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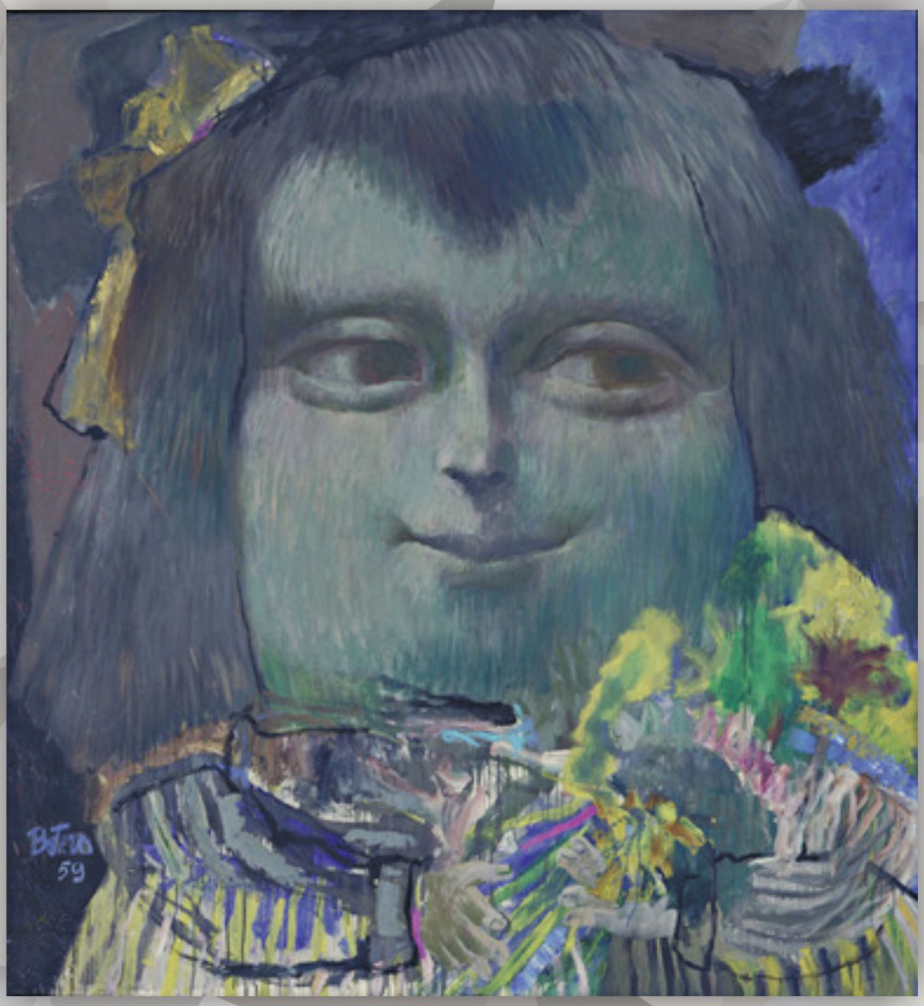

## "Beauty is in the eye of the beholder"
## Fernando Botero

EDITORIAL

# DIABULEMIA: WHAT IS THIS?

It is a “nickname” to describe an eating disorder in patients with type 1 diabetes mellitus (ED-DMT1). This mental disease is still not well recognized by the endocrinologists, consequentely it is not yet included in the *Diagnostic and Statistical Manual of Mental Disorders*. The researches have total knowledge about psychosocial variables implicated in the adoption of intensive diabetes management strategies such as depression, anxiety, eating disorders, fear of hypoglycemia and weight gain with insulin therapy. *Diabulemia* is commom among girls but it is devastating when occurs in boys.

Some authors have reported higher mortality rates among women with *Diabulemia*. Sometimes this is a subclinical eating disorder that manifest through hyperglycemia and glycosuria due to patient insulin omission as a form of caloric purging.

The warning signals of diabulemia and insulin restriction are:

1-Chronic hyperglycemia with increased HbA1c levels;

2-Decreased weight despite normal eating intake;

3-To many hospitalizations due to ketoacidosis;

4-Failure in blood glucose control;

5-Fear of hypoglycemia;

6-Fake capillary glycemia notes that are incompatible with HbA1c levels;

7-Symptoms of diabetes;

8-Depression;

9-Fatigue, weakness and lethargy due to intensive physical activity to lose weight;

10-Amenorrhea;

11-Anemia, dry skin and hair loss.

The early diagnosis of *Diabulemia*, specially in women with type 1 diabetes is important to prevent increased rates of diabetes complications and mortality. The early recognition of *Diabulemia* is important in order to establish a multidisciplinary care.

**Mirnaluci Paulino Ribeiro Gama**

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# REVIEW
# TYPE 2 DIABETES IN HIV-POSITIVE PATIENT A NEW EPIDEMIC?

## *DIABETES TIPO 2 EM PACIENTES HIV POSITIVO UMA NOVA EPIDEMIA?*

LUCAS CARDON DA COSTA*

Key words : HIV positive, Antiretroviral drugs, AIDS
Descritores: HIV positive, Drogas antiretrovirais, AIDS

***Abstract***

After new antiretroviral drugs and new treatment guidelines, life expectancy of HIV positive patients rose significantly. However, despite greater survival, new metabolic complications appeared in these patients. This happens not only because of evolution of the HIV infection itself, but also by chronic exposure to antiretroviral drugs.

Type 2 diabetes mellitus (T2DM) is emerging as one of the most common metabolic disorders in a considerable number of patients using antiretroviral drugs. Nevertheless, lipid abnormalities can also be found in these patients together with organ damage in liver and kidneys and lipodystrophyc syndromes. Some studies have shown a relationship between disease duration and appearance of T2DM. **Endocrinol diabetes clin exp 2016 1832 -1835.**

**Resumo**

Com o surgimento de novas drogas antirretrovirais e novos esquemas terapêuticos, a
expectativa de vida aumentou significativamente para os pacientes com HIV. Todavia, junto com esse aumento na expectativa de vida, novas complicações metabólicas apareceram, tanto com pela evolução da infecção pelo HIV como quanto pela exposição prolongada às drogas antirretrovirais.

O diabetes mellitus tipo 2 (DM T2) é uma das principais desordens metabólicas que incide atualmente em número considerável de pacientes em uso da terapia antirretroviral. Não obstante ocorrem, também, alterações no perfil lipídico hepatopatias, nefropatias e lipodistrofias. Alguns estudos demonstraram a relação com tempo de exposição e o aumento da incidência complicações metabólicas dentre as quais o DMT2. **Endocrinol diabetes clin exp 2016 1832 -1835.**

### 1 - HIV AND TYPE 2 DIABETTES MELLITUS

HIV-positive patients have the same incidence rate for type 2 diabetes mellitus (T2DM) as the general population. However some factors linked to the progression of infection and to the establishment of acquired immunodeficiency syndrome (AIDS) may interfere with this balance. Antiretroviral drugs may play an important role in the endocrinological and metabolic complications seen in this context (1).

Risk factors related to development of T2DM are: antiretroviral therapy (acute and chronic risk), advanced age, male gender, chronic infection, low CD4 lymphocytic count, high body mass index, great waist circumference or waist to hip ratio, high viral load, lower socioeconomic class and ethnicity (with high risk in black African) (1, 2). Another relevant information is that patients addicted to the use of injectable drugs belong to a risk group to develop T2 DM (2).

HIV-positive patients with T2 DM can be classified in three subgroups: (a)- patients with T2DM diagnosed prior to the HIV infection; (b)- those who develop T2DM at the onset of the infection and (c)- those who begin to experience hyperglycemia after the use of antiretroviral therapy. This classification is important because it may influence therapeutic decisions. (1).

The infection with the immunodeficiency virus (HIV) increases release of proinflammatory cytokines that promote the onset and perpetuation of a chronic inflammatory process, specially in the intravascular environment, increasing the risk of heart disease in these patients. This explains why HIV-positive patients with T2DM have increased risk for heart conditions in comparison with general population. The chronic inflammatory process increases insulin resistance in HIV-positive population (3,4).

Pro-inflammatory cytokines, mainly tumor necrosis factor (TNF), are also secreted in the intrahepatic tissue. In this environment, chronic local inflammation promotes lipid infiltration (steatosis and/or steatohepatitis) and increases hepatic resistance to insulin. This disorder is observed mainly on patients co-infected by hepatitis C virus (HCV) and HIV (5-11).

### 2 - ETIOPATHOGENESIS OF T2DM IN PATIENTS ON ANTIRETROVIRAL DRUG THERAPY

The antiretroviral drug most often associated with dyslipidaemias and metabolic abnormalities is stavudine. However, others must be mentioned such as zidovudine and didanosine as they are also linked to metabolic abnormalities, although at lower level when compared to stavudine. These drugs belong to the nucleoside analogs reverse transcriptase inhibitors (NRTIs) (12,13).

In the past, some studies had shown that drug induced glucose intolerance and T2DM in HIV treated patients was caused exclusively by protease inhibitors (PI). However, recently it has been demonstrated that, while PI represent acute risk for onset of diabetes, NRTIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) causes chronic and cumulative effects that are responsible for diabetes onset and other metabolic disorders such as lipid abnormalities (13).

#### 2.a- Protease inhibitors (PI)

PI drugs do not have a class effect to trigger T2DM. In other words, PI drugs have a different etiopathogenetic mechanism. One of them is the effect of PI over the steroid regulatory element binding protein-1c (SREBP -1c), resulting in abnormal glucose metabolism because of the production of a malfunctioning peroxisome proliferator activated receptor gamma (PPARγ). PPARγ has great importance on lipid and glucose metabolism (14,15).

Lipid and fatty acids metabolism abnormalities are caused by the inhibition of cellular retinoic acid-binding protein type 1 (CRABP-1). CRABP-1 interacts with PPARγ, and this interaction results in adipocyte inflammation that has a direct relation with antiretroviral induced lipodystrophy. Adipocyte inflammation

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causes local insulin resistance and subsequent release of free fatty acids that will be stored in the liver and skeletal muscle. Skeletal muscle and liver lipid accumulation induces insulin resistance (14,15).

PI have been shown to increase insulin resistance and reduce insulin secretion by interfering with GLUT-4 mediated glucose transport also (15,16).

**2.b- Nucleoside analogs reverse transcriptase inhibitors (NRTIs)**

Mitochondrial toxicity (mainly by stavudine) is caused by depletion of the mitochondrial DNA. This effect is conspicuous after one month of drug exposure. The mitochondrial dysfunction is caused by oxidative phosphorylation impairment. The toxicity of mitochondrial DNA in the skeletal muscle is associated with increase in the insulin resistance (13,17,18).

**2.c- Other drugs used by HIV - positive patients**

Antiretroviral drugs are not the only offenders in HIV--associated T2DM. Other drugs used to control the AIDS comorbidities may also cause it. It is worth mentioning some of them like antibiotics (pentamidine) and appetite stimulants (megestrol acetate) that are frequently used in these patients (19,20). Pentamidine is used to treat infection caused by Pneumocystis jiroveci and it is associated to T2DM because it induces beta cell toxicity resulting on acute hypoglycemia. Patients using pentamidine may have low levels of peptide C (a reliable insulin secretion marker) reinforcing the beta cell toxicity mechanism. This happens specially in patients using high doses of this medication chronically and in those with renal insufficiency (19, 20, 21).

