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MEMORABLE DATES: July 14th

The fall of the Bastille

LIBERTÉ – EGALITÉ- FRATERNITÉ

EDITORIAL

MEMORABLE DATES: July 14th LIBERTÉ – EGALITÉ- FRATERNITÉ The fall of the Bastille

Bastille was built in the mid to late 1300s to house royal soldiers belonging to Charles V. This fortress were installed to protect the eastern flanks of Paris from English raiders during the Hundred Years' War (1337-1453). There were rarely more than 20 or 30 prisoners in majority political prisoners. Notables and revolutionary men were detained there, including Voltaire, Diderot, Jacques Brissot and, the pornographer Marquis de Sade

For the French people, the Bastille was a physical manifestation of the tyranny and opression of theirs sovereign. In Paris, the working classes had endured months of bread shortages and high prices. The cost of bread peaked at 14.5 sous per loaf . Parisians were spending at least three-quarters of their daily income to buy bread.

By the late 1780s, become a symbol of royal absolutism. The revolutionaries had requested to the king a constitution with equal rights for all the French people. However, there rich men who oppose the revolution. The French revolutionaries believed that they were under attack from internal and external enemies.

When the finance minister, who was sympathetic to the revolutionaries was dismissed the people of Paris attacked the Bastille

On July 14th the crowd ransacked the Invalides, stealing weapons, then marched on the Bastille to capture its supplies of gunpowder. The French Guard, was called out to restore order but its soldiers refused to open fire on the people, and many of them joined the insurrectionists., Marquis Bernard de Launay, the Bastille's governor, received representatives from the crowd but refused to hand over the power (1,2)

The attack did not mean the freedom of only seven prisioners but the beginning of equality concept that changed the world! Nowadays there are people fighting for:

LIBERTÉ – EGALITÉ- FRATERNITÉ

The 14th of July is to the French people of huge symbolic significance Its became a symbol of the old and hated regime fall's . Now this day is a public holiday celebrating freedom and equality (3,4)

1. https://alphahistory.com/frenchrevolution/fall-of-the-bastille/
2. The fall of the Bastille by Jennifer Llewellyn, Steve Thompson
3. https://historycollection.co/day-history-fall-bastille/
4. https://www.thoughtco.com/the-bastille-overview-

Mirnaluci Paulino Ribeiro Gama

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REVIEW
OSTEOPOROSIS IN MEN LEPROSY CARRIERS
OSTEOPOROSE EM HOMENS PORTADORES DE HANSENÍASE

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Key words: Leprosy, osteoporosis, gonadal dysfunction, men, hypogonadism
Descritores: Hanseníase, osteoporose, disfunção gonadal, homens, hipogonadismo.

Abstract

Leprosy, also called Hansen's disease, is a stigmatizing disease characterized by a chronic granulomatous infection especially affecting the skin and peripheral nerves having as etiology the Mycobacterium leprae, and remains an important cause of morbidity with approximately 200,000 new cases per year in the world. Among the endocrine changes in leprosy the osteoporosis is present, being attributed to secondary gonadal dysfunction due to testicular atrophy. Leprosy affects either the seminiferous tubules or the Leydig cells, and may therefore lead to isolated increases in LH and FSH alone. Lepromatous leprosy is my commonly associated with hypogonadism, and recommend the routinely screening these patients for hypogonadism. It is important that those involved in leprosy management be aware of the osteoporosis as a consequence of the disease and their treatment in all of its aspects. Leprosy as secondary cause of osteoporosis in men is revised highlighting understanding of epidemiology, pathophysiology, diagnosis, and treatment of osteoporosis in men with leprosy. **Endocrinol diabetes clin exp 2019 / 2125 - 2128.**

Resumo

A hanseníase é uma doença estigmatizante, caracterizada por uma infecção crônica granulomatosa afetando principalmente a pele e os nervos periféricos e tem como agente etiológico o Mycobacterium leprae, um microorganismo intracelular, sendo uma importante causa de morbidade, com aproximadamente 200.000 casos novos por ano no mundo. A osteoporose está presente entre as alterações endócrinas da hanseníase, sendo atribuída a disfunção gonadal secundária à atrofia testicular. A hanseníase afeta tanto os túbulos seminíferos como as células de Leydig, podendo assim levar a aumentos isolados de LH e FSH. A hanseníase virchowiana é comumente associada ao hipogonadismo, o que recomenda uma triagem de rotina desses pacientes para o hipogonadismo. É importante que os envolvidos no atendimento da hanseníase estejam cientes da osteoporose como uma consequência da doença e seu tratamento em todos os seus aspectos. Neste artigo a hanseníase como causa secundária de osteoporose em homens é revisada, destacando-se uma abordagem sobre a epidemiologia, fisiopatologia, diagnóstico e tratamento da osteoporose em homens com hanseníase. **Endocrinol diabetes clin exp 2019 / 2125 - 2128.**

INTRODUCTION

Leprosy, also called Hansen's disease, is a stigmatizing disease characterized by a chronic granulomatous infection especially affecting the skin and peripheral nerves having as etiology the Mycobacterium leprae (1). Leprosy is a curable disease with well-defined etiology, but lacks better diagnostic tools, preventive and therapeutic strategies.

Leprosy is still an endemic disease more prevalent in tropical regions, and the endocrine manifestations caused by leprosy have been underestimated, even by specialists, in special the hypogonadism in male patients. In male hypogonadism associated with bone loss, it is important to determine the bone loss continues and increased risk of fracture (2).

Osteoporosis most commonly affects the hip and the lumbar vertebrae, but other bones, such as the radius, tibia, and ribs, may also fracture. The main feature of the etiology of the disease is that low bone mineral density results in increased susceptibility to bone fracture. Contrary of women, there is a subjacent cause for the osteoporosis in approximately half of affected men. The osteoporosis of male leprosy patients are attributed to secondary gonadal dysfunction due to testicular atrophy, however, the Leydig cell hyperplasia appears to preserve bone volume (3).

The study indicates that bone mass loss is an early event in leprosy patients and frequently is already present at diagnosis, and patients with a long-standing diagnosis of leprosy present not only osteoporosis when evaluated by densitometry but also a predisposition to fracture (3,4).

There is still no well-established treatment for osteoporosis in male patients with leprosy, because no clinical trials have examined the efficacy of treatment on bone mineral density or fracture incidence in patients with leprosy (5). It is important that those involved in leprosy management are aware of the osteoporosis as a consequence of the disease, and their treatment in all of its aspects.

Osteoporosis in men is increasingly recognized as an important health problem, especially in patients with leprosy. Leprosy as a secondary cause of osteoporosis is revised highlighting current understanding of epidemiology, pathophysiology, diagnosis, and treatment of osteoporosis in men with leprosy.

OSTEOPOROSIS IN MEN WITH LEPROSY

Epidemiology

The global prevalence of leprosy is elevated mainly in India, sub-Saharan Africa, Latin America, and the Caribbean, being a considerable cause of morbidity with 203,600 new cases per year (6). A difficulty in study of the transmission of leprosy is variation in bacterial genomic DNA. Four genotypes of M. leprae grounded on three single-nucleotide polymorphism were also discovered to be usable for analysis of the global dissemina-

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tion of leprosy (7). Any less 5% of individual in touch whit M. leprae develop clinical disease, and treatment for patients with leprosy is effective, with a cure rate of 90%, and can develop at any age, however, manifests most often in individuals aged 5 to 15yr or > 30yr (8). Leprosy has been the target of a World Health Organization (WHO) multiple drug therapy campaign to eliminate it as a national public health problem in member countries, as a result of its leprosy elimination campaign, the WHO reports a 20% annual decrease in new cases detected globally since 2001 but endemic regions persist.

