risk of acute *cardiovascular* events [104][105].

For what concerns endocrine dysfunction, GCs can cause secondary hypogonadism, GH-deficiency and secondary hypothyroidism [100].

GCs interfere with both intestinal and renal calcium absorption, causing nephrolithiasis and reduced bone density. As a result, many of these patients suffer from osteoporosis that is also provoked by the stimulation of osteoclastogenesis and by the inhibition of the function of osteoblasts operated by these drugs [102][106].

Cushing's syndrome is also characterized by *myopathy* because GCs affect both transcription and translation of enzymes involved in the metabolism of fats and in the process of protein synthesis in the muscle [107][108].

Although steroids are known to inhibit arachidonic acid and consequently cyclooxygenase 1 (COX-1) that is essential for gastric mucosa protection, the risk of developing gastritis and *gastrointestinal* ulcers during long-term GCs therapy is debated [109][110][111][112].

Corticosteroid treatment can also cause posterior sub-capsular cataract (PSC), as first described in 1960 in 44 patients affected by rheumatoid arthritis chronically treated with GCs. The main mechanism of pathogenicity responsible for this condition is the alteration of eye epithelial proteins transcription [113][114]. Another eye disturb that can be provoked by GCs therapy is glaucoma probably because of the decreased trabecular meshwork outflow that results in an increased intra-ocular pressure [115][116][117].

For what concerns dermatological manifestations of Cushing's syndrome it is well established that GCs alter collagen, mucopolysaccharides, fibroblast and keratinocytes proliferation leading to vascular fragility and skin atrophy [118].

The use of GCs in predisposed patients can cause a variety of psychiatric conditions, including mania, psychosis, depression, and delirium. Lewis et al. reported severe psychotic reactions in 5.7% of patients taking GCs and mild-to-moderate reactions in 28% of patients [119][120]. Moreover, along with the above-cited disturbs, a recent study described a negative association between cumulative exogenous corticosteroid exposure and the volume of the entire hippocampal region, affecting also dentate gyrus and CA3 regions. This finding can be the explanation of the negative impact of

glucocorticoids on memory retrieval, concentration and efficiency that prompted the investigators to coin the term *steroid dementia*. This disturb showed to be reversible after GC therapy suspension [121].

As previously described, GCs have a strong immuno-suppressant activity so it is has been frequently described an increased infection rate for people with Cushing's syndrome, especially from intracellular and opportunistic pathogens [122][123].

3.2. Adrenal Insufficiency and Corticosteroids' Withdrawal Syndrome

Chronic exposure to exogenous glucocorticoids also causes a suppression of hypothalamic-pituitary-adrenal axis (HPA) [101].

This condition is called tertiary adrenal insufficiency. While the risk of adrenal insufficiency (AI) is known if GCs therapy is stopped suddenly in chronic users or during acute illness if patients are under GC low doses, its risk is underestimated in other conditions (e.g., GCs tapering, in patients under medium GC doses that experience an acute illness or a surgical intervention). The syndrome that follows reduction or discontinuation of glucocorticoids bears similar but not identical symptoms and signs of adrenal insufficiency and it is called corticosteroids' withdrawal syndrome. They include hypotension, hypoglycemia, fatigue, dizziness, weakness and lethargy [124][125].

The withdrawal syndrome is experienced by the patients after discontinuation of glucocorticoid therapy. It has been considered a withdrawal reaction due to an established physical dependence on supraphysiological glucocorticoid levels [125][126][127].

Although the risk of developing hypoadrenalism/corticosteroids'withdrawal syndrome is higher for patients treated with oral steroids with a dose ≥ 20 mg/day of prednisone (or equal dose of other steroids) for ≥5 days, there is a wide variability of the individual response to exogenous GCs [124][125][126][127][128]. Moreover, the full recovery time of adrenocortical hypoplasia or atrophy induced by GCs can last weeks, months and in some cases years, even with blood tests that show normal ACTH and cortisol secretion [124][125][126][127][128].