Another drug is the megestrol acetate used as appetite inducer to increases caloric ingestion in this group of patients. This drug has a corticoid-like action (22).

**3- OTHER METABOLIC DISORDERS RELATED TO ANTIRETROVIRAL THERAPY**

**3.a - Lipodystrophy**

Treatment with antiretroviral agents such as protease inhibitors has created a syndrome of abnormal fat redistribution, insulin resistance, dyslipidemia and impaired glucose metabolism that is known as lipodystrophy syndrome of HIV (SLHIV) (23).

Although this syndrome is strongly linked to PI, some NRTI (specially stavudine) are also implicated on its genesis (24,25).SLHIV is also called: metabolic syndrome associated to antiretroviral therapy, abnormal fat distribution syndrome and, more recently, dislipidemic lipodystrophy associated to HIV/ highly active antiretroviral therapy (26-30). The dyslipidemia associated to HIV infection features are: high total cholesterol, reduced high density lipoprotein cholesterol, high low density lipoprotein cholesterol and increased triglycerides. This lipid profile is known to be highly atherogenic.

In the HIV lipodystrophy syndrome the following glycemic abnormalities may be seen: impaired fasting glucose (prediabetes);glucose intolerance; diabetes mellitus (26).

The lipodystrophy can be subdivided in three groups: (a)- isolated lipoatrophy with reduction on peripheral fat that is present on arms and legs; (b)- isolated lipoaccumulation of abdominal fat, dorsal gibbosity and gynecomastia and (c)- a mixed syndrome of lipoatrophy combined with lipohypertrophy.

Until the present moment there is no guideline to diagnosis and treatment of HIV lipodystrophy syndrome. Some treatment options are: substitution of older PI for newer drugs, regular exercise including a combination of strengthening exercises and cardiovascular training, use of statins, fibrates, metformin, glitazones and GH therapy (23, 24, 25, 26, 27, 28, 29, 30, 31, 21, 33, 34, 35, 36, 37,38).

**4-TREATMENT**

**4.a - Lipid profile**

Lipid abnormalities treatment begins initially with dietary modification followed by medication. Drug interactions between lipid-lowering drugs and antiretrovirals are common and consulting a web-based resource is helpful (www.hivdruginteractions.org). Generally low-dose pravastatin, atorvastatin, fibrates and niacin are safe to use with protease inhibitors (PI) (39,40).

**4.b - Glucose intolerance**

Glucose intolerance should be managed with dietary measures alongside with physical exercises and oral drugs. Metformin is the first choice although it is important to know that there is a theoretical risk of lactic acidosis in these patients. However, such risk does not preclude using the combination in patients with normal renal function (41). Metformin is more likely to cause diarrhea than other drugs. HIV patients on metformin should be educated about symptoms of lactic acidosis (abdominal pain, fatigue, weight loss, nausea, dyspnea and arrhythmia) (42,43).

Pioglitazone is emerging as a therapeutic option in HIV-positive patients with T2DM. This drug has shown to be effective as monotherapy or associated with metformin. Pioglitazone is indicated not only for glycemic control but also to treat lipoatrophy. However, postmenopausal women that use pioglitazone have increased fracture risk, hat is greater when pioglitazone is used with tenofovir (that causes reduction in bone density). In these patients, it is advised a periodic surveillance aiming its prevention (44).

In the case of therapeutic failure, subcutaneous insulin should be started immediately. Therapeutic failure has been defined as a failure to accomplish the goals of treatment (glycated hemoglobin superior to 7% in patients adhering to treatment). Subcutaneous insulin is the drug of choice to control glycemic levels in HIV-positive patients with T2DM because it has no interactions with antiretroviral drugs, it is not contraindicated for nephropathic patients neither in patients with hepatopathy. It has no gastrointestinal side effects also. Insulin has significant advantages when compared to other drugs because of its anabolic effects, because it corrects not only insulin resistance but also hypoinsulinemia, because it has no cardiovascular risk and it does not reduce appetite (45,46).

The use of human insulins is discouraged because they have less predictable effect being associated with episodes of hypoglycemia. So, the use of modern insulins or insulin analogs should be preferred over human insulins. Initially patients will require high insulin doses for an optimal glycemic control; however, the insulin requirement may drop in some weeks. This can be explained by the correction of glucotoxicity present in the hyperglycemic environment and by the control of the HIV infection. It is possible that, when appetite and caloric intake increase, the insulin requirement will rise again (47). The standard dose to treat an average patient is 1.0U/kg/day. This value should be distributed according to the following proportion: 40% as basal insulin and 60% as bolus. These values are decrease after a few weeks on treatment to 0.5U/kg/day to be administered in two or three equal doses of premixed lispro/aspart. In patients severely infected, basal insulin may be not enough to control glucose levels (48).

**4.c - Additional measures**

All patients with type2DM should receive three additional drugs: aspirin, statin and angiotensin converter enzyme inhibitor (ACE inhibitor) or angiotensin receptor blocker (ARB) that also reduces the risk of HIV nephropathy (49).

Glucose intolerance should be monitored by patients at home using daily capillary blood measures and by glycated hemoglobin (45).

Patients diagnosed with T2 DM prior to HIV infection should

maintain their treatment scheme but they should be warned about a possible worsening of glycemic control after the implementation of antiretroviral therapy (50).

An interesting observation is that in patients on antiretroviral therapy the glycated hemoglobin (HbA1c) level may slightly underestimate the serum glucose levels. Nevertheless the clinical relevance of this information is still uncertain (45).

## CONCLUSION

Patients with HIV should not be treated by only one specialist but by a multidisciplinary team designed to control the disease and its complications.

Although the knowledge in this issue is growing, several topics remain uncertain like which are the specific mechanism of T2DM induction as well as the mechanisms about interactions between some drugs

T2DM in HIV patients is an area where few clinical data is sparse but we do expect new studies in this topic that will help to control both diseases that have high rates of morbidity and mortality. Also, new guidelines should be elaborated with more drug options and with knowledge about specific interactions between them.

As the survival of these patients is growing thanks to new antiretroviral therapy all efforts should be done to improve the consequences of its complications and to improve their quality of life.

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# MINI REVIEW
# CORRELATION BETWEEN THYROID GLAND AND SKIN: THE LINK BETWEEN DERMATOLOGY AND ENDOCRINOLOGY

## *CORRELAÇÃO ENTRE GLÂNDULA TIREOIDE E PELE: O ELO ENTRE DERMATOLOGIA E ENDOCRINOLOGIA*

LAYLA COMEL CORSO*
LUMA STEFANELO LORO*

Keywords: Skin, Thyroid, Hormones.
Descritores: Pele, Tireóide, Hormônios.

***Abstract***

The action of thyroid hormones and their various changes in the skin and its appendages have been increasingly studied. Different layers of the human skin express specific markers. The ability of the skin to generate transcription factors that act on the hypothalamus-pituitary-thyroid axis has been extensively investigated, and it is known that the thyroid hormones exert their effects through binding to nuclear receptors (TRa and TRb), which are known to be expressed in the skin. Knowing the correlation between skin and thyroid will enable better understanding of the different manifestations, its consequences and thus create mechanisms to prevent autoimmune diseases in the future. **Endocrinol diabetes clin exp 2016 1836 -1838.**

**Resumo**

A ação dos hormônios tireoidianos e suas diferentes alterações provocadas na pele e seus anexos estão sendo cada vez mais estudadas. As diferentes camadas da pele humana expressam marcadores específicos. A capacidade da pele de gerar fatores de transcrição que atuam no eixo hipotálamo-hipófise-tiróide tem sido extensivamente investigada; sabe-se que os hormônios da tireóide exercem os seus efeitos através da ligação a receptores nucleares (TRa e TRb), que são expressos na pele humana. Conhecer a correlação entre a pele e a glândula tireóide irá permitir uma melhor compreensão das diferentes manifestações, suas consequências e, assim, criar mecanismos para prevenir doenças auto-imunes no futuro. **Endocrinol diabetes clin exp 2016 1836 -1838.**

**INTRODUCTION**

The skin encompasses a stratified epithelium (epidermis) separated by a basement membrane from the underlying connective tissue (dermis) (1). Keratinocytes in the basal layer of the epidermis are able to proliferate and differentiate, progressing through three layers: stratum spinosum, stratum granulosum and stratum corneum. Those layers express specific markers: basal-layer keratinocytes express keratin (K) 5 and K14, spinous cells express K1 and K10; filaggrin, loricrin and transglutaminase 3 are produced in the granular layer (1,2).

The thyroid hormones exert their effects binding to nuclear receptors (TRa and TRb), which are known to be expressed in the skin. TRs interact with thyroid hormone responsive elements (TREs) (2,3).

Thyroid problems and their consequent skin reactions have been increasingly studied. It is known that the deficiency or excess of thyroid hormones act directly on the skin and its appendages through the above mentioned receptors (2,3,4).

Cutaneous manifestations of thyroid disorders occur by three different mechanisms: by direct action of the hormone in the skin, direct action of the hormone in the appendages and by autoimmune mechanisms (2).

**Table 1:** Clinical implications of the expression of thyroid hormones receptors in the skin. Adapted from Paus, R (3).

| |
|---|
| • In patients with hypothyroidism, who have elevated TSH serum levels, TSH likely can exert direct effects on the skin and appendages, because those tissues express functional TSH receptors. |
| • TSH receptors that are expressed in the skin can lead to antithyroid autoimmunity, and vice-versa. |
| • If human skin really generates key hormones of the hypothalamic-pituitary-thyroid axis in vivo, disorders in the cutaneous production of TSH can affect the thyroid function. |

In hypothyroid humans, the skin is cool and dry, the epidermis is thin and hyperkeratotic, alopecia may develop and there is diffuse myxedema showing that thyroidal status influence skin morphology and function (1).

To illustrate these actions, studies in rats with thyroidectomy have shown that there is a modification in the stratum corneum and impaired function of this skin barrier in hypothyroidism (2). A TRa mutant mice has been found to display retarded hair growth. Using a genetically modified mouse, researchers have recently observed that the effects of thyroid hormone on cell proliferation are mediated through interactions with both TRa and TRb (1).

Moreover, it has been studied that the topical form of thyroid hormone can serve to accelerate wound healing. The topical application of supra-physiologic T3 doses increased the speed of wound healing in normal mice. These studies have raised debates about the use of topic T3 in the improvement of tissue repair (2,7).

Another example is about the retinoids. Retinoids play an important role in skin homeostasis. When administered topically, they cause skin hyperplasia, abnormal epidermal differentiation and inflammation (1).

Reduced proliferation found in the skin of hypothyroid mice may be reversed with thyroxine treatment, demonstrating that thyroid hormone is required for the normal response to retinoids. Since retinoids are commonly used for treatment of skin disease, the interaction of this agent with TRs may have important therapeutic implications.