Osteoporosis is an important and difficult disorder that is enough prevalent worldwide and mostly ignored in men (9). All men diagnosed with osteoporosis should be evaluated for secondary causes of bone loss, especially those with leprosy. The men account for approximately one third of all osteoporotic fracture worlds and at age 50 have a lifetime fracture risk as high as 20%, however the prevalence and impact of osteoporosis in men remains unclear to many clinicians (10). Certain men with multiple risk factors for osteoporosis may develop the disease sooner.

The prevalence of osteoporosis among men varies depending on the skeletal site used to measure bone mineral density and the reference data applied to calculate it, because there no uniform opinion on the T score threshold that should be applied when making the diagnosis of osteoporosis in men (11). Hence, prevalence figures reported have shown a variation of 4 to 8.1% (12-15).

Osteoporosis can result from bony changes due to leprosy. Ishikawa et al. showed more than 30% of osteoporosis in male leprosy patients (16). A study conducted to determine osteoporosis in male leprosy patients caused by testicular atrophy showed significant differences in the average bone volume measurements among the 7 patients with nodular Leydig cell hyperplasia (12.24%) and the 22 patients without hyperplasia (7.35%) and 6 patients without leprosy (12.98%). The osteoporosis of male leprosy patients were attributed to secondary gonadal dysfunction due to testicular atrophy, and Leydig cell hyperplasia appears to preserve bone volume (17).

Pathophysiology

There is no doubt that pertinent aspects of the pathophysiology of leprosy are not yet completely understood, but the patient who does develop leprosy probably have a poorly defined genetic predisposition, because cases cluster in families, and there is a high concordance rate in identical twins.

Leprosy encompasses various clinical presentations ranging between tuberculoid leprosy and lepromatous leprosy. Between these polar forms, immunologically overlapping cases are classified as borderline tuberculoid. The principal means of transmission is by aerosol spread from infected nasal secretions to expose nasal and oral mucosa. The mean incubation period is 4 years for tuberculoid leprosy and is 10 years for lepromatous leprosy (18).

The strength of the host's immune system influences the clinical form of the disease. Therefore, a spectrum of disease exists such that cell-mediated immunity dominates in mild forms of leprosy and decreases with increasing clinical severity. Meanwhile, humoral immunity is relatively absent in mild disease and increases with the severity of disease (19). The 2 common types of leprosy reactions are type 1 or reversal reactions, mediated by an upgrade in cellular immune responses to the bacterium, and type 2 or erythema nodosum leprosum, which corresponds to a systemic response to immune complex deposition created by dead and dying Mycobacterium leprae (20).

The identification of the host genes that influence host susceptibility/resistance will allow a greater understanding of disease pathogenesis. Several genes that may modulate cell-mediated immunity have been investigated and some appear to have a role, in either susceptibility to leprosy per se, or to leprosy type. Studies have linked susceptibility to leprosy with the genes that directly modulate development of the adaptive response as HLA, MICA, TAP2, CTLA4, VDR, or that serve bridge the innate and adaptive responses as NRAMP1, TLR2, HSP70, TNF-α, MRC1 (21).

Osteoporosis is the reduction in bone density or mass resulting in a weakening of the skeletal ability to maintain a person's mechanical support, and continues to be an under-recognized problem in men. The disease can be generalized across the axial of the skeleton or be selective, affecting one segment of the skeleton. Whatever the cause, osteoporosis develops when the process of bone reabsorption and bone formation is disrupted. Studies of the genetics of osteoporosis may provide new approaches to diagnosis. The interactions between local and systemic factors, particularly between estrogen, cytokines, and prostaglandins, have suggested a mechanism for bone loss in rodent models. Nutritional deficits of calcium, vitamin D, and vitamin K may play a role in pathogenesis (22).

Among the endocrine changes in leprosy the osteoporosis is present, being attributed to secondary gonadal dysfunction due to testicular atrophy, and also the acute orchitis of type 2 reactions. Leprosy can lead to hypognadism as Mycobacterium leprae may invade the testes in up to three quarters of cases of leprosy (23). Leprosy affects either the seminiferons tubules or the Leydig cells, and may therefore lead to isolated increases in LH and FSH alone (24). Lepromatous leprosy is my commonly associated with hypogonadism, and recommend the routinely screening these patients for hypogonadism. The hypogonadism causes infertility and sexual dysfunction development as the tests become small, soft, and insensitive and investigation may demonstrate oligospermia or azoospermia. The study shows a significant correlation was seen between duration of disease and FSH when age was taken into account, indicating that testicular dysfunction is probably cumulative and irreversible (25).

Thus, osteoporosis in leprosy occurs due the effects of androgens on bone cells that are regulated by three major factors: TGFb, IGFs and IL-6 (26). Androgens may preserve bone by inducing TGFb and IGFs which increase bone formation or by inhibiting IL-6, which stimulates osteoclastogenesis. There are likely also to be direct effects of androgens on osteoclasts as well as indirect effects by effects on bone marrow stromal cells to modulate receptor activator of nuclear factor-kB ligand-induced osteoclast formation. Taken together, these data suggest a major component of action of testosterone on bone may be mediated directly through the androgen receptor.

Clinical and laboratory diagnosis

The diagnosis of leprosy is of paramount importance, and accurate diagnosis of leprosy is also of vital importance to all aspects of the leprosy control program and research, such as epidemiology, chemotherapy, prevention of disability and assessment of interventions. There is no single diagnostic laboratory test for leprosy and clinical diagnosis is still the most useful tool for detecting the leprosy. The basic criteria in the Ridley and Jopling classification are the bacillary load measured by bacilloscopic exams and the cell-mediated immune response time, which is evaluated by the result of Lepromin test (19).

Three cardinal signs still form the basis of the clinical diagnosis of leprosy, as affirmed by WHO Expert Committee on Leprosy in 1997: anaesthetic skin lesions enlarged peripheral nerves and acid-fast bacilli in the skin smear. Diagnosis is complete once the clinical signs are established through clinical examination (27). Therefore, as the clinical management of leprosy is becoming integrated into the general health services, the majority of the patients will be diagnosed and managed by non-specialists.

With increases in knowledge about in the leprosy two additional laboratory diagnostic approaches were developed: serological reactions, and immunological reactions. Recently,

diagnostic methods for leprosy based on Mycobacterium leprae DNA sequences have been developed (28).

All cases of leprosy should be confirmed histologically, and slit skin smear to detect acid-fast bacilli from lesional skin provides a fast confirmation of multibacillary leprosy (29). Lepromin test is an intradermal test with autoclaved Mycobacterium leprae antigen. It is a guide for the cell-mediated immunity of the patient against leprosy. A negative test can be useful to exclude leprosy in patients with peripheral neuropathy (30). Phenolic glycolipid-1 IgM antibody detection is of limited clinical use. It is positive in 100% of multibacillary leprosy, but in only 21 % in paucibacillary leprosy and 14% in household contacts (31).

Osteoporosis is a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, and susceptibility to fracture (32). Criteria for diagnosing osteoporosis in men are evolving, and bone mineral density (BMD) measurement with a T-score of -2.5 or less indicates osteoporosis. In men over 50 years of age, a diagnosis of osteoporosis may be considered when the T-score is –2.5 or less. In men younger than 50 years, it is recommended that simple z scores be used to describe the degree to which the bone-density measurement differs from normal: Z scores less than –2 are below the expected range for age (33).