In the pathogenesis of corticosteroids'withdrawal syndrome several mediators may be involved, including CRH, vasopressin, POMC, central noradrenergic and dopaminergic systems, cytokines, and prostaglandins [126][127][128].

CRH in the brain not only activates the HPA axis but also mediates stress-related behavioral effects. Moreover, a well-functioning CRH system in the brain seems necessary for adequate mesolimbic dopaminergic function. Thus, central CRH hyposecretion may contribute to anxiety and depression via inadequate stimulation of dopaminergic neurons terminating in the nucleus accumbens. Some investigators feel that hyposecretion of central CRH plays an important role in the pathogenesis of atypical depression. [120][128][129]. In this scenario of both physical and psychophysical symptoms related to corticosteroid's withdrawal, the term "GCs addiction" was coined [130].

Although not being directly related to the hypocortisolism, glucorticosteroids' withdrawal also may lead to a relapse of the underlying autoimmune rheumatological condition treated with GCs [131].

As a result, to avoid that and to prevent the effects of GC withdrawal syndrome, a gradual tapering of glucocorticoid therapy has become the standard of practice.

3.3. Is There a Safe GC Treatment Regimen?

GCs adverse events were shown to be more relevant among patients receiving a moderate (>5 mg and <10 mg of Prednisone Equivalent Dose or PED) or high (>10 mg) daily dose compared to low-dose (<5 mg) users [132]. In fact, a recent study by Mebrahtu et al., including 111,804 patients affected by rheumatological diseases with a follow up period of 5.5 years, found that for every increase of daily dose of 5 mg PED the risk for adrenal insufficiency increased by 7%, 9% for Cushing syndrome and 6% for mortality. The incidence of Cushing's syndrome and adrenal insufficiency were reported to be respectively 0.55 and 0.41 for 1000 people/year [125].

This knowledge led to the recommendation of the rheumatological associations like EULAR (European Alliance of Associations for Rheumatology) to carefully monitor the formers agreeing that the risk of harm is acceptably low for low GC dose users [132].

However, there are other variables besides daily dose that can dictate the extent and severity of adverse events suffered by patients taking corticosteroids.

One factor is the duration of use, since many patients are on long-term GC treatment.

Another aspect of the toxicity of GCs is the cumulative dose. It is a parameter linked to the duration of use but includes also the short-term increments of the daily dose needed when a relapse of the underlying rheumatological disease occurs [133].

Since most randomized trials are too short, we have no valuable information of the risks of long treatment periods. Despite that, a retrospective analysis on patients on low-dose GC treatment of 5 years demonstrated that these patients were prone to a significantly higher prevalence of fragility fractures, arterial hypertension and myocardial infarctions increasing with the duration of treatment [134]. In particular, osteoporosis is a common and severe adverse effect of glucocorticoid excess that occurs even in patients treated with a protracted therapy with very low GC doses. A UK database stated an increase of clinical vertebral fractures by 55% for a prednisone dose of <2.5 mg/day [135]. As a result, osteoporosis represents one of the major limitations to long-term glucocorticoid therapy. The highest rate of bone loss occurs within the first 3–6 months of GC treatment, and a slower decline continues with persistent use. Also high cumulative GC doses (>1 g of prednisone) were shown to increase the risk of fracture, particularly vertebral fracture due to the greater effects of GCs on trabecular bone than on cortical bone [136][137].

Recently, a study by George et al. also found that infection risk in patients treated with daily doses of prednisone 5 mg or less per day was significantly higher [138].

Moreover, as previously described, GC treatment is considered an independent factor for a shortened life expectancy, which is rarely mentioned in overviews over GC toxicity. In particular low-moderate daily dose had a hazard ratio of 2.22 for premature death in a study by Listing et al. [139]. Another study found a total cumulative dose of 40 g as the threshold for increased mortality [140]. That corresponds to 5 mg/day for 21 years or 7.5 mg/day over 14.5 years. Such time periods can easily be reached in the treatment of rheumatological diseases like rheumatoid arthritis.