**DIRECT THYROID HORMONE ACTION ON SKIN TISSUES**

The skin changes due to alterations of the direct action of thyroid hormone are summarized in table 2. (2)

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**Table 2:** Skin alterations secondary to hyperthyroidism and hypothyroidism

| | | |
|---|---|---|
| ***Hypothyroidism*** | | |
| | **Epidermal Changes** | Thin skin |
| | **Dermal Changes** | Myxedema (hands, face, eyelids) |
| | | Hypercarotenemia |
| | | Pallor |
| | **Hair and Nail Changes** | Dry and brittle hair |
| | | Alopecia |
| | | Loss of lateral third of eyebrows |
| | | Thin and brittle nails |
| | **Sweat Gland Changes** | Dry skin |
| | | Decreased sweating |
| ***Hyperthyroidism*** | | |
| | **Epidermal Changes** | Warm and thin skin |
| | **Hair and Nail Changes** | Fine hair |
| | | Alopecia |
| | | Friable nails |
| | | Plummer's nails (onycholysis) |

## EVENTS ON OTHER TISSUES

Both hypo and hyperthyroidism are associated with various cutaneous changes. Hypothyroidism is associated with thick, dry skin, livedo reticularis of the extremities and dry hair. Hyperthyroidism is associated with thin, soft hair with possible progression to alopecia, onychodystrophy, and hyperpigmentation of the hands, feet and mouth (4).

The thyrotoxic patient may suffer generalized hyperhidrosis, usually more prominent on the palms and soles of the feet. The intense sweating is a result of the accelerated metabolism, which is thought to be related to greater adrenal activity resulting from action between catecholamines and thyroid hormones (2). Hyperpigmentation has been described in patients with Graves disease and it is usually localized in the palms and soles, gingivae, buccal mucosa, similar to that of Addison disease. This hyperpigmentation maybe due to increased release of pituitary adrenocorticotropic hormone secondary to accelerated cortisol degradation bu thr hyperthyroid state.

The pallor and coldness of the skin in hypothyroidism may be due to reduced skin perfusion which can be diagnosed by nailfold capillaroscopy. It is believed that the reduced perfusion is caused by vasoconstriction. This vasoconstriction is the body's attempt to compensate for reduced central temperature; the low central temperature appears because hypothyroidism causes low thermogenesis (2,8).

Hashimoto's thyroiditis usually has clinical manifestations similar to hypothyroidism, but it has an autoimmune etiology similar to Graves' disease. Due to this shared etiology in both diseases, similar dermatologic and ophthalmologic findings are seen such as conjunctivitis, diplopia, blurred vision and cutaneous myxedema that can occur in pretibial, scalp or pre radial distribution (4,7,8).

Abnormalities in fibroblast function, with decrease in elastin, irregularly shaped microfibrils, glycosaminoglycan and hyaluronic acid accumulation in the dermis and rarely in the subcutis are seen in autoimmune Graves disease. These skin alteration is called thyroid dermopathy (2,9).

Hyaluronic acid is the major glycosaminoglycan that accumulates in myxedema with deposition in the skin, tongue, myocardium, kidney and other tissues of the body. Transmural capillary escape of albumin resulting in extravascular accumulation and edema is seen in this situation; inadequate lymphatic drainage explains the formation of exudates in myxedema (2,10).

**Table 3:** Skin manifestations of thyroid hormone action on other tissues. Adapted from Safer, JD (2).

| Hypothyroidism | Hyperthiroidism |
|---|---|
| Cold intolerance | Heat intolerance |
| Pallor | Erythema |
| Purpura | Hyperpigmentation, Telangiectasia |
| Nerve entrapment syndromes | Hyperhydrosis |

## AUTOIMMUNE EVENTS

The importance of screening for other autoimmune diseases in patients with autoimmune thyroid disorders is worth mentioning (1,3,7.8). We can list as autoimmune skin diseases: vitiligo, alopecia areata, pernicious anemia, dermatitis herpetiformis, urticaria and SLE (2). See table 4.

**Table 4: Associated autoimmune phenomena**. Adapted from Safer, JD (2).

| |
|---|
| Dermopathy (pretibial myxedema) |
| Urticaria |
| Vitiligo |
| Pernicious anemia |
| Bullous disorders |
| Eczema |
| Connective tissue diseases |

A strong relationship between chronic urticaria and angioedema associated with thyroid autoimmunity is found. This is associated with high level of serum thyroid peroxidase antibodies (anti-TPO) of IgE type, which is greater in patients with urticaria. The treatment with thyroid hormone can decrease the title of anti-TPO, improving the patient's clinical condition (2).

## LOCATION OF THE THYROID HORMONE RECEPTORS IN THE SKIN

Regarding the importance of exact location of TSH receptors in the skin, it may be relevant to consider that receptors on intraepithelial regions can trigger different autoimmune responses when compared to intra-mesenchymal location (3). In normal human skin there is an axis equivalent to Hypotalamus–Pituitary–Thyroid (HPT) with feedback regulatory loops, similar to those that characterize the central HPT axis. It is possible that intracutaneously expressed TSH receptors could rise antithyroid autoimmunity, and that anti-TSH receptor autoantibodies could stimulate intracutaneous TSH receptors (10,11).

In the epidermis, there is expression of immunosuppressive agents such as TGFβ1, α-MSH, and IL-10 and a presence of Langerhan's cells supposedly to be immunologically more tolerant; in mesenchymal region there is presence of Langerhan's cells more immunogenic and also of multiple pro-inflammatory mechanisms (2,3,8,9,11).

## CONCLUSION

The knowledge of the relationship between skin and thyroid gland may open new ways to understand not only thyroid function, but also dysfunction and the occurrence of autoimmune diseases. This enables their recognition and may generate information that could be valuable to build strategies for prevention and treatment of thyroid and skin diseases.

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# CASE REPORTS
# ASSOCIATION BETWEEN PSORIASIS, HYPOTHYROIDISM AND TYPE 2 DIABETES – CASE REPORT

## *ASSOCIAÇÃO ENTRE PSORÍASE, HIPOTIROIDISMO E DIABETES TIPO 2*

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Key words: Psoriasis, Hypothyroidism, Type 2 diabetes
Descritores: Psoríase, Hipotiroidismo, Diabetes tipo 2

***Abstract***

Psoriasis is a chronic disorder, relatively common, whose main expression is in the integumentary system. Its pathophysiological basis leads to a complex association with other immune-mediated diseases, like thyroid disease. Also, the systemic inflammation generated by this disorder predisposes to a greater cardiovascular risk, increasing the cardiovascular morbidity by myocardial infarction, cerebrovascular accident and type 2 diabetes mellitus. **Endocrinol diabetes clin exp 2016 1839 -1841.**

**Resumo**

A psoríase é uma desordem crônica, relativamente comum, cuja principal manifestação se dá no sistema tegumentar. Sua base fisiopatológica leva a uma complexa associação com outras doenças imuno mediadas, como as tireoidopatias. Além disso, a inflamação sistêmica gerada por esta desordem predispõe a um maior risco cardiovascular, aumentando-se a morbidade por infarto do miocárdio, acidente vascular cerebral e diabetes mellitus tipo 2. **Endocrinol diabetes clin exp 2016 1839 -1841.**

**INTRODUCTION**

Psoriasis is a systemic inflammatory disease immune--mediated by T cells and its association with comorbidities has been largely described in literature. The connection between psoriasis and arthritis was already well established, the psoriatic arthritis (1,2). It is also known that patients with psoriasis have higher chances to suffer from cardiovascular diseases such as hypertension, hyperlipidemia, type 2 diabetes and autoimmune diseases (3,4,5).

This case report's goal is to show a typical case of psoriatic arthritis with its many comorbidities and therapeutic challenges.

**CASE REPORT**

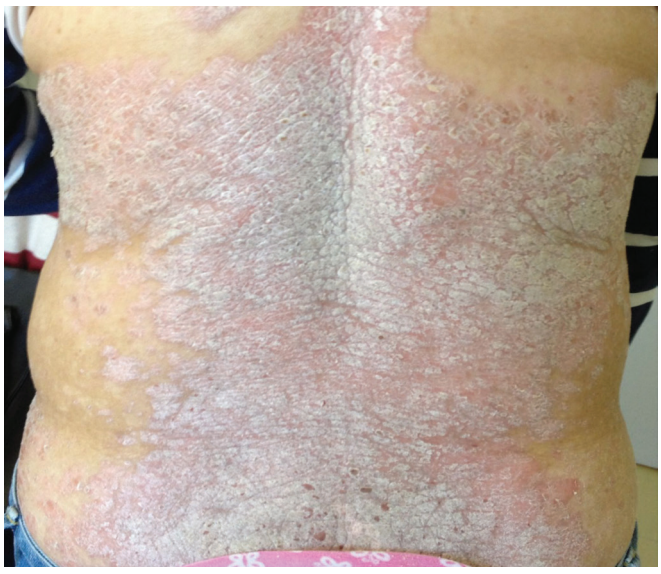
CRR, female, 62 years old, presenting systemic arterial hypertension and type 2 diabetes mellitus (DM2), started attendance in the dermatology clinic at Hospital Universitário Evangélico de Curitiba (HUEC) due to desquamative erythematous plaques on the torso, gluteal area and legs, with previous diagnostic of psoriasis, but without attendance for the last three years. She also showed signals of asymmetric oligoarthritis on her hands, with involvement of interphalangeal and metatarsophalangeal, which started a few months after the appearance of the cutaneous manifestations.

The treatment of DM2 and hypertension was being conducted with oral antidiabetics (metformin and gliclazide), insulin and three classes of antihypertensives (hydrochlorothiazide, enalapril and amlodipine). The exam showed her to be overweight (BMI 26,2Kg/m2) with an abdominal circunference of 92cm.

At first, topical treatment was chosen to treat the cutaneous injuries, but the patient returned after six months with worse cutaneous and articular conditions. After the diagnosis of psoriatic arthritis has been made, the use of methotrexate was started and the patient was sent to attendance with rheumatology in the HUEC.

During the attendance, the patient showed good response to the methotrexate treatment, with improving in the PASI score (psoriasis area and severity index). However, after seven months using the medicament, the patient suspended the treatment affirming anxiety reasons. The condition presented with worsening of the injuries, cycles of phototherapy were initiated.

In regard to the comorbidities, control exams revealed fasting glucose persistently above 200mg/dl. Due to the difficult control of diabetes, the patient was sent to joint attendance with endocrinology in the HUEC. Even so she kept fasting glucose exams above 200 to 300mg/dl and glycated hemoglobin above 12%. She was treated with insulin (basal NPH and regular insulin). In the follow up with endocrinology service was also made the diagnosis of hypothyroidism with positive antibodies (antithyroglobulin 19,4UI/ml; anti-TPO 72,8UI/ml) and initiated hormonal replacement with levothyroxine. Concomitantly, she started medical monitoring with the ophthalmology department, where it was detected the presence of mild diabetic retinopathy and, in subsequent evaluation, increased intraocular pressure secondary to diabetes.



Vulgar psoriasis with extensive involvement

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## DISCUSSION

Psoriasis is a chronic disorder, relatively common, prevalent in 2 to 4% of the adult population (2). It affects mainly the integumentary system, but studies reveal that it is largely associated to other autoimmune diseases and to cardiovascular morbidities.

The patient described in this report presents an association between psoriatic arthritis and hypothyroidism with high levels of antithyroperoxidase and antithyroglobulin antibodies, suggesting autoimmunity (5). According to Antonneli et al, there is a higher prevalence of autoimmunity in patients with psoriatic arthritis. Given this fact, it is suggested to be conducted routinely in such patients screening with thyroid function tests, antithyroperoxidase antibody search and thyroid ultrasound (6). Regardless of these literary facts, it does not seem to exist any difference in the prevalence of thyroid diseases between psoriasis patients without the arthritis component and healthy patients, according to Gul et als study (7).