Male osteoporosis remains a heterogeneous entity, with multiple underlying causes. Currently, osteoporosis in men has become increasingly recognized as an important clinical and public health problem. All men diagnosed with osteoporosis should be evaluated for secondary causes of bone loss. Hence the need to identify and screen men at a particular risk for osteoporosis, as hypogonadism induced by leprosy, has become important. Hypogonadism affects approximately 50% men with leprosy due to gonadal atrophy from testicular Mycobacterium leprae infection consequently osteoporosis is very common in men with leprosy. The study of bone metabolism in male leprosy patients, the osteoporosis was present when men had lumbar compression fractures or a mean BMD -2 SD (2).

Men with secondary causes of low bone density or bone loss may be clinically diagnosed with osteoporosis, taking BMD into consideration. However, controversy exists regarding which sites to measure for densitometric diagnosis of osteoporosis in men. Moreover the evaluation of secondary osteoporosis to leprosy should include a detailed history of clinical risk factors for fractures and the underlying medical conditions and medications that cause bone loss, a thorough physical examination and laboratory tests. The laboratory evaluation with standard renal and liver function tests, a complete blood count, serum calcium and phosphate levels, C-reactive protein, bone-specific alkaline phosphatase, serum 25-hydroxyvitamin D, serum levels of basal thyrotropin, serum testosterone levels, free serum levels of PTH, serum protein electrophoresis, and 24-h urinary calcium excretion (34).

Treatment

Treatment of the leprosy is pivotal. No clinical trials have examined the efficacy of treatment on BMD in male patients with leprosy, however the management of secondary osteoporosis is aimed at treating the underlying disease, and treating osteoporosis for preventing further fractures.

Drugs like alendronate, risedronate, and zolendronic acid, and teriparatide are currently U.S. Food and Drug Administration approved for the treatment of osteoporosis in men.

The oral administration of risedronate contributed to the prevention of vertebral fractures by suppressing bone resorption and increasing in lumbar BMD in the elderly male patients with leprosy (3). However the same authors another study demonstrated that the treatment with risedronate associated with alfacalcidol contributed to the increase in BMD; however, the treatment did not prevent fracture due to osteoporosis in this male patient with leprosy (5). Alendronate increases the BMD and decreases the incidence of vertebral fractures, and was also effective in the prevention and treatment of osteoporosis in men (35). No have studies in leprosy patients with osteoporosis using zolendronic acid.

Based on the current state of uncertainty regarding testosterone treatment of men with osteoporosis, the Institute of Medicine has recommended that a series of clinical trials be done to help determine the efficacy of testosterone for several important outcomes (36). However, documented hypogonadism justifies testosterone replacement therapy, although its anti-fracture efficacy has not been studied. Testosterone replacement therapy also has been used for prevention of hypogonadismo and osteoporosis subsequent (37).

Adequate calcium and vitamin D nutrition is a prerequisite prior to initiating pharmacological therapy, because the efficacy of anti-osteoporotic drugs has only been demonstrated in the presence of vitamin D and calcium supplementation (38).

CONCLUDING REMARKS

Leprosy is a secondary cause of osteoporosis due secondary gonadal dysfunction due to testicular atrophy, and also the acute orchitis of type 2 reactions, and the majority of men with fractures remain untreated because there is not well-established treatment for osteoporosis in male patients with leprosy, and the treatment is based on professional opinion rather than the highest level clinical evidence. The bone mass loss is an early event in leprosy patients and frequently is already present at diagnosis, hence the importance of people in leprosy management be aware of the osteoporosis as a consequence of the disease and their treatment in all of its aspects.

With appropriate care, osteoporosis can be prevented, and when present, it can be easily diagnosed and managed. Unfortunately, no clinical trials have examined the efficacy of treatment on bone mineral density or fracture incidence in patients with leprosy. Androgen deficiency is a common secondary cause of osteoporosis in men with leprosy and treatment with testosterone is required. The testosterone replacement is important is effective in men with androgen deficiency secondary to leprosy, because the androgens may preserve bone by stimulation osteoclastogenesis. The use oral of bisphosphonates as alendronate and risedronate have been used to prevent bone loss ever associated with vitamin D and calcium supplementation.

New therapies are currently under investigation for osteoporosis, however in leprosy the treatment of the underlying disease is pivotal.

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EXPERIMENTAL ENDOCRINOLOGY

ORIGINAL ARTICLE
HISTOPATHOLOGICAL ANALYSIS OF RAT LIVERS INDUCED TO DIABETES BY DIFFERENT EXPERIMENTAL MODELS

ANÁLISE HISTOPATOLÓGICA DO FÍGADO DE RATOS INDUZIDOS AO DIABETES POR DIFERENTES MODELOS EXPERIMENTAIS

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SIMONI MACHADO MEDEIROS*

Key words: Diet, High-fat, Alloxan, Fatty Liver
Descritores: Dieta, Dieta hiperlipídica, Aloxano, Fígado gorduroso

Abstract

This article aims to compare the histopathological changes in diabetic rat livers induced by two different methods, the application of intravenous alloxan and the ingestion of a hypercaloric diet. To do so, the ethical standards required by the Committee on Animal Research and Ethics were followed. The animals were divided into three groups: control, alloxan-induced diabetics and hypercaloric-induced diabetics. Blood glucose levels were checked to confirm the hyperglycemic state. After 120 days of the experiment, the animals were euthanized and the livers fixed in formaldehyde and taken for histological processing. Samples were sectioned in a rotating microtome and stained with hematoxylin and eosin, assembled with Canada balsam on a microscope slide and coverslip. The experiment revealed significant histopathological alterations among the groups. Due to the development of the non-alcoholic fatty liver disease, diabetic animals presented different levels of fatty degeneration and disarrangement of the hepatic architecture when compared to the control group. However, the presentation was different among the induction models. The alloxan model promoted alterations in liver structure. The hypercaloric diet model promoted alterations along the time of exposure to the risk factor (diet). **Endocrinol diabetes clin exp 2019 / 2129 - 2132.**

Resumo

O presente estudo teve por objetivo comparar as alterações histopatológicas do fígado de ratos diabéticos induzidos por dois métodos diferentes, a aplicação de Aloxano intravenoso e a ingestão de dieta hipercalórica. Para tanto, foram obedecidos os padrões éticos exigidos pelo Comite de Ética em Pesquisa com Animais. Os animais foram divididos em três grupos, controle, diabéticos por aloxano e diabéticos por Dieta hipercalórica. Foi verificada a glicemia para confirmação do estado hiperglicêmico. Após 120 dias de experimento, os animais foram eutanasiados e o fígado fixado em Formol e levado para processamento histológico. Amostras foram seccionadas em micrótomo rotativo e cortes corados com Hematoxilina e Eosina, montados com bálsamo do Canadá em lâmina e lamínula. Foram observadas alterações histopatológicas significativas entre os grupos. Animais diabéticos apresentaram diferentes níveis de degeneração gordurosa, com desarranjo da arquitetura heática quando comparados ao grupo controle. Este fato se dá pelo desenvolvimento da Doença Hepática Gordurosa Não Alcoólica, contudo a apresentação foi diferentes entres os modelos de indução pelo razão do modelo por Aloxano promover alterações agudas na estrutura hepática, e o modelo por ingesta de dieta hipercalórica promover alterações por tempo de exposição ao fator de risco (dieta). . **Endocrinol diabetes clin exp 2019 / 2129 - 2132.**

INTRODUCTION

Diabetes is a chronic disease that affects more than 150 million people in the world. However, according to the WHO, that number can reach 300 million in some years. The pathology is related to others, such as the development of atherosclerosis, non-alcoholic fatty liver disease (NAFLD), known as hepatic steatosis (1,2).