As described in the last paragraph, after GC withdrawal even patients receiving low doses of GCs may experience AI. If fact, a randomized placebo-controlled withdrawal clinical trial by Pincus T. in patients with rheumatoid arthritis found that in patients treated with prednisone doses around 3 mg/day, it was rarely possible to withdraw the drug [141].

Another critical factor for the development of AI and Cushing's syndrome is cumulative dose. The above-cited study by Mebrahtu et al. reported that the risk of developing AI or Cushing's syndrome for patients with a cumulative dose of 1 g in the previous year was more than doubled [125].

To conclude, since there is not a safe GC therapy regimen, it seems advisable for physicians to vigilate for glucocorticoid-related adverse events and to counsel patients about possible risks, even among low-dose long-term users.

3.4. Follow up of GC Therapy

Although it is essential to inform patients about the possible adverse effects of chronic GC therapy in order to detect those dysfunctions at the earliest stage possible, prescribers should also estimate their risk of developing a specific GC-induced condition. For example, as described before, GC-induced osteoporosis is more frequent among high GC dose users but also among people with low body weight, low bone mineral density, previous fractures, family history of osteoporosis and among females [95]. Hence, it would be reasonable to perform a bone density scan before starting GC therapy and repeat it basing on the individual risk of the patient. That should also be the basis for the prescription of calcium and vitamin D supplementation, bisphosphonates or other drugs [132][142]. Another example is the need to examine pre-existing hyperglycaemia or diabetes mellitus, schedule tailored blood glucose and glycated haemoglobin tests and where necessary give advice for treatment [143]. It is also important to plan follow-up visits to allow patients to ask questions, to inform physicians about the possible adverse events and for doctors to perform an accurate physical examination to check dysfunctions related to GC therapy (cushingoid appearance, skin lesions, high blood pressure, etc.).

4. Conclusions

Rheumatological and thyroid autoimmune diseases are strongly related and the evidences derive from studies focused on prevalence, genetic and environmental aspects. However, those studies lack of homogeneity and there are probably multiple reasons.

First, systemic rheumatological diseases are heterogeneous and have different physiopathological mechanisms. Second, the prevalence of those diseases is much lower than thyroid diseases' so it is difficult to link them with precision.

In addition, many studies have only focused on patients with an overt thyroid dysfunction so it is reasonable to think that the correlation between them has been underestimated. This is because there is a wide subset of autoimmune thyroid diseases without thyroid function impairment but with typical ultrasound features like a pseudo-nodular pattern, gland hypoechogenicity and heterogeneous echotexture.

Moreover, the design of the majority of the studies available did not include a control group.

To conclude, it is reasonable to consider both a morphologic and functional evaluation of the thyroid gland in all patients affected by rheumatological diseases in order to identify promptly a possible related autoimmune thyroid disease.

The above-described iatrogenic Cushing's syndrome and glucocorticosteroid's withdrawal syndrome related to protracted GCs treatment are still very frequent in rheumatologic disorders despite the rising role of biologic drugs like monoclonal antibodies. In these patients, it is essential to know the importance of prescribing a correct regimen of glucocorticoids' withdrawal to prevent hypocorticosurrenalism and the related symptoms. Moreover, the same attention should be payed to administer GCs at the lowest possible dose to avoid the multi-systemic dysfunctions due to the iatrogenic hypercortisolism without provoking the relapse of the underlying rheumatologic disease.

To sum up, our paper highlights that it is necessary to acknowledge the importance of thyroid diseases as other endocrine disorders in autoimmune rheumatological diseases. Hence, it seems advisable for new studies to focus on treatments for autoimmune rheumatological diseases based on rebalancing the immune system dysfunction in order to avoid or prevent endocrine disorders.

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