Several autoimmune pathologies seem to be associated with psoriasis, such as: vitiligo, rheumatoid arthritis, pernicious anemia, systemic lupus erythematosus, Addison's disease and autoimmune thyroid disease (1). According to Jin et al., environmental factor and variations in some specific genes are involved in the pathophysiological basis of self-immunity (1). Researches show that the NALP1 gene encodes a great relevance protein to the regulation of the inate immune system, and variations in the DNA sequence of this genomic region are associated to these self-immune diseases (1,8).

In psoriatic arthritis, the self-immunity mechanism seems to involve cytotoxic T-cells, activation of Th1 and Th17, increasing of alpha TNF and many interleukines such as IL 17, 21, 22 and 23. In genetic studies, the main association found between psoriasis and psoriatic arthritis was the MHC gene's allele of class I, HLACw*0602, related to a premature beginning of the disease. These molecules' role is to present proteins from cytoplasm to lymphocytes TCD8+. Many gene's alleles from MHC molecules of class II were also associated with the susceptibility to the disease and molecules like HLA DRB1*04, HLA DRB1*07, HLA DR 17 present peptides to the TCD4+ lymphocytes. Psoriasis also associates to the allele of the TNFAIP3 e TNIP1 genes, which codify proteins involved in sensitizing the alpha TNF (9,10). Besides the association with autoimmune diseases, psoriasis is related to higher incidence of cardiovascular and metabolic diseases such as myocardial infarction, cerebrovascular accident, metabolic syndrome and DM2 (2,3).. The pathophysiological mechanism behind this is still not totally elucidated, but it is believed that the chronic inflammation present in psoriasis creates an increase in the resistance to insulin, a mechanism dependent of the Th1 cytokines, causing metabolic alterations and a greater cardiovascular morbidity (2,11).

Armstrong et al. demonstrated in his study a higher prevalence of DM2 in patients with psoriasis if compared to the control group (without the disease) and that the severity of psoriasis is directly related to an increased prevalence (12). This relation between the degree of the psoriasis' severity and the prevalence of comorbidities was evaluated by other studies which corroborate this statement and acknowledge that these patients also have a higher incidence of other pathologies besides DM2, such as chronic lung diseases, kidney diseases, rheumatoid arthritis, myocardial infarction and peptic ulcer (13,14).

The diabetes mellitus treatment in cases of association with psoriasis involves challenges. It predisposes to a greater use of pharmacological therapy and to a more premature insulinization (15). In the reported case, the patient presented a DM2 of difficult clinical control, even with progressively higher doses of insulinization (2,15). There are many possible explanations to this fact. One of the most accepted theories is that the systemic inflammation, which follows the psoriasis, causes a decrease of the signaling to the insulin receptors, increasing the insulin resistance (15). Another possible reason lies in the use of corticosteroids for the psoriasis control therapy, resulting in a worsening of the glycemic control by presenting a counter insulinic action and decrease of translocation of the glucose transporter(GLUT4) insulin dependent in the muscle(11).

The psychological issue existent in this context cannot be underestimated. There is an inclination of the individual to feel burdened when he faces multiple pathologies, like the association between psoriasis and diabetes. It predisposes the patient to neglect the diabetes treatment. It is known there is an incidence three times higher of depressive disorder in the group of individuals with DM2 and psoriasis, if compared to those who are only diabetic (15).

These findings show that the psoriasis is deeply connected to a higher prevalence of type 2 diabetes mellitus, with consequent increase of cardiovascular risk. Patients with this pathology must be oriented about the changes in their lifestyle, avoiding a sedentary life and adopting healthy eating habits to decrease the chances of complications.

## CONCLUSION

In view of these considerations, it is to be concluded that psoriasis is a complex pathology which can be associated to many other comorbidities. The physician's job is to pay attention to the possible coexistence of other autoimmune pathologies, signals of insulin resistance, cardiovascular alterations and psychological disorders, so premature diagnosis of psoriasis complications can be done. Also, it is important to refer the patient to another specialties when necessary.

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# ORIGINAL ARTICLE
# EVALUATION OF BIOCHEMICAL AND HEMATOLOGICAL PROFILE OF PACIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE UNDER CORTICOSTEROID TREATMENT

## *AVALIAÇÃO DO PERFIL BIOQUÍMICO E HEMATOLÓGICO DE PACIENTES PORTADORES DE DPOC EM TRATAMENTO COM CORTICOSTERÓIDES*

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Keywords: Chronic obstructive pulmonary disease (COPD), Glycaemia, Corticosteroids, Adverse effects.
Descritores: Doença pulmonar obstrutiva crônica (DPOC), Glicemia, Corticosteróides, Efeitos adversos

***Abstract***

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease, which is caused by a partly reversible limitation of airflow. It is usually progressive and it is mainly related to smoking. Pharmacological treatment involves the use of corticosteroids to prevent and control symptoms. Corticosteroids are also used to reduce the frequency and severity of exacerbations to improve people's quality of life. Both inhaled and oral corticosteroids can cause systemic changes. Under these circumstances, this study aimed to appraise the biochemical-hematological profile of COPD patients under corticosteroids treatment. Records and database of 89 patients with COPD were analyzed. They participated in a Pulmonary Rehabilitation program between February 2009 and December 2011. From the results, it was observed a higher prevalence among former smoker, men, mean age of 70 and who mainly used inhaled corticosteroids. There was significant difference in cholesterol between inhaled corticosteroids users and inhaled and oral corticosteroids users. There was also difference in HDL between inhaled corticosteroids and oral corticosteroids users. No difference on glucose concentration was found among patients. However, all diabetic patients were in the inhaled corticosteroids users group. In conclusion, there are significant changes in biochemical parameters; therefore it is essential that professionals frequently monitor these patients. **Endocrinol diabetes clin exp 2016 1842 -1849.**

**Resumo**

A doença pulmonar obstrutiva crônica (DPOC) é uma doença prevenível e tratável causada por uma limitação parcialmente reversível do fluxo aéreo, geralmente progressiva, relacionada principalmente ao tabagismo. O tratamento farmacológico envolve o uso de corticosteroides, os quais são utilizados para prevenir e controlar os sintomas, reduzir a frequência e a gravidade das exacerbações melhorando a qualidade de vida destes indivíduos. Visto que os corticosteroides inalatórios podem causar alterações sistêmicas tanto quanto os orais, o presente trabalho teve por objetivo avaliar o perfil bioquímico e hematológico de pacientes portadores de DPOC que utilizam corticosteroides em seu tratamento. Foram analisados prontuários e banco de dados de 89 pacientes portadores de DPOC que participaram de um programa de Reabilitação Pulmonar no período de fevereiro de 2009 a dezembro de 2011. Diante dos resultados, observou-se maior prevalência de indivíduos ex-tabagistas, sexo masculino, com idade média de 70 anos, e maior utilização de corticosteroides inalatórios. Houve diferença significativa nos níveis de colesterol total entre os grupos que utilizavam corticosteroides inalatórios e que utilizam inalatórios e orais, com também de HDL entre os que utilizam pela via inalatória e pela via oral. Já a concentração de glicose não apresentou diferença estatisticamente significativa entre os grupos, porém todos os pacientes diabéticos se encontravam no grupo que utilizava corticosteroides pela via inalatória. Conclui-se que houve alterações significativas em parâmetros bioquímicos, sendo imprescindível que estes pacientes realizem seu acompanhamento frequente. **Endocrinol diabetes clin exp 2016 1842 -1849.**

**INTRODUCTION**

Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable disease. It is characterized by a usually progressive obstruction of airway flow (1,2). This obstruction is not totally reversible and it is associated with an abnormal lung inflammatory response to inhalation of particles or toxic gases, mainly caused by smoking as well as occupational dust, chemical irritants, environment pollution and genetic predisposition. Exacerbations and comorbidities contribute individually to the disease severity in each individual, significantly impacting the prognosis (3, 4, 5, 6).

Clinical diagnosis is based on dyspnea presence, initially to great efforts and that will progressively become more intense, chronic cough and presence of secretion, along with history of exposure to risk factors. Besides symptoms, spirometry is used to diagnose COPD that is defined by pulmonary obstruction degree, which is evaluated by the relation between forced expiratory volume in the first second (FEV1) and the forced vital capacity (FVC), <0.70 after bronchodilator, and being divided in four stages, relating the first stage to mild, and the fourth to very severe (6). It should also be noted the fact that COPD impact on a certain individual not only depends on degree of airflow limitation, but also on symptoms severity, systemic effects and any other comorbidity through which the individual may be affected (1,7)

It is known that compounds originated from toxic gases inha-

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lation reach the systemic circulation and may involve several organs other than lungs, consequently triggering other comorbidities, for instance, cardiovascular diseases, lung cancer, muscle disorders, metabolic disorders (carbohydrates, lipids, proteins, insulin, among others) and neurohormonal activation. Moreover, the hypothesis that the possible link among COPD, systemic manifestation and these comorbidities may be due to inadequate and exacerbated inflammatory response is not discarded (8,9).

In 2011, seven million Brazilians over 40 years old were already affected by COPD and it is estimated that this disease will be the third leading cause of death worldwide by 2020 (10,11). These individuals present reduction of respiratory muscle strength, ventilator abnormalities and limitations to physical exercise. Thus, pulmonary rehabilitation programs involving multidisciplinary teams aim to minimize symptoms, reduce exacerbations, improve physical condition, and also improve social inclusion of these patients (12).

For a treatment plan to be effective, four key components must be included: disease assessment and monitoring, stabled COPD treatment and also the reduction of risk factors. Therefore, the main objectives of COPD therapeutic approach, both pharmacological and non-pharmacological, are reducing disease symptoms, frequency and exacerbations severity, improving patient's quality of life and tolerance to exercises (6,13)

In this context, and regarding the studies about collateral effects of corticosteroids, the present study aimed to evaluate the biochemical and hematology profile of COPD patients under corticosteroids treatment.

## MATERIAL AND METHODS

### Study Design

General strategy of study design was of a quantitative, retrospective longitudinal study performed by database analysis of 89 COPD patients between the years 2009 and 2011. The adopted inclusion criteria were: previous participation in the extension program of Pulmonary Rehabilitation in partnership with the Pharmaceutical Care in the Community project, which takes place at Laboratory of Physical Activities, Exercise and Sports Studies (LEAFES) from Feevale University, during the analyzed period and being a patient with COPD who had performed the pharmaceutical interviews, biochemical and hematological tests.

### Data collection

Data were collected through medical records and database of participants from referred extension projects. Several aspects were taken into consideration, among them are: sex, age, DPOC severity (staging), previous diseases, used medication and how are they used it (correctly or incorrectly). These data were obtained in the extension programs through an interview with the participants, in which they also mimic the way they use the inhalers, and they clarify whether they were or are a smoker and for how long. Also, if they are an alcoholic, use corticosteroids and by which administration route. Participants had biochemical and hematological tests done and their reports were indexed to medical records and registered in the database. Regarding the biochemical parameters, glucose levels (mg/dL), lipid profile equivalent to total cholesterol (mg/dL), LDL (mg/dL), HDL (mg/dL) and triglycerides (mg/dL) were analyzed. Moreover, the hematological parameters corresponding to erythrocytes (millions/mm3), hemoglobin (g/dL), hematocrit (%), leucocytes (mm3) and platelets (mil/mm3) values were investigated. These data were collected at the moment the patient started participating in the project through a data collecting record and they were latter inserted in a Microsolf Excel® spreadsheet.