The liver performs many metabolic functions including glycemic control. Its structure is remarkably sensitive to hyperglycemia and diabetes; these conditions can cause disarray of tissue architecture and accumulation of lipids in the hepatocytes depending on the experimental model adopted for this purpose (3)

Experimental models can promote diabetes mellitus in animals. Type I (DMI) can be induced with the application of alloxan (ALX), which exerts a toxic effect on pancreatic cells by stopping the production of insulin. Type II (DM II), characterized by insulin resistance, can be induced by ingesting a high-fat diet (HD) (4,5).

Therefore, studies that aim to understand the pathophysiology of diabetes are essential, even those that describe chronic lesions in different organs as a result of this pathology. Thus, the investigation aimed to compare the histopathological changes in the diabetic rat livers induced by two different methods, ALX and HD.

MATERIAL AND METHODS

Animals

Eighteen male Wistar rats, 60 days old, from the Bioterium at Iguaçu University (UNIG) were used. The animals were maintained during the experimental period at a constant temperature of 23 ± 1ºC, under an artificial 12-hour photoperiod, with free access to food and water.

Ethical aspects

All procedures were performed according to the principles of animal experimentation and followed the norms established by the Brazilian Law of Animal Experimentation. Licensing (protocol: PEBIO/UNIG No. 007/2017) from the Ethics Committee on Animal Use (CEUA).

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Diets

The normocaloric diet (ND) consisted of commercial rat diet (Nuvilab®), containing by weight: 19.0% protein, 56.0% carbohydrate, 3.5% lipids, 4.5% cellulose, 5.0% vitamins and minerals, total 17.03kJ/g (6).

The high-fat diet (HD) consisted of a mixture of hypercaloric foods in the following proportions: 15g of standard ration (Nuvilab®), 10g of roasted peanuts, 10g of milk chocolate and 5g of corn starch biscuit. All ingredients were ground, mixed and offered as pellets, containing by weight: 20% protein, 48.0% carbohydrate, 20.0% lipids, 4.0% cellulose, 5.0% vitamins, and minerals. The high-fat diet energy content is 21.40kJ/g (7).

Experimental Groups

The animals were divided into three groups (n = 6). G1 (Control): fed ND during the whole experiment; G2, fed HD between 60 and 120 days of life. G3 fed ND throughout the experiment and with 45 days of life administered 2% alloxan (Alox-Sigma - St. Lous - USA), injected intravenously, at a single dose of 42 mg/kg body weight, using the tail vein (1).

Capillary Blood Glucose Monitoring

Blood glucose monitoring was performed on a 12-hour fast, with blood samples obtained from the animals' tail vein, deposited in glucose test strips and verified in glucose meter (G-TECH) at 60, 90 and 120 days of life. The results were obtained with GraphPad Prism 6.0 for Windows.

Histopathological analysis

For the histopathological study by optical microscopy, fragments of liver lobes were removed in longitudinal portions and fixed in 10% buffered formaldehyde. Subsequently, the samples were embedded in paraffin and sectioned in a rotary microtome using a thickness of 5µm. The sections were stained using the hematoxylin & eosin (HE) technique and the slides were assembled with Canadian balsam.

RESULTS AND DISCUSSION

Blood glucose

We analyzed the glycemia of the experimental groups with 60, 90 and 120 of life. Notably, the glucose levels of the ALX diabetes-induced group remained at the highest levels during the experiment (approximately 400mg/dL). On the other hand, the HD-induced group presented a high level of capillary blood glucose from 90 days of life, reaching about 200mg/dL. The control group kept blood glucose levels lower, less than 100mg/dL. **(Figure 1)**. These results demonstrate that the ALX induction model leads to acute hyperglycemia, while the HD induction model would require a longer induction time to reach similar levels. Diabetes induction in rats by HD administration is demonstrated in other studies, as reported by Carmiel-Haggai 2005 and Oliveira et al 2017; 2018 (6,8,9).

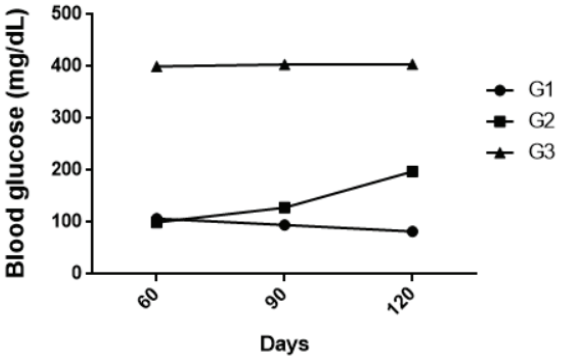

Figure 1: *Evolution of capillary blood glucose. Note the normoglycemic levels in G1 and the increase in blood glucose from 90 days onwards in G2, due to HD intake. In G3 it is observed that a few days after the administration of ALX, the animals became diabetics with high levels of capillary blood glucose (p<0.05).*

Histopathological analysis

Sectioned samples of the liver of animals in the control group (G1) showed hepatic parenchyma with a general preserved structure, hepatic lobules consisting of normal hepatocytes, surrounded by sinusoids containing Kupffer cells, radially distributed towards the centrilobular veins. The portal spaces were also normal (Figure 2 A-B).

About the liver of the animals of the group fed a high-fat diet (G2), we observed the maintenance of liver architecture, sinusoids, and Kupffer cells; however, we observed the formation of mild microvesicular fat degeneration (Figure 2 C-D), without any other abnormality. Such findings are compatible with those observed by da Silva et al 2018, who observed moderate fat degeneration in rats fed a hyper-calorie diet. Steatosis is one of the first liver changes to be observed, not only in non-alcoholic diseases but also in alcohol. The continuity and evolution of this alteration may lead to lesions such as fibrosis and cirrhosis. Carmiel-Haggai (2005) demonstrated similar histopathological alterations in obese rats with the non-alcoholic fat disease, which led to steatohepatitis, with the presence of macroesteatosis extending from the periportal area to the central zone. The non-alcoholic fat disease can lead patients to systemic arterial hypertension, obesity and metabolic syndrome (8,10,11).

Finally, the group of diabetic animals induced by Aloxane (G3) shows disarrangement of liver architecture, with a widening of sinusoids evidenced mainly when observed in the greater increase (Figure 2 E-F). The induction of diabetes by alloxan is a classic and historically used model to study the effects of hyperglycemia on biochemical and histopathological parameters in animals. According to Kerstein et al. (2000), the toxicity of diabetogenic drugs, such as alloxan, follows two phases before the diabetic state itself (12). The first phase occurs soon after their administration, where there is initial hyperglycemia due to adrenergic response, with decreased plasma insulin levels and increased plasma levels of glucagon and cortisol. The decrease in plasma insulin levels was attributed to an intracellular decline in Nicotinamide Adenine Dinucleotide (NAD) levels. The second phase is characterized by hypoglycemia associated with an increase in plasma insulin levels, attributed to the release of insulin by the degeneration of beta cells.