### Data Analysis

At first, data were compiled in a Microsolf Excel® spreadsheet and, later statistically analyzed by SPSS (Statistical Package Social Sciences) 22.0.

Data were expressed in percentage, mean and standard deviation for samples with normal distribution, and in median and variation for those without normal distribution.

The comparison of glycemic, lipids and hematological parameters among the group of patients that do not use corticosteroids (G1), that use inhaled corticosteroids (G2), oral (G3) or yet, oral and inhaled (G4) was performed using ANOVA for independent samples. The significance level was 5 %.

### Ethical Aspects

The Research Ethics Committee of the Feevale University under the report number 75505 approved this study. Participants' anonymity and the confidentiality of information provided were respected, meeting the standards and guidelines in human research, according to the resolution number 196/96 of the National Health Council. All material from this study will be filed for 5 years and it will be later destroyed.

## RESULTS

By analyzing the records and the database of the 89 patients included in this study, it was observed that 56 (63%) were male and 33 patients (37%) were female, from which 81 (91%) were former smokers while only four (4%) had never smoked and 4 (4%) continued smoking.

**Table 1** shows the general characteristics of the analyzed patients. According to the classification regarding the use of corticosteroids, it was found that the vast majority made use of inhaled corticosteroids (G2), followed by those who used both inhaled as well as oral (G4), in third were those who used oral (G3) and only 7 did not use in their treatment (G1). As for the staging of the disease, the most severely ill patients were in the G2 group G4?, in which 28 had COPD in severe stage and 17 were in very severe stage. Also, six patients had severe COPD and 4 were in very severe stage in the G4 group. Yet, in the G3 group, patients showed moderate to severe COPD, and COPD was mild to moderate in the G1 group.

The highest body mass index (BMI) was observed in the patients from the group that were not under corticosteroids treatment, the G1 (23.77 ± 3.55 Kg/m2). The lowest BMI was in the group that used oral corticosteroids, the G3 (20.98 ± 2.54 Kg/m2), but there were no statistically significant differences when compared to the others. Age did not vary much among groups and the overall mean was around 70 years.

**Table 1** – General characteristics of the analyzed patients classified according to the use of corticosteroids

| Variables | G1 | G2 | G3 | G4 | |
|---|---|---|---|---|---|
| **Classification regarding the use of corticosteroids** | Nonusers | Inhalation | Oral | Inhalation and Oral | |
| **Number of patients** | 7 | 65 | 5 | 12 | |
| **Stage of COPD** | | | | | |
| **- Mild** | | | | | |
| **- Moderate** | 2 | 3 | 0 | 1 | |
| **- Severe** | 5 | 17 | 2 | 1 | |
| **- Very Severe** | 0 | 28 | 1 | 6 | |
| | 0 | 17 | 2 | 4 | |
| | | | | | p |
| **Age (years)*** | 74 ± 8 | 70 ± 8 | 72 ± 8 | 65 ± 9 | 0.884 |
| **BMI (Kg/m$^2$)*** | 23.77 ± 3.55 | 22.25 ± 3.75 | 20.98 ± 2.54 | 22.00 ± 2.69 | 0.582 |

*Regarding age and BMI: Mean ± Standard Deviation; p: level of statistical significance (significant = $p < 0.05$).

During the analysis, it was observed that COPD was never an isolated disease, since these patients also presented other comorbidities, which range from a simple cold to chronic diseases such as hypertension and diabetes. **Table 2** identifies the comorbidities associated with COPD most seen in patients in their first interview. The most prevalent were hypertension (61%), followed by hypercholesterolemia (19%), heart diseases (18%) and diabetes (11%), among others. It is important to highlight that all diabetic patients were in the G2 group (users of inhaled corticosteroids).

**Table 2** – Comorbidities associated with COPD

| Disease | Number of patients | Percentage (%) |
|---|---|---|
| Hypertension | 54 | 61 |
| Hypercholesterolemia | 17 | 19 |
| Heart diseases | 16 | 18 |
| Diabetes | 10 | 11 |
| Osteoporosis | 10 | 11 |
| Insomnia | 8 | 9 |
| Depression | 7 | 8 |
| Gastritis | 5 | 6 |
| Prostatic disease | 4 | 4 |
| Thrombosis | 4 | 4 |
| Others | 22 | 25 |

As for pharmacotherapy, it was identified the use of approximately 115 different drugs among the 89 participants of the study, some of these being both used by inhalation route, such as bronchodilators, corticosteroids combined with bronchodilators, and by oral route, such as the proton pump inhibitors, antidepressants, nonsteroidal analgesics, diuretics, and others. Also, regarding the use mode of inhaled corticosteroids, it was found that most patients used them incorrectly, which represents 60% among patients of G2 and 67% of the G4 group patients.

The most used drugs among the 89 patients are listed in **Table 3**, in which it is observed that the most used (47%) is formoterol + budesonide 12/400 mcg, followed by omeprazole 20 mg (35%), tiotropium 18 mcg (31%) and acetylsalicylic acid 100 mg (19%).

**Table 3** – Drugs most used by studied patients

| Drug | Administration route* | Number of patients | Percentage (%) |
|---|---|---|---|
| Formoterol + Budesonide12/400 mcg | IR | 42 | 47 |
| Omeprazole 20 mg | OR | 31 | 35 |
| Tiotropium18 mcg | IR | 28 | 31 |
| Acetylsalicylic acid 100 mg | OR | 17 | 19 |
| Furosemide 40 mg | OR | 15 | 17 |
| Simvastatin 20 mg | OR | 14 | 16 |
| Prednisone 20 mg | OR | 14 | 16 |
| Captopril 25 mg | OR | 14 | 16 |
| Salbutamol spray | IR | 13 | 15 |
| Formoterol + Budesonide 160/4.5 µg/dose | IR | 12 | 14 |
| Salmeterol + Fluticasona 50/250 mcg | IR | 11 | 13 |
| Calcium carbonate | OR | 10 | 11 |
| Ipratropium + Fenoterol | IR | 10 | 11 |
| Formoterol 12 mcg | IR | 10 | 11 |
| Bamifylline 600 mg | OR | 9 | 10 |
| Salmeterol + Fluticasone 25/250 mcg | IR | 7 | 8 |
| Insulin | SC | 7 | 8 |
| Sertraline 50 mg | OR | 6 | 7 |
| Aminophylline 200 µg | OR | 6 | 7 |

*IR: Inhalation Route; OR: Oral Route; SC: Subcutaneous.

Biochemical and hematological parameters are detailed in table 4. It is possible to observe that glucose levels differed more between groups G2 (105.08 ± 24.82 mg/dL) and G3 (87,8 ± 7,60 mg/dL), however there was no statistically significant difference when compared among themselves and to other groups. On the other hand, total cholesterol levels presented a significant difference between groups G2 and G4 (p = 0.007), and HDL levels between G2 and G3 (p = 0.03). Moreover, similar to glucose, triglyceride levels, erythrocytes, hemoglobin, hematocrit, leukocytes and platelets also showed no statistically significance when compared among groups. It is noteworthy that the statistical tests were applied excluding the diabetics of group G2, however, there was no difference in results obtained for these parameters, and therefore these patients were included. **Table 4**

**Table 4** – Average results obtained for biochemical-hematological parameters of studied groups

| Parameters | G1 | G2 | G3 | G4 | p |
|---|---|---|---|---|---|
| **Glucose (mg/dL)** | 99 ± 14 | 105 ± 25 | 88 ± 8 | 97 ± 27 | 0.326 |
| **Total cholesterol (mg/dL)** | 215 ± 39 | 185 ± 38* | 209 ± 35 | 221 ± 34* | 0,007 |
| **LDL (mg/dL)** | 132 ± 39 | 114 ± 38 | 99 ± 30 | 135 ± 43 | 0.158 |
| **HDL (mg/dL)** | 60 ± 13 | 52 ± 15* | 74 ± 17* | 62 ± 14 | 0.003 |
| **Triglycerides (mg/dL)** | 111 (51 – 177) | 113(40 – 284) | 185(124 – 300) | 129(65 – 218) | 0.060 |
| **Erythrocytes (millions/mm$^3$)** | 4.8 ± 0.3 | 4.8 ± 0.5 | 5 ± 0.7 | 4.8 ± 0.6 | 0.712 |
| **Hemoglobin (g/dL)** | 14.3 ±0.6 | 14.1 ± 1.7 | 15.2 ± 1.7 | 14.2 ± 1.7 | 0.776 |
| **Hematocrit (%)** | 42.6 ± 2.1 | 42.6 ± 4.9 | 45.4 ± 6.0 | 42.6 ± 4.9 | 0.663 |
| **Leukocytes (mil/mm$^3$)** | 6.25±1.29 | 7.14±2.76 | 7.52±1.40 | 6.61 ±1.66 | 0.726 |
| **Platelets (mil/mm$^3$)** | 217.7± 68.7 | 244.1 ± 72.7 | 237.4 ± 52.4 | 252.7 ± 73 | 0.769 |

Mean ± Standard Deviation; median (variation). *Statistically significant relationship (p<0.05).

## DISCUSSION

As it is known, COPD is the major cause of morbidity and mortality worldwide. Consequently, much has been studied about the disease in order to minimize this impact. Pharmacological and non-pharmacological treatment, such as the pulmonary rehabilitation programs, are a key part in the treatment, assigning benefits independently of gender, age and severity of disease (6, 4).

By analyzing the data obtained, it was observed that most patients were male, former smokers and aged in average 70 years old. These results corroborate with previous studies, in which COPD is associated with smoking, age over 60 years and male prevalence (15,16,17). This is due to the fact that cellular modifications caused by aging and by the inhalation of particulates and toxic gases, such as in smoking, are interrelated. Therefore, in the same way that smoking accelerates the aging, aging can enhance the susceptibility to lesion or amplify the mechanisms involved in lung destruction by cigarette smoking, considering that men still represent the majority in this group (18).

On the other hand, as regards to age and gender, no data in the literature state that both by themselves entailed increased risk for COPD, except for the fact that these people are more exposed to risk factors, such as male for smoking more and the elderly for having a higher susceptibility to lesion than younger people (19). Still, it is quite important to consider that smoking has been increasing among women and, in a near future, it will likely be possible to compare women to men regarding the incidence rate for this disease (20).

In this study, it was found that the vast majority of patients made use of corticosteroids, especially by inhalation, in agreement with the literature, in which several authors state that corticosteroids are the drugs of choice for the treatment of stable COPD (1, 6, 21, 22). These drugs, in turn, promote the induction or suppression of various genes involved in cytokines production, adhesion molecules and receptors relevant in the inflammation process, thus promoting their anti-inflammatory effect (21). Nonetheless, to start the disease treatment the recommendation are given according to its severity, therefore, COPD stage is important to establish the prognosis and prioritizing the treatment (6). According to the data collected, it can be observed that patients in the G1 group had mild to moderate COPD, while G2, G3 and G4 groups in the vast majority had severe and very severe COPD. These results were already ex-

pected, since oral and inhaled corticosteroids are included in the treatment from the severe stage of the disease. However, in the milder stages, which ranges from mild to moderate, treatment is done only with the use of bronchodilators of short and long duration and anticholinergics, alone or associated, depending on each individual needs (6).