CONCLUSION

This study showed that the experimental models for diabetes induction promoted distinct histopathological changes. We believe that this situation is because the ALX induction model promotes acute changes in liver architecture due to the occurrence of type I DM. On other hands, the hypercaloric diet induction model, remarkably effective in the induction of type II DM, promotes discrete changes in liver architecture, which would occur with longer exposure time to HD, since it is a model that requires chronicity to promote more conspicuous changes.

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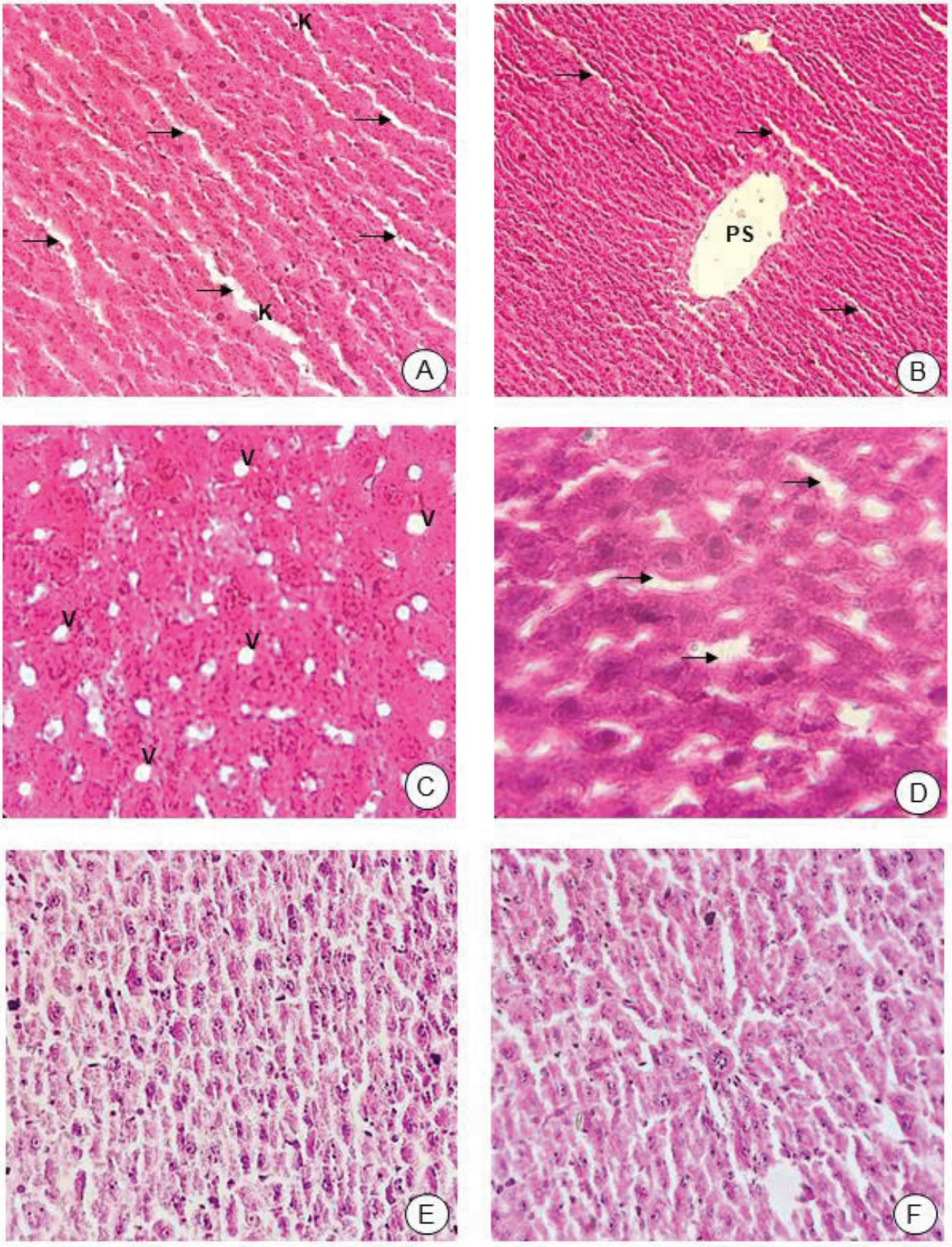

Figure 2. A – B: Histological pattern of liver from control rats (G1) showing normal-appearing of hepatocytes, portal space (PS), sinusoids (arrows) and Kuppfer cells (K). C – D: liver from diabetic rats induced by DH (G1), showing normal-appearing of hepatocytes, but the beginning of sinusoidal enlargement (arrows) and small amount of fatty vacuoles (v). E – F: liver from diabetic rats induced by ALX (G3), disruption of hepatic architecture, showing diffuse microvacuolization.

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TOPICS IN MEDICAL CLINIC

ORIGINAL ARTICLE

RHEUMATOID FACTOR IN SCLERODERMA

FATOR REUMATÓIDE EM ESCLERODERMIA

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THELMA L SKARE**

Key words: Scleroderma; Systemic sclerosis, Autoantiboy, Rheumatoid factor
Descritores: Esclerodermia; Esclerose sistêmica, Auto-anticorpos, Fator reumatoide.

Abstract

Background: Rheumatoid Factor (RF) may be found in patients with scleroderma (Ssc) although its meaning is not completely understood. **Aim:** To study the prevalence of RF in a sample of Brazilian patients with SSc and to compare the clinical and serological profile of positive and negative patients. Material and Methods: retrospective study of 108 patients with SSc from a single rheumatology unit. Clinical, epidemiological and serological data (including presence of RF) were extracted from the charts. **Results:** The prevalence of RF was of 40/108 (37%) in the studied sample. Epidemiological and clinical data was similar in RF positive and RF negative Patients (all with p=ns). Regarding serological profile, SSc patients with anti Scl-70 autoantibody had less RF (OR=8.3; 95% CI=1.04-66.9; p=0.02). **Conclusions:** RF does not influence clinical profile of SSc. Its presence is protector for Scl-70 positivity. **Endocrinol diabetes clin exp 2019 / 2133 - 2136.**

Resumo

Justificativa: O Fator reumatoide (RF) pode ser encontrado em pacientes com esclerodermia (SSC), embora seu significado não seja completamente compreendido. **Objetivo:** Estudar a prevalência de FR em uma amostra de pacientes brasileiros com SSc e comparar o perfil clínico e sorológico de pacientes positivos e negativos. **Material e Métodos:** Estudo retrospectivo de 108 pacientes com SSc de uma única unidade de Reumatologia. Dados clínicos, epidemiológicos e sorológicos (incluindo presença de FR) foram extraídos dos prontuários. Resultados: A prevalência de FR na amostra estudada foi de 40/108 (37%). Os dados epidemiológicos e clínicos foram semelhantes em pacientes com fr positivo e FR negativo (todos com p = ns). Em relação ao perfil sorológico, os pacientes com SSc com autoanticorpos anti Scl-70 apresentaram menos FR (OR = 8,3; 95% IC = 1,04-66.9; p = 0,02). **Conclusões:** A presença de FR não influencia o perfil clínico da SSc. Sua presença é protetora para a positividade de SCL-70. **Endocrinol diabetes clin exp 2019 / 2133 - 2136.**

INTRODUCTION

Rheumatoid factor (RF) is an autoantibody (usually, but not always, IgM) directed against the Fc portion of an IgG, that is the immunoglobulin portion that links to complement or to phagocytes (1). Although this autoantibody is considered the hallmark of rheumatoid arthritis (RA), it can be found in a variety of diseases including infectious diseases, tumors, other connective tissue diseases and even in normal elderly individuals (1). RA patients with RF are considered to have a disease with worse prognosis than those without (1); the meaning of a positive finding in other diseases are not completely understood. In systemic lupus erythematosus (SLE) , RF seems to have a protective role against nephritis (2).