For this classification of COPD severity (stage), the base used is still the relation between forced expiratory volume in the first second (FEV1) after bronchodilator use, and forced vital capacity (FVC), being the improvement of its rate of decline the most used method in clinical studies to evaluate the prevention of disease progression and clinical response to treatment. But generally this relationship does not provide the information needed to evaluate the patients' performance during the activities done in their day-to-day, thus, presenting the necessity of creating new disease severity, progression and prognosis markers, which also allow evaluating the influences of the functional repercussions on the symptoms and patients' limitations. These markers have already been instituted and used, for instance, to smoking cessation (23).

Monitoring nutritional state is an important factor in COPD patients, because in most cases these patients present a great reduction in weight, and this, in turn, reduces the diaphragm mass and contributes to strength and endurance decrease of the respiratory muscles, which consequently causes more dyspnea, increased lung hyperinflation, and a greater limitation to exercise in these patients than in those with an ideal weight (24)

In this study, there were no significant differences in the body mass index (BMI) among groups as also, no patient was observed with malnutrition or overweight. Nevertheless, in accordance with the values obtained in the analysis for the group G3 (use of oral corticosteroids), it could be considered the group with the highest risk of developing the problems mentioned above, presenting BMI of 20.98 ± 2.54 Kg/m2. It is noteworthy that the use of corticosteroids, as in the G3 group patients, has a significant negative impact on their nutritional status, due to medium to long-term effects of decreased appetite, bone demineralization and muscle mass weakness. However, low weight may be due to the severity of the disease, since the group of patients that are not under corticosteroid treatment (G3) and presents mild to moderate COPD, presented the highest BMI (23.77 ± 3.55) (24).

Although BMI does not allow determining the body composition and does not express the distribution of fat, it is a useful indicator in defining the risk of many diseases. Nutritional problems are associated with increased morbidity and mortality, and with a negative impact on quality of life in elderly (25) and in patients with COPD; thus, it is crucial that they maintain an adequate diet.

Once COPD diagnosis is confirmed, patients should be carefully evaluated to identify which factors contribute to the disease. Potential systemic manifestations should be identified because, these may strongly influence on decisions about treatment (26). Comorbidities should be evaluated and the most common ones associated with COPD are: skeletal muscle abnormalities, hypertension, diabetes, heart diseases, depression, pulmonary infections and osteoporosis (27, 28, 29). These diseases were found in the results of this study, being hypertension the most prevalent comorbidity. Interestingly, the use of oral corticosteroids with residual mineralocorticoid activity (such as prednisone and prednisolone) may be a risk factor for hypertension, as well as others. It is believed that some drugs from this class also have effects on blood pressure via a mechanism that is not related to salt and water retention theory by an effect on the mineralocorticoid receptor (30).

Similarly, corticosteroids may also cause alterations in plasma lipoprotein concentrations increasing both cholesterol and triglyceride levels (31). It can also trigger diabetes due to stimulation of glucose production by the liver from amino acids and glycerol, glucose storage in the form of glycogen in the liver, and reduction of glucose use in the periphery, resulting in increased glycaemia (32,33).

In addition, cardiovascular problems are referred as the main comorbidities associated with COPD, being the main predictors of mortality rate increase due to the strong inter-relationship between the two diseases, which also suggests more aggressive treatments (34). However, the incidence of osteoporosis in COPD patients, as well as its progression and weakness, may be related to malnutrition and reduced muscle mass associated with the metabolic alterations of COPD itself and the sedentary lifestyle as a consequence of aerobic restrictions of the disease (34). Additionally, repetitive and prolonged use of corticosteroids also contributes to this scenario, since glucocorticoids can activate the transcription of anti-inflammatory proteins such as IL-10, annexin and inhibitory factor of NF-κβ, besides increasing the expression of dickkopf-1 (an antagonist of the Wnt signaling - which mechanism is crucial for the regulation of osteogenesis and terminal differentiation of osteoblasts) (36) in osteoblasts and activating glycogen synthase kinase-3β, which is involved in apoptosis of these cells (37).

The most used drug was the combination of formoterol and budesonide 12/400 mcg by 42 patients (47%). This association of long-acting β2–agonist with corticosteroids is very common and aims to improve lung function, clinical management, and bring greater benefits in patients with severe COPD compared to the use of one of the drugs alone (38, 39).

Tiotropium, used by 28 patients (31%) and appearing in third place, is a long-acting anticholinergic that is very effective by reducing the frequency of exacerbations and by also improving the resistance to exercise (6).

Regarding the use of corticosteroids by inhalation, the percentage of patients who used them incorrectly was analyzed. And 60% among patients of G2 group (inhalation) and 67% patients of G4 patients (inhalation combined with oral) fit this aspect. According to literature, soon after the inhalation with the aerosol dispenser, about 10 to 20% of the released dose is deposited in the lungs, thus the greatest part impacts in the oropharynx and it is swallowed (40). Therefore, the amount of drug delivered to the lungs depends not only on the type of inhaler used, with different particle sizes, but also in the inhalation technique and the use or not of spacers, wherein the incorrect use of inhalers can result in an ineffective and inadequate therapeutic of COPD. Moreover, because the inhaled doses are much lower than the oral doses, it is of great importance to alert the patient as to the correct use of these techniques (41, 42).

During many years inhaled corticosteroid were considered free of serious adverse effects, however, they produce systemic effects as much as those used by the oral route, increasing the risk of developing hyperglycemia, particularly when administered in high doses. Still, the long-term use of oral corticosteroids is associated with the development of more severe adversities such as Cushingoid appearance, muscle weakness, osteoporosis as well as hyperglycemia; hence they should be less used (6, 33, 43).

Regarding the glycemia of the analyzed patients, there was no statistical difference among groups. However, it was not only observed that all diabetic patients were in the G2 group, in which were the patients taking corticosteroids by inhalation, but also that this group presented values above of referred as normality of standard, thus, they presented values of 105 ± 25 mg/dL. When compared to the reference value of 99 mg/dL (44), this indicates that most of patients from this group were dysglycemic. Results remained unaltered even when diabetics were excluded from this group for statistic analyzes. Patients from group G3 use oral corticosteroids and they presented the lowest glycemia mean of the four analyzed groups (88 ± 8 mg/dL). This may seem a controversial result, since the side effects occur more with oral administration of corticosteroids due to

high systemic exposure (45).

Contrary to that, patients who were not using corticosteroids (G1) presented glycemia values above the expected (99 ± 14 mg/dL). This result may be related to weight since the patients from this group also had the highest BMI rate (23.77 ± 3.55 Kg/m2). In relation to total cholesterol levels, a statistically significant difference between the group that used the inhaled corticosteroids (G2) and the one that used the inhaled and oral corticosteroids (G4) was found. The action of corticosteroids on the metabolism of lipids is less understood and more complex. In vitro data indicate that GC can rapidly interfere with many cellular processes such as second messenger cascades, cellular levels of calcium and phosphorylation events (46). In addition, glucocorticoids increase the transcription of SRC-1 (steroid receptor coactivator-1), that is a coactivator for many members of the steroid-hormone receptor superfamily of ligand-inducible transcription factors, increasing transcription of specific genes (47). Therefore, the use of corticosteroids may result in the development of a secondary dyslipidemia, causing alterations in plasma concentrations of lipoproteins. The increase of triglyceride levels is due to the increase of hepatic gluconeogenesis and consequently the biosynthesis of glycerol, fatty acids and TGs, through a genomic mechanism of action of corticosteroids (31,32). On the other hand, the increase of cholesterol occurs due to the metabolic deregulation like VLDL synthesis increased, fatty acids production and hepatic lipase activity (31,32,33). However, regarding the triglycerides, there was no statistical significance between the groups in this study, although G3 group presented values (185 ± 73 mg/dL) above the reference levels (less than 150 mg/dL). Similarly, LDL, which predicts cardiovascular damage as lower levels to 130 mg/dL for non-diabetic patients and less than 100 mg/dL in patients with diabetes, showed no difference among groups.

HDL showed statistically difference between G2 and G3. The G3 group had levels above the reference levels, which for men is 55 mg/dL and for women is 65 mg/dL (22). In contrast, the G2 group showed a lower mean, which opposes to the literature that predicts that corticosteroids have the ability to increase serum levels of cholesterol, LDL, VLDL and triglycerides levels (48).

Hematological changes are also among the systemic effects of COPD, due to pulmonary inflammation and from corticosteroids usage. There may be a slight effect on erythropoiesis and hemoglobin concentration, as well as an increase in the number of intravascular polymorphonuclear leukocytes, neutrophils, platelets and red blood cells and reduction in the number of circulating lymphocytes, monocytes, basophils and eosinophils. Corticosteroids usage also reduces migration of inflammatory cells to sites of injury and consequently increasing infection rates, especially after chronic administration (30).

Among the analyzed groups, no significant differences in erythrocytes, hemoglobin and hematocrit values were observed, as well as the results showed no differences between the mean values when compared to reference values, which is equivalent to 3.5 to 5.5 million/mm3 for erythrocytes, 12.0 to 15.0 g/dl for hemoglobin and 36 to 48% for hematocrit (49).

Presence of chronic inflammation in COPD patients allowed corticosteroids to be used with the aim of reducing the decline in lung function, and despite numerous side effects they are the best therapy available. The use of inhaled long-acting beta--agonist associated with corticosteroids can reduce mortality and exacerbations rates, improving the COPD patients' quality of life, and the use of oral corticosteroids during exacerbations helps reduce symptoms and improve FEV1 of these individuals in a shorter period (6, 50).

Some factors may be considered as a limitation of this study, as a low number of patients in some groups (G1 and G3 mainly) and the irregular distribution of patients among the groups, which could have influenced and reduced the statistical power of the tests. In addition, lack of some patients' data, withdrawal from the project or no records in medical charts and in the database consequently reduced the sample, since these patients had to be excluded from the study.

## CONCLUSION

It can be concluded that COPD affects more former smokers, elderly and male individuals. Also, it should be treated as a "Chronic Systemic Inflammatory Syndrome" due to the incidence of associated comorbidities, which are responsible for concomitantly using several drugs and also by the high mortality rates.

Through this study it was also possible to emphasize the previously performed studies, which demonstrate that the use of corticosteroids can affect biochemical parameters, especially when they are chronically used, such as total cholesterol and HDL levels. As for glucose, it can not be affirmed that there was an increase due to their use because no statistically significant difference were observed among groups, although some groups presented higher values when considering their mean and standard deviation, and all diabetics were in this group. Thus, it is possible to ensure that it is imperative that these patients undergo frequent monitoring of these values.

On the other hand, it was also possible to understand that it is extremely important to educate the patient regarding the correct use of their medications, since many use them wrongly, their doses and frequencies, and also, warn them about the side effects, helping to prevent more serious problems that may arise.

Regarding the use of corticosteroids, despite the adverse effects that may be associated with them, as the development of other comorbidities and alteration of biochemical parameters, they still consist the best therapy for the treatment of pulmonary inflammation, thus reducing the incidence of exacerbations, improving FEV1 and the individuals' quality of life.

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# ORIGINAL ARTICLE
# TOPICS IN MEDICAL CLINIC
# CARPAL TUNNEL SYNDROME AND FIBROMYALGIA- A STUDY BY ULTRASONOGRAPHY.

## *SÍNDROME DO TÚNEL DO CARPO EM PACIENTES COM FIBROMIALGIA – UM ESTUDO ULTRASSONOGRÁFICO*

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Key words: Fibromyalgia, Carpal tunnel syndrome, Parestesias
Descritores: Fibromialgia, Síndrome do túnel do carpo, Parestesias

***Abstract***

**Background:** Fibromyalgia (FM) and carpal tunnel syndrome (CTS) can both cause pain, stiffness and paresthesia in the hands. **Objective:** To study the prevalence of CTS in FM patients by ultrasonography and the value of clinical findings such as paresthesias complaints, Tinel's and Phalen's signs in this diagnosis. **Methods:** Forty one FM patients and 42 controls paired for age, gender and body mass index had the median nerve area (MNA) measured by US and were submitted to a questionnaire on paresthesia and to Tinel's and Phalen's test. A MNA with more than 11.2 mm2 was considered diagnostic of CTS. **Results:** The prevalence of CTS was of 8/41 (19.5%) in the FM group and of 13/42 (30.9%) in controls (p= 0.20). FM patients with and without CTS had the same prevalence of paresthesias (p=1.0), positive Tinel test (p=0.30) and Phalen test (p=0.70). **Conclusion:** FM patients do not have more STC than controls and that the usual clinical evaluation for CTS should be interpreted with care. **Endocrinol diabetes clin exp 2016 1850 -1853.**

**Resumo**

**Justificativa:** Fibromialgia (FM) e síndrome do túnel do carpo (STC) podem causar, ambas, dor, rigidez e parestesias nas mãos. **Objetivo:** Estudar a prevalência de STC em pacientes com FM por ultrassonografia e o valor de achados clínicos como queixas de parestesias e positividade dos sinais de Tinel e Phalen para o diagnóstico. **Métodos:** Quarenta e um pacientes com FM e 42 controles pareados para idade, gênero e índice de massa corporal tiveram estudo da área do nervo mediano (ANM) feita por ultrassonografia. Os dois grupos foram submetidos a questionário para verificação de parestesias e aos sinais de Tinel e de Phalen. A área do nervo mediano acima de 11.2 mm2 foi considerada diagnóstica de STC. **Resultados:** A prevalência de STC foi de 8/41 (19.5%) nos pacientes com FM e de 13/42 (30.9%) nos controles (p=0.20). Pacientes com FM com e sem STC tiveram a mesma prevalência de parestesias (p=0.10); teste de Tinel positivo (p=0.30) e teste de Phalen positivo (p=0.70). **Conclusão:** Pacientes com FM não têm mais STC que controles e, nesta população, a abordagem clínica para STC deve ser interpretada com cuidado. **Endocrinol diabetes clin exp 2016 1850 -1853.**

**INTRODUCTION**

Fibromyalgia (FM) is a chronic non inflammatory rheumatic syndrome characterized by diffuse musculoskeletal pain, muscle stiffness, fatigue and sleep disturbance (1). It is associated with a central amplification of pain perception characterized by allodynia and hyperalgesia (1). FM is a poorly understood disorder. Recent research suggests that the chronic widespread pain, the hallmark symptom of FM, is neurogenic in origin (2).

Paresthesias have been reported in 26% to 84% of FM patients and may complicate the diagnosis of associated entrapment neuropathies (1,3,4,5) . Indeed some authors believe that carpal tunnel syndrome (CTS), the most frequent of these neuropathies, is more commonly seen in FM patients than in controls (5). The pain amplification seen in FM patients may interfere with the interpretation of CTS symptoms.

At present we studied the prevalence of CTS in FM patients through ultrasonography (US) of the wrists and the association of its presence with symptoms and physical examination maneuvers commonly used to diagnose it.

**MATERIAL AND METHODS**

After approval of local Committee of Ethics in Research and having the participants signed consent we studied 41 (82 extremities) FM patients and 42 ( 84 extremities) controls for the presence of CTS . All patients were diagnosed with FM according to 2010 ACR (American College of Rheumatology) Criteria for this disease (6); the controls were obtained from hospital staff. Individuals with less than 18 years old, with diabetes mellitus, uncontrolled hypothyroidism, pregnant women, with any neurological disorder, alcoholism, those with inflammatory rheumatic disease or recent trauma to the extremities were excluded. All included individuals were right handed and none performed repetitive wrist activities. Patients and controls were paired for age, gender and body mass index.

All participants filled a questionnaire for pain and numbness in the median nerve area (8). Physical examination included Phalen and Tinel's test. Tinel's test (7) was performed by tapping the median nerve at the wrist, and this was repeated four to six times. The presence or absence of radiating pain or paraesthesia in the median nerve distribution was recorded. Phalen's test (7) was executed by asking each subject to hold hand with the wrist in complete palmar flexion with elbow extended and forearm pronated. The Phalen's test was considered positive if symptoms were reproduced in 1 minute.

Boston Carpal Tunnel Questionnaire (BCTQ) was used to measure hand function and CTS symptoms severity (8) .

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BCTQ measures two different domains. The first one is severity of symptoms and has 11 questions graded with a Likert scale, which ranges from 1 to 5 points per item. The second refers to patient's functional status and contains 8 items graduated in 1 to 5 points per item according to ability to perform a given task using the hands. BCQT higher scores are associated to higher symptom's severity and higher functional impairment.

Generalized pain was measured through a analogic visual scale (AVS) that ranges from 0-10 and where 0 means no pain and 10, the worst possible pain.

Median nerve area (MNA) was measured by US using a Toshiba, Xario® equipment, with a multifrequential linear transductor of 12 MHz at volar distal surface of the wrist (at the level of pisiform and tuberosity of scaphoid) by a blind technician. For the examination patients should be seating in a chair with arms extended, hands with finger semi extended. A MNA with more than 11.2 mm2 was considered diagnostic of CTS (9).

Data were collected in frequency and contingency table. The sample distribution was tested by Kolmogorov-Smirnov test. Central tendency was expressed in mean and standard deviation in parametric samples and median and interquartile range (IQR) in the non-parametric. Association studies were done by chi-squared test when data was nominal and by unpaired t test and Mann Whitney when nominal. Adopted significance was of 5%. Calculation was done with help of the software graph Pad Prism version 5.0.

## RESULTS

### 1 - Study of FM patients in comparison with controls.

Descriptive and pairing data of patients and controls is seen in **table 1**.

**Table 1** – Descriptive and pairing data of fibromialgia patients and controls

| | FM pacientes N=41 | Controls N=42 | p |
|---|---|---|---|
| Gender | 2M/39F | 6M/36F | 0.26 |
| Body mass index (Kg/m2) | 20.0-45.0<br>Median 29.0<br>IQR= 25.0-33.5 | 25.39 - 36.68<br>Median 28.8<br>IQR=27.8-29.4 | 0.81 |
| Age | 25.0-66.0<br>Median 54.0<br>IQR=49.0-59.0 | 45 a 73<br>Median 51.0<br>IQR=48.0-54.0 | 0.23 |

M= male; F= female; IQR= interquartile rate; (*) chi squared test ; (**) Mann Whitney test

MNA by US in the control group ranged from 4.0-21.0 mm (median 9.0; IQR=7.0-11.0) and in the FM group from 4.0-14.0 (median 9.0: IQR=8.0-11.0) with p=0.66; Mann Whitney test. The prevalence of STC in FM was 8/41 (19.5%) of and in controls of 13/42 (30.9%) with p= 0.20 (chi squared test)

### 2- Comparison of FM patients with and without STC:

The comparison of FM patients with and without STC showed no difference in demographic data, body mass index, VAS of generalized pain and results of BCTQ. **Table 2**.

**Table 2** – Comparison of fibromialgia patients with and without carpal tunnel syndrome

| | FM with STC | FM without STC | P |
|---|---|---|---|
| Age (years) | 41-60<br>Mean 52.7±6.9 | 25.0-66.0<br>Mean 53.2±8.2 | 0.87 * |
| Disease duration ( years) | 0.3-20<br>Median 2.0;IIQ=0.5-8.5 | 0.6-20<br>Median 5.0 IIQ=2.0-9.2 | 0.23** |
| Body mass index (kg/m$^2$) | 24.0-45.0<br>Mean 31.4±6.4 | 20.0-38.0<br>Mean 28.5±4.9 | 0.15* |
| Generalized Pain - visual analogic scale | 5.0-10.0<br>Median 8.0;IIQ=6.0-9.0 | 4,0-10.0<br>Median 8.0;IIQ=7.0-9.7 | 0.46** |
| BCTQ results | 41.0-82.0<br>Mean 61.3±11.9 | 30.0-83.0<br>Mean 57.1±12.3 | 0.40* |

*- unpaired t test ; ** Mann Whitney test; IIQ= interquartile rang; BCTQ= Boston carpal tunnel questionnaire.

The comparison of presence of paresthesia and numbness, positive Tinel and Phalen test on extremities with or without STC can be seen in **table 3**.

**Table 3** – Comparison of clinical findings in extremities with and without carpal tunel syndrome

| | With CTS<br>14 extremidades | Without CTS<br>68 extremidades | p |
|---|---|---|---|
| Parestesia | 11/14-78.5% | 52/68- 76.4% | 1.00 * |
| Tinel | 7/14- 50% | 24/68- 35.2% | 0.30* |
| Phalen | 9/14 - 64.2% | 40/68 - 58.8% | 0.70* |

* chi squared test.

## DISCUSSION

FM and CTS are common diseases that occur more frequently in females and can both cause morning stiffness and parestesias in the hands increasing especially at night (5). The similarity between the symptoms of both FS and CTS and the common epidemiologic background of both entities may lead to diagnostic confusion and favor one disease to mask the other.

At present it was not possible to demonstrate that FM patients have more CTS diagnosed by US than controls. Our studied sample (controls and FM) had a high prevalence of CTS and this may be explained by the relatively high BMI of both samples, as overweight is associated with higher CTS prevalence (10). To diagnose CTS we used the measurement of median nerve area by US that is considered a valuable diagnostic instrument and that has shown high concordance with nerve conduction study (NCS) in defining CTS severity (9,11)

Nacir et al (5), studying STC by electrophysiological tests showed that FM patients have higher prevalence of STC than controls (20.63% vs 2.82%) but Sarmer et al (12) could not prove that STC were more common in FM than control subjects as we found.

Paresthesias in the extremities are a common complaint in fibromyalgia (FM) patients, and the role of the peripheral nervous system in its appearance is not clear. However, paresthesia is considered to be a result of an abnormal sensory perception occurring due to central sensitization (4,5). As FM

patients show increased subjective sensitivity in response to multisensory stimulation in daily life and reduced tolerance to non-nociceptive sensory stimulation , this may interfere with the interpretation of carpal tunnel paresthetic symptoms. Such interference can be reinforced by the finding of poorer response of CTS to local steroid treatment (13) and more dissatisfaction with surgery results in FM than controls (14).

The present study also showed that it is almost impossible to distinguish clinically FM patients with STC from those without it by demographic as well as by clinical findings. Neither Tinel's or Phalen's tests could help in this differentiation. Also the Boston carpal tunnel questionnaire, that is considered a valuable tool in the evaluation of function and severity of STC symptoms, (8) could not distinguish the two populations.