Scleroderma (SSc) patients may also have a positive RF. According to a study by Mimura et al (3) SSc patients may have positivity for IgM RF in 39%, of IgA RF in 23% and IgG RF in 32% of the cases. In this same study, IgM RF was associated with high C reactive protein (CRP) and presence of phalangeal contractures; of IgG RF with digital scars and elevated ESR (erythrocyte sedimentation rate), and of IgA RF with cutaneous telangiectasias, esophageal involvement, pulmonary fibrosis and low vital capacity at spirometry.

No studies were done in the SSc Brazilian population on this context. Herein we aimed to study the prevalence of IgM rheumatoid factor in a sample of SSc patients and its possible association with the epidemiological, clinical and serological profile of this disease.

MATERIAL AND METHODS

This is a retrospective study approved by the local Committee of Ethics in Research. It included all patients seen in a single rheumatology Unit for the period of 5 years that had the search for IgM RF. In our institution RF is measured by latex agglutination test (BioSystems, S. A., Barcelona, Spain) in which a particulate latex suspension coated with human gamma-glubulin agglutinates in the presence of RF in the patient serum. RF values <30UI/ml were considered negative.

Clinical (form of SSc, presence of Raynaud, digital scars, lung involvement, pulmonary hypertension, myocarditis, esophageal dysmotility, microscotomy, degree of skin involvement (measured by Rodnam m or modified Rodnam - index) and disease severity, (measured by Medsger index), epidemiological (age, ethnic background, age at disease onset and sex) and autoantibodies profile (Antinuclear antibodies or ANA, anticentromere and anti Scl-70 or anti topoisomerase) were collected from patients charts.

Rodnan m consists of the addition of the graduation of skin involvement in 17 anatomical sites, graduated in 0 = normal skin; 1 = slight thickening (the skin is thickened, but still manages to be pinched); 2 = moderate thickening (the skin is thickened and it is not possible to paint it, but it is not completely adhered to the deep planes, it may still make a slight slip of the skin); 3 = intense thickening (very thickened skin, not susceptible to being clamped, adhered to deep planes, and cannot be slid) (4). The analyzed sites were: dorsum of the fingers, hands, arms and forearms, face, median region of the thorax and abdomen, thighs, legs and feet

The degree of severity of the disease was assessed by the index of Medsger that evaluates 9 items of systemic involvement are graduated that cover the devices and systems most involved in the SSC: skin, general wellbeing, tendon and articular involvement, gastrointestinal, lung, cardiac, renal, vascular and kidney (5). It goes from zero (mild disease) to 36 (severe disease).

SSc patients were divided in two groups: positive and negative for IgM RF and compared.

Patients with mixed features of SSc with RA were excluded.

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We also excluded individuals with associated chronic inflammatory diseases and/or chronic infections and those with history of neoplasm.

Fisher and chi-squared tests were used to compare nominal data; unpaired t test and Mann Whitney , for nominal data. The adopted significance was of 5%.

RESULTS

We included 108 patients. The clinical and serological profile of studied sample is on **table 1**. In this sample IgM RF was positive in 40/108 (37.0%).

The comparison of clinical and serological features between SSc RF positive and negative is on **table 2**.

Table 1- Description of studied sample: 108 scleroderma patients

Gender	Female – 100/108	92.5%
	Male – 8/108	7.4%
Age (years)	17 a 86	Mean 56.3±14.5
Auto declared ethnic background	Caucasians – 77/108	71.2%
	Asiátics-1/108	0.9%
	Afrodescendants - 30/108	27.7%
Age at disease onset (years)	9-71	Mean 39.1±14.7
Clinical form	Difuse - 25/108	23.1%
	Limited – 64/108	59.2%
	Overlap – 12/108	11.1%
	Sine esclero – 7/108	6.4%
Tobacco exposure	current – 8/108	7.4%
	No– 76/108	70.3%
	Ex- 24/108	22.2%
Rodnam m (skin score)	0-50	Median 14.5 (7.0-20.0)
Medsger index	1 A 19.0	Median 5.0 (3.0-7.0)
Raynaud	95/108	87.9%
Digital scars	47/108	43.5%
Telangiectasias	32/108	29.6%
Microstomy	28/108	25.9%
Esophageal dismotility	41/108	37.9%
Lung fibrosis	31/108	28.7%
Pulmonary Hypertension	30/108	27.7%
Myositis	0	0
Myocarditis	1/108	0.9%
Renal crisis	0	
Arthralgia	14/108	12.9%
Arthralgia	14/108	12.9%
Arthritis	13/108	12.0%
Antinuclear antibody	101/108	93.5%
Anti Ro	18/108	16.6%

Scl 70 (anti topoisomerase)	13/108	12.0%
Anti-centromer	29/108	26.8%

Table 2-Comparison of patients with rheumatoid factor (RF) with those without it.

	Positive RF n=40	Negative RF n=68	P
Gender	Homens -2/40	Homens -6 /68	0.70
	Mulheres -38/40	Mulheres -62/68	
Age (years)	19- 80	17-86	0.92
	Mean 56.5±13.6	Mean 56.2±15.1	
Ethnic background	Caucasians -32/40	Caucasians -45	0.26
	Afrodes cendants-8/40	Asiatics-1	
		Afrodescendants -22	
Age at disease onset	11-68	9-71	0.89
(years)	Mean 39.9±14.1	Mean 39.0±15.1	
Clinical form	Limited -24/40	Limited-41/68	0.58
	Difuse -8/40	Difuse -17/68	
	Overlap -6/40	Overlap -5/68	
	Sine esclero -2/40	Sine esclero -5/68	
Tabacco exposure	Current-3/40	Current 5/68	0.65
	Ex -7/40	Ex- 17/68	
	No -30/40	No -46/68	
Cutaneous score	0-50.0	0-38	0.28
	Median 16.0 (7.0-22.0)	Median 13.5 (6.0-18.0)	
Medsger index	1-11.0	1.0-19.0	0.28
	Median 4.5 (3.0-6.0)	Median 5.0 (3.0-7.0)	
Raynaud	36/40 (90%)	57/68 (83.8%)	0.56
Digital scars	15/40 (37.5%)	32/68 (47.05%)	0.33
Telangiectasias	13/40 (32.5%)	19/68 (27.9%)	0.61
Microstomy	7/40 (17.5%)	21/68 (30.8%)	0.12

Esophageal dysmotility	16/40 (40%)	25/68 (36.7%)	0.73
Lung Fibrosis	9/40 (22.5%)	22/68 (32.2%)	0.27
Pulmonary hypertension	12/40 (30%)	18/68 (26.4%)	0.69
Miocarditis	0	1/68 (1.4%)	-
Arthralgia	3/40 (7.5%)	11/68 (16.1%)	0.24
Arthritis	4/40 (10%)	9/68 (13.2%)	0.76
Antinuclear antibody	38/40 (95%)	63/68 (92.6%)	1.00
Anti-Ro	5/40 (12,5%)	13/68 (19.1%)	0.43
Anti-Scl 70	1/40 (2.5%)	12/68 (17.6%)	0.02 (*)
Anti-centromer	12/40 (30%)	17/68 (25%)	0.57