## CONCLUSION

At conclusion we found at present that FM patients do not have more STC than controls and that the usual clinical evaluation for CTS should be interpreted with care.

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# ORIGINAL ARTICLE
# TOPICS IN MEDICAL CLINIC
# IMMUNOGLOBULIN IGA DEFICIENCY IN ADULT PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

## *DEFICIÊNCIA DE IMUNOGLOBULINA IGA EM PACIENTES ADULTOS COM ARTRITE JUVENIL IDIOPÁTICA*

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Key words: Juvenile idiopathic arthritis, Immunoglobulin A, Uveitis, Immunedeficiency
Descritores: Artrite idiopática juvenil, Imunoglobulina A, Imunodeficiência.

***Abstract***

Patients with juvenile idiopathic arthritis (JIA) may have immunoglobulin A deficiency (IgA D). A common genetic background, a higher rate of infectious diseases supplying antigenic stimulation and a direct role of IgA in the immune system function are some of the possible explanations for this link. At present, 85 adult patients with JIA have been studied for the presence of IgA D and its association with clinical and serological disease profile. IgA D in adult patients with JIA was more common than in control sample (p<0.0001) but not than in JIA pediatric patients (p=0.69). Adult JIA patients with IgA D had more uveitis (p=0.003) and earlier onset of disease onset (p=0.019). No differences were noted in serological profile, patients' functional state and disease subtype. **Endocrinol diabetes clin exp 2016 1854 -1856.**

**Resumo**

Pacientes com artrite idiopática juvenil (AIJ) podem ter deficiência de imunoglobulina A (IgA D). Um fundo genético comum, uma taxa mais elevada de doenças infecciosas que fornecem estimulação antigênica e um papel direto de IgA na função do sistema imunológico são algumas das possíveis explicações para esta associação. Neste estudo, 85 pacientes adultos com AIJ foram estudados para a presença de IgA D e sua associação com perfil da doença clínica e sorológica. IgA D em pacientes adultos com AIJ foi mais comum do que na amostra de controle (p <0,0001), mas não do que em pacientes pediátricos com AIJ (p = 0,69). Adultos com AIJ e com IgA D tinham mais uveíte (p = 0,003) e início mais precoce de início da doença (p = 0,019). Não foram observadas diferenças no perfil sorológico, e funcional dos pacientes, nem na proporção de subtipos da doença.. **Endocrinol diabetes clin exp 2016 1854 -1856.**

**INTRODUCTION**

Immunoglobulin (Ig) A is the human immunoglobulin with highest rate of daily synthesis and the second most abundant in the blood (1). Selective IgA deficiency (IgA D) is a very common immune deficiency and the affected individuals seem to have a paradoxical high prevalence of autoimmune phenomena such as Graves' disease, systemic lupus erythematosus, celiac disease and miastenia gravis (1). Juvenile idiopathic arthritis (JIA) is among the commonest auto immune disease found in IgA D patients (2); it was found in 23.2% of a sample of 56 IgA deficient individuals studied by Petty et al (3).

JIA is a group of heterogeneous disease that begins under 16 years of age but that may extend through adulthood in almost one third of the cases (4) but the factors that may influence such persistence are not known. So, all differences between child and adult patients with JIA are worthy to be studied to see if they can provide some clue to the diseases' persistency.

At present we studied an adult sample of JIA patients for IgA deficiency aiming to know if the prevalence of Ig A deficiency in this group is higher than in those with childhood disease. We also aimed to see if IgA deficiency is related to any peculiar aspect of the disease.

**MATERIAL AND METHODS**

After approval of the local Committee of Ethics in Research and written consent of all participants, we studied 85 adult JIA patients for demographic, clinical and serological data through questionnaires and chart review. This group represents the whole sample of adult JIA patients from a single rheumatology center that attended for regular appointment in one year and that agreed to participate in the study. Patients on sulphasalazine, d-penicilamine, phenytoin, with concomitant C virus or HIV infection were excluded since they are associated with acquired IgA D (5). The JIA classification followed ILAR criteria (4). Uveitis was considered present when confirmed by a certified ophthalmologist. Serum IgA was measured by nephelometry and patients with levels under 50 mg/dL were considered as deficient (6). HAQ (Health Assesment Questionnaire) to evaluate functional status was measured simultaneously with determination of IgA levels (7).

For comparison we used data of previous studies that showed a prevalence of 1/965 of IgA D in a healthy sample (blood donors) (8) and a prevalence of 8.5% (6/70) in a pediatric population of JIA (2). These studies were done both in the same geographical area as the present.

Patients with IgA deficiency were compared with those without it using chi squared and Fisher test for nominal and unpaired t test and Mann Whitney for numerical data. The central tendency was expressed in media and standard deviation when the sample was parametric and median and interquartile rate (IQR) when non parametric. Sample distribution was determined by the Kolmogorov Smirnov test. The significance adopted was of 5%. Calculation was done with help of the software Graph Pad prism.5.0.

**RESULTS**

In the 85 adult JIA patients 30.5% were male and 69.4% females with median age of 26 years (range 18.0-51.0 years), and with age at disease onset from 2.0-16.0 (mean 8.9±4.06

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years). In this sample: 20% sere polyarticular rheumatoid factor (RF) positive form; 34.1% were polyarticular RF negative form; 29.3% were oligoarticular; 10.5% enthesitis-related arthritis and 4.7%, the systemic form. Uveitis were found in 42.3% (36/85), RF in 22/85 (25.8%), antinuclear antibody (ANA) in 18/85 (21.1%). About 18/85 (21.1%) have had joint replacement and 43/85 (50.5%) have had hip involvement. The median HAQ was 1.0 (range from 0-3; IQR of 0-2). Methotrexate was being used in 52/85 (61.1%), anti TNFα in 34/85 (40%); antimalarial in 20/85 (23.5%); leflunomide in 14/85 (16.4%); tocilizumab in 2/85 (2.3%) and oral glucocorticoid in 37/85 (43.2%).

IgA levels ranged from 22.0-485.0 mg/dL (mean of 239.0±121.1). It was found IgA D in 9/85 (10.5%) of the sample. This prevalence was higher than the prevalence of 1/965 found in healthy blood donors from previous work done in the same geographical area (7) with p< 0.0001 (OR= 114.2; 95% CI de 14.2-913.5). The IgA D prevalence in adult JIA was similar to those of pediatric patients (2) with p= 0.69.

The comparison of IgA deficient patients with those without this deficiency showed the results of table 1 where it is possible to see that IgA deficient patients had earlier disease onset and more uveitis. **Table 1**.

**Table 1** – Comparison of juvenile idiopatic arthritis patients (JIA) with and without IGA deficiency

| | **With IgA deficiency N=9** | **Without IgA deficiency N=76** | **p** |
|---|---|---|---|
| Gender (female/males) | 6 /3 | 53/23 | 1.00 * |
| Age at disease onset (years) | 2-14; Mean 6.0±4.3 | 2- 16; Mean 9.3±3.8 | 0.019** |
| Disease subtypes | | | 0.25§ |
| Oligoarticular | 3/9 | 22/76 | |
| Poliarticular RF+ | 0 | 17/76 | |
| Poliarticular RF- | 5/9 | 24/76 | |
| Systemic | 1/9 | 3/76 | |
| Entesitic | 0 | 9/76 | |
| Uveitis | 8/9 – 88.8% | 28/76 -36.8% | 0.003* (#) |
| Hip involvement | 6/9 – 66.6% | 37/76 – 48.6% | 0.48 * |
| Antinuclear antibody | 1/9 – 11.1% | 17/76 – 22.3% | 0.67 * |
| Rheumatoid fator | 0 | 22/76 -28.9% | 0.10* |
| Joint replacement | 2/9 – 22.2% | 16/76- 21.05% | 1.00 * |
| HAQ | 0-3 Median 2.0 (0.5-2.5) | 0-3 Median 1.0 ( 0.0-2.0) | 0.26§§ |

* Fisher test; § chi squared; ** unpaired t test; §§Mann Whitney test; HAQ= Health assessment questionnaire (#)-OR =13.7; 95%IC =1.62-115.5

**DISCUSSION**

The reason for the association of IgA D with autoimmune disease has been speculated. Some authors favor the idea that this deficiency is associated with failure to eliminate infections, mainly at mucosal site, and this can be a source of antigenic stimulation (1). High-affinity IgA antibodies defend intestinal mucosal against invasion by pathogenic microorganisms; low-affinity IgA antibodies are central to confine commensal microbes to the intestinal lumen (1). Others believe that IgA D and autoimmune diseases appear together because they have a common genetic background. IgA D is associated with the human leukocyte antigen (HLA)-B8, DR3, DQ2 haplotype (10,11,12) and up to 45% of IgA D patients have at least one copy of this haplotype compared to 16% in the general population (12). Remarkably, this haplotype is also reported to be associated with Graves' disease, systemic lupus erythematosus, type 1 diabetes and celiac disease (9).The analysis of genetic background in JIA is challenging because it encompasses a heterogeneous family of diseases . Neverthless, there is some suggestion that genes within B8, DR3 also contribute to JIA susceptibility (9).

It has also been demonstrated that IgA itself can exert both pro and anti-inflammatory roles (1). When associated with antigens, IgA stimulates the receptor Fcα R1 (CD89) expressed by myeloid cells generating a pro-inflammatory response (1). However in the absence of antigen, the serum monomeric IgA binds to this same receptor and dampens the immune response (1). Also the secretory form of IgA (SIgA) may have an anti-inflammatory effect due to its ability to interact with dendritic cells (1). Experimentations with bone marrow dendritic cells pretreated with SIgA stimulate the growth of regulatory T cells (Tregs) (13).

In our study we found a high prevalence of IgA D in JIA when compared to controls but not when compared with

pediatric JIA patients showing that the persistence of this disease into adulthood is not associated with this immunoglobulin deficiency.

Our adult sample of JIA with IgA D had some peculiar clinical manifestations such as higher prevalence of uveitis and disease onset at an earlier age. Isolated uveitis has been linked to this deficiency by others (6,14). Although no explanations have been offered to this association it is interesting to observe that some viral infections (that may be favored by IgA D) have been considered to play a role in the pathogenesis of JIA-associated uveitis (15). Also T-reg cells seem to exert a protective function in uveitis, as they can attenuate a variety of physiological and pathological immune responses and regulate activation of Th1 and Th17 cells (15).Uveitis is a manifestation that can be associated with high morbidity (16); to understand the mechanism why Ig A D may favor eye involvement it is important to create mechanisms to avoid or to treat this complications. Also finding IgA D in a group of JIA patients may help to identify the high-risk group for eye problems.

The association of IgA D with more precocious disease onset of JIA may be a surrogate for a more severe disease. No differences in functional state were found presently but the aggressive treatment available nowadays may have prevented it. It is interesting to speculate if IgA D may help in the imbalance of immune system, favoring the earlier disease appearance. Accordingly with our findings, uveitis is more frequently seen in JIA patients with earlier disease onset (16).

CONCLUSION

We concluded that the adult population of JIA has a high prevalence of IgA deficiency, comparable to that seen in the pediatric patients. This deficiency is associated with earlier disease onset and uveitis.

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