(*) – OR=8.3 (95% CI=1.04-66.9)

DISCUSSION

Our results have shown that more than 1/3 of SSc patients are positive for IgM RF, reproducing the results of Minura et al. (3) in their 69 SSc patients, and lower than the results of Wieloz et al. (6) that found a positivity in 71% of their 100 patients from Poland. In this last study, IgM RF positive was connected with the presence of arthralgias but not arthritis. However their sample had a very high prevalence of articular symptoms (almost 1/3 of the sample) than the prevalence found in our sample. Another study found an association of musculoskeletal symptoms with double positivity: for rheumatoid factor and for anti CCP (anti-cyclic citrullinated peptide). We did not find any association with articular symptoms but with the presence of anti Scl-70, however we did not studied the presence of anti CCP. The prevalence of RF may differ according to the studied population.as this autoantibody is linked to a genetic predisposition being more common in those with HLA- DR4 (7,8)

Patients with RF in the current study had 8.3 times less chance to have Scl-70 autoantibody. Anti Scl-70 or anti topoisomerase 1 is an autoantibody linked to diffuse and aggressive forms of scleroderma. Anti-Scl-70 directs against a breakdown product of DNA topoisomerase-I, the enzyme responsible for the relaxation of the double DNA helix during the transcription and duplication processes (9,10). Some authors consider its presence highly predictive of scleroderma development in a patient with primary Raynaud (11). A negative relationship of Scl-70 with RF, could mean that RF is present is the last severe forms of diseases. We did not find any association of RF with Medsger index. Nevertheless, this index is time dependent and does not mean that those with mild index at the time of RF search would continue on this way with disease progression.

This work has some limitations: de small number of patients, its transversal design and not studying the form of articular involvement are some of them. However, it shows the prevalence of RF in local population of SSc patients. The exact meaning of its association with SCl-70 deserves further research.

CONCLUSIONS

The prevalence of RF in a Brazilian sample is of 37.0%. In this sample RF was associated negatively with the presence of anti-Scl-70 antibody

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TOPICS IN MEDICAL CLINIC

ORIGINAL ARTICLE

SYSTEMIC LUPUS ERYTHEMATOSUS: A COMPARATIVE ANALYSIS BETWEEN PRE AND POST-MENOPAUSAL DISEASE ONSET.

UMA ANÁLISE COMPARATIVA DO PERFIL CLÍNICO E SOROLÓGICO DO LÚPUS ERITEMATOSO SISTÊMICO DE INÍCIO NA PRÉ E NA PÓS MENOPAUSA.

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Abstract

Background: SLE (Systemic Lupus Erythematosus) is a disease with female predominance. Estrogens are considered to play role in this context. **Aim:** To compare clinical and serological profile of SLE patients with diseases beginning prior or after menopause. **Material and Methods:** Retrospective analysis of 401 females with SLE diagnosis from a single rheumatology center. Data on clinical and serological profile were collected from the charts and patients were divided in two groups: (1)- disease beginning prior to menopause and (2)- after to menopause. and compared. **Results:** The only differences found in the clinical profile were on alopecia (p= 0.0005; OR=3.5; 95%CI=1.6-7.4) that was more common in the pre-menopausal women and thrombosis that were more commons in the post-menopausal period (p=0.0003;OR= 5.3; 95%CI=1.9-14.1). No differences were found in the serological profile. **Conclusions:** SLE beginning in the pre and post menopause have similar clinical and serological profile except for alopecia e and prevalence of thrombosis. **Endocrinol diabetes clin exp 2019 / 2137 - 2140.**

Resumo

Justificativa: LES (lúpus eritematoso sistêmico) é uma doença com predominância em mulheres. Os estrogênios parecem desempenhar papel importante neste contexto. **Objetivo:** Comparar o perfil clínico e sorológico de pacientes com LES com doença de início antes e depois da menopausa. **Material e Métodos:** Análise retrospectiva de 401 mulheres com diagnóstico de LES de um único centro de Reumatologia. Os dados sobre o perfil clínico e sorológico foram coletados dos prontuários e as pacientes foram divididas em dois grupos: (1)-doença iniciada antes da menopausa e (2)- doença iniciada após a menopausa . Os dois grupos foram comparados. **Resultados:** As únicas diferenças encontradas no perfil clinico foram na alopecia (p = 0, 5; OR = 3,5; 95%IC= 1,6-7,4) que foi mais comum na pré-menopausa e prevalência de trombose que foi mais comuns no período pós-menopausa (p = 0.0003; OR = 5,3; 95%IC = 1,9-14,1). Não foram encontradas diferenças no perfil sorológico.**Conclusões:** LES com início na pré e na pós-menopausa têm perfil clínico e sorológico semelhantes, exceto pela ocorrência de alopecia e prevalência de trombose. **Endocrinol diabetes clin exp 2019 / 2137 - 2140.**

INTRODUCTION

Estrogens are considered to be important in the pathophysiology of systemic lupus erythematosus (SLE) (1). This may explain the preference of this disease for females. According to certain studies, SLE has shown to be 10 times more common in women than in men (1). There is also same data that suggest that this disease has higher prevalence around menarche, in pregnant women and in those receiving exogenous estrogens (2).

The female hormones are implicated in the prevalence and occurrence of flares of this disease (2); however, it is unknown if they may influence its phenotype. Differences in clinical profile has been noted between man and women (3) but few studied addresses to the possibility that this disease may show differences if it begins after menopause.

In this study we aimed to know if the SLE clinical and serological profile differ in disease that begins prior to or after menopause.

MATERIAL AND METHODS

This is a retrospective study that was approved by the local committee of Ethics in Research. Charts of females with SLE that came for regular consultations during a 10 year period in a single rheumatology unit were reviewed. Patients with disease onset prior to 16 years were excluded. Epidemiological (age, gender, age at disease onset, auto declared ethnic background and tobacco use, age of menarche and menopause), clinical (malar rash, photosensitivity, oral ulcers, discoid lesions, serositis, glomerulonephritis, convulsions, psychosis, hemolytic anemia, leukopenia, lymphocytopenia and arthritis according to the definition of 1997 ACR classification criteria for SLE (4) and considered in a cumulative way) and serological data [anti-dsDNA (or anti-double stranded DNA), anti-Ro/SS-A (or Syndrome de Sjogren antigen A); anti-La/SS-B (or Syndrome de Sjogren antigen B), anti-RNP (or anti-ribonucleoprotein), anti-Sm (or anti-Smith), aCl (anticardiolipin) IgG, aCl IgM, LA (or lupus anticoagulant), rheumatoid factor and direct Coombs] were extracted from the charts. At our institution anti Ro/SS-A, anti La/SS-B, anti RNP, anti Sm, aCl IgG, aCl IgM were done by ELISA (using ALKA and Orgentec Kits®), anti-dsDNA is done by immunofluorescence technique (IFT) using Crithidia luciliae as a substrate. Lupus anticoagulant is searched through a screening test, the dRVVT (dilute Russell viper venom test),

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and mixing patient's plasma with normal plasma and confirmed by RVVT. The direct Coombs were performed using monoclonal anti human globulin Fresenius-Kabi-Brasil®. APS (antiphospholipid antibody syndrome) was diagnosed according to 2006 modified APS criteria (5). Females were divided in two groups according disease beginning prior to or after menopause and the two groups were compared.

Obtained data was analyzed trough frequency and contingency tables. The Shapiro Wilk test was used to judge data distribution. Central tendency was expressed in media and standard deviation or median and interquartile rate (IQR). Fisher and chi squared tests were used to compare nominal data and unpaired t test and Mann Whitney to compare numerical data. The adopted significance was of 5 %.

RESULTS

The studied sample had 401 females: 360 (89.7%) with disease onset prior to menopause and 41 (10.2%) pos menopause with a relation of 8.7 to 1. In the post menopause group, this had occurred at mean age of 44.6±6.2 years.

The comparison of clinical data in these two groups in on **Table 1**. On this table is possible to observe that alopecia was more common in the pre-menopause group while thrombosis is more common in the post-menopause group.

Table 2 - shows the comparison of autoantibody profile displaying that both groups are similar on this aspect.

Table 1- Comparison of clinical data in a sample of systemic lupus patients with disease onset prior and after menopause.

	Total n=401	Pre-menopause n=360	Post-menopause n=41	p
Median age of onset (IQR)	31.0 (24-39)	30 (24.0-37.0)	50 (46.0-57.0)	< 0.0001
Menarche (mean age)	12.8±1.59	12.8±1.5	12.8±1.7	0.99
Ethnic background (afro vs euro)	138/353	121/299-40.4	17/37 – 45.9	0.20
Tobacco exposition	129/376	121/348- 34.7%	18/38 – 47.3%	0.50
Discoid rash	50/373	43/343-12.5%	7/40- 17.5%	0.42
By rash	207/380	190/341-55.6%	17/39-43.5%	0.17
Photossensitivity	290/385	262/347-75.5%	28/38-73.6%	0.80
Raynaud	187/376	172/339-50.7%	15/37 -40.5%	0.23
Oral ulcers	174/377	161/339- 47.4%	13/38 – 34.2%	0.11
Alopecia	202/350	191/314-60.2%	11/36-30.5%	0.0005 OR=3.5 (95%CI=1.6-7.4)
Articular involvement	311/394	279/354-78.8%	32/40 – 80%	0.86
AVC	17/298	15/269- 5.5%	2/29- 6.8%	0.67
Psychosis	18/374	16/345-4.6%	2/39- 5.1%	0.64
Convulsions		34/345-9.8%	2/33-6.0%	0.75
Serositis	80/384	69/344-20.0%	11/40- 27.5%	0.27
Hemolysis	44/417	40/347-11.5%	4/40-10%	1.00
Leukopenia	98/385	90/347-25.9%	8/38-21.0%	0.51
Limphopenia	61/381	59/342-17.2%	2/39- 5.1%	0.06
Thrombocytopenia	86/383	76/344-22.0%	10/39-25.6%	0.61
Glomerulonephritis	142/385	129/345- 37.3%	13/40- 32.5%	0.60
Thrombosis	52/354	44/336-13.0%	8/38-21.0%	0.0003 OR= 5.3 (95%CI=1.9-14.1)
Antiphospholipid antibody syndrome	31/337	27/304-11.7%	4/33-12.1%	0.52
Secondary Sjogren	23/97	20/90-22.2%	3/7 – 42.8%	0.35

Table 2; Comparison of serological profile between systemic lupus erythematosus patients with disease onset prior and after menopause.

	Total n=401	Pre-menopause n=360	Post- menopause n=41	P
Anti- Ro	156/368	144/330-43.6%	12/38 -31.5%	0.15
Anti-La	77/369	73/331-22.0%	4/38-10.5%	0.13
Rheumatoid fator	90/361	81/322-25.1%	9/39-23.0%	0.77
Anti-Sm	91/345	84/311- 27.0%	7/34-20.5%	0.41
Anti-Ds DNA	134/374	124/335-37.0%	10/39- 25.6%	0.16
Anti- RNP	197/341	99/304 – 32.5%	8/37 – 21.6%	0.17
Acl IgG	53/375	51/336- 15.1%	2/38-5.2%	0.14
Acl IgM	48/373	45/335-13.4%	3/38-7.8%	0.44
Lupus anticoagulante	42/351	37/314- 11.7%	5/37 – 13.5%	0.78
Direct Coombs	48/325	42/291-14.4%	6/34-17.6%	0.61

DISCUSSION

Although the prevalence of SLE in the post menopause period, according to this study, is much lower than in the pre menopause, with almost 1/9 ratio, our results showed few difference between SLE clinical profile in these two group. Only the prevalence of alopecia and thrombosis were different. Curiously, alopecia is a clinical finding that is more common in females than males showing the influence of sex hormones in the presence of this clinical finding (6). The paucity of differences found may be explained by the fact that estrogens may be important to regulate the intensity of the disease but does not modulate disease's clinical expression. This explanation is consistent with the finding that estrogens, in particular 17-β estradiol (E2) and prolactin act as enhancers of humoral immunity, while testosterone and progesterone as natural immunosuppressants (7). Changes in the severity of autoimmune diseases are observed during pregnancy, when estrogens and progesterone reach the highest levels (7). It is also well known that estrogens promote the escalation of the Th2 immune response, aggravating Th2-dominant disorders such as SLE (8). Experimental studies by Xue et al. (9) has demonstrated that estrogens induce expression of tumor necrosis factor-like weak inducer of apoptosis (TWEAK) accelerating the progression of lupus nephritis.

However, estrogens are not the only players in the female predominance in autoimmune diseases such as lupus. The presence of two X chromosomes in females versus one X and one Y chromosome in males, diverse response to ambiental influences, such as microbial exposure and diet are other explanations (10). The female karyotype has two X chromosomes. To avoid double quantity of X chromosome-derived proteins, one of the X chromosomes is silenced in the early phases of embryogenesis. Nevertheless, X chromosome inactivation is not complete and about 15% of the genes escape from this inactivation, causing overexpression of some X-linked genes (10). Several genes linked to immune regulations are encoded in X chromosome such as CD40 ligand, chemokine receptor CXCR3, O linked N-acetylglucosamine transferase, forkhead box P3(FOXP3), toll-like receptor (TLR)7, TLR8, IL-2 receptor gamma, tyrosine-protein kinase BTK, and IL-9 receptor (6). This may explain the SLE predominance in females independently of estrogen effect. Patients with Turner syndrome (karyotype XO) or Klinnefelter (karyotype XXY) have altered predisposition for SLE (10). MicroRNAs (miRNAs) or short non-coding RNAs that regulate gene expression mainly at the post-transcriptional level may also play a role in these context. The X chromosome is very rich in miRNAs whereas only two miRNAs, at least in humans have been found in the Y chromosome (7). However, the exact meaning of this finding is not clear.

Differences in diet and microbiome are other explanations (10): Animal studies have shown that that gut microbiome has influence in the appearance of autoimmune diseases such as type 1 diabetes (11). Structure of gut microbiota in mouse models of lupus has been found to be diverse in female and male adult mice (12,13).

It is possible that genetic factors and the role of microbiome in SLE may not suffer influence of estrogens levels in the menopause period explaining the paucity of differences found in this work. On the other side it is known that other genes – not associated with gender - may be responsible for differences in the clinical profile (14).

Unluckily, we did not study the severity of the SLE according to the period that the disease starts to know the influence of estrogens on this aspect of the disease. This is a limitation of the present study and a suggestion for future researches.

CONCLUSION

The present study failed to show major differences in SLE clinical and serological profile according to the period of disease onset: pre and pos menopause. Alopecia and the prevalence of thrombosis were the only verified discrepancies.

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