ISSN 1517-6932
ISSN ON LINE 2447-181X

ENDOCRINOLOGIA & DIABETES CLÍNICA E EXPERIMENTAL

HOSPITAL UNIVERSITÁRIO EVANGÉLICO DE CURITIBA
FACULDADE EVANGÉLICA DO PARANÁ

VOL. 17 - NUMBER 2 MAY/JUNE/JULY/AUGUST/2018

EDITORIAL

THE SPRING : THE GOOD SEASON OR PRIMO VERE

In the beginning the seasons of the year were divided in two: one, was the good with nice wheather, sun and flowers and other called *hiems* or *hibernus* the bad season with a lot of rain and very cold.

In the XVI century five seasons of the year was adopted by the Spanish people they were called Spring, Summer, *Estio*, Autumn and Winter. In the beginning of XVII century the seasons were named as we know. At the spring or equinox, the days and nights have approximately twelve hours long, with day length increasing and night length decreasing as the season progressesIn the north hemisphere, the Swedish meteorologists define the beginning of spring when average of day time temperature exceeds zero degrees Celsius for seven consecutive days. Subartics areas do not have spring. In Spring there are more longer cycles or events created by the ocean currents and temperatures like *El Ninõ*. Flooding happens often near the snow covered mountains, because the snow-melt is accelerated by the warm rains. Tornadoes and thunderstorms are commons in Spring. It is a gap between the winter and the summer in our South Hemisphere when the Earth's angle tilt toward the sun.

The equinoxes are the time when the edge between night and day, called solar terminator is perpendicular to the equator, so the northern and southern hemispheres are equally iluminated. Equinox comes from latin *aequus* (equal) and nox (night). Equinoxes and solstices are related with seasons of the year. Some people consider that Spring starts the new year as in Hindu and Persian calendar. The equinoxes occured every year in the same month. In north the equinox happens in March when the sun crosses the equator from South to north and in South in September when the sun crosses the equator from north to South. The equinox happens in other planets with a tilted rotational axis. Mars has it equinox in May 22, 2018.

Editors from **Endocrinologia & Diabetes: Clinica e Experimental** invite all of our readers to celebrate flowers, to celebrate sun, to celebrate life!

It is Spring time!

Enjoy it!

References

United States Naval Observatory 2018

Sunrise and Sunset 2002

Wikipedia. Org 2018

Google 2018

Contents

Our Cover: It is Spring time! Enjoy it!
Source: Google.com

Endocrinol. diabetes clín. exp. - VOL.XVII - NUM. 2

Endocrinology & Diabetes - Clinical and Experimental is a journal of open access that publishes case reports, original article, reviews with new insights in pathogenesis, physiology and metabolism of hormone secretion, cellular mechanisms and tissue action. This journal belongs to the Discipline of Endocrinology and Metabolism of Faculdade Evangélica do Paraná and Service of Endocrinology and Diabetes - Diabetes Unit - Hospital Universitário Evangélico de Curitiba - Paraná - Brazil

Endocrinologia & Diabetes Clínica e Experimental
Disciplina de Endocrinologia e Metabologia da Faculdade Evangélica do Paraná, Serviço de Endocrinologia e Diabetes do Hospital Universitário Evangélico de Curitiba. – v.17, nº 2 (Maio, Junho, Julho, Agosto/2018) – Curitiba:
FEPAR/HUEC, 2000-
p.2041 - 2058: il.; 29cm

Quadrimestral
ISSN 1517-6932
ISSN on line 2447-181X

1.Endocrinologia – Periódicos. 2. Saúde – Periódicos. I. Faculdade Evangélica do Paraná. II. Hospital Universitário Evangélico de Curitiba.

CDD 616.4
CDU 612.34

ORIGINAL ARTICLE
ASSOCIATION BETWEEN HYPOTHYROIDISM AND TYPE 2 DIABETES MELLITUS: A STUDY IN 100 PATIENTS AND REVIEW OF LITERATURE

ASSOCIAÇÃO ENTRE HIPOTIREOIDISMO E DIABETES MELLITUS TIPO 2 : UM ESTUDO COM 100 PACIENTES E REVISÃO DA LITERATURA

FERNANDA SENECHAL DUARTE1
LUIS EDUARDO BORGES DE MACEDO ZUBKO1
MIRNALUCI PAULINO RIBEIRO GAMA2
THELMA LAROCCA SKARE3

Keywords: Type 2 Diabetes, Hypothyroidism, Thyroid Function, Insulin resistance, Thyroid Function and Diabetes.
Descritores: Diabetes Mellitus tipo 2, Hipotireoidismo, Função tireoidiana, Resistência à insulina, Função da tireoide e diabetes.

Abstract

Background: The association between hypothyroidism and type 1 diabetes mellitus (DM) is well known. Studies on this association with type 2 DM are scarse. **Objective:** To establish the relationship between hypothyroidism, pre-diabetes and type 2 DM, through the analysis TSH, free T4, fasting glycaemia and glycated hemoglobin. **Methods:** We reviewed 100 medical records of the Endocrinology Service of the Hospital Evangélico de Curitiba, in the form of retrospective cohort study, with analysis of laboratory data for fasting glucose, HbA1c and thyroid function tests the period of five consecutive appoitments. The results were classified according to the TSH and free T4 quartiles and to their reference values described in the literature. **Results:** There was a significant relationship between the lowest interval in the reference range of TSH (< 0,5 mU/L) and pre-diabetes (OR=2,05; 95% IC= 1,23 to 3,40; p = 0,005). When comparing to stablished type 2 DM, the same was not found.**Conclusions:** The intensive control of hypothyroidism may leave the patient at risk for T2D. **Endocrinol diabetes clin exp 2018 2045 - 2049.**

Resumo

A associação de hipotireoidismo com Diabetes mellitus (DM) tipo 1 é bem reconhecida. Poucos estudos existem quandose trata da associação com DM tipo 2. **Objetivo:** Estabelecer a relação entre hipotireoidismo, pré-diabetes e Diabetes Mellitus tipo 2 (T2D), através da análise de dados laboratoriais, como valor do TSH, T4 livre, glicemia de jejum e hemoglobina glicada. **Método:** Avaliação de 100 pacientes do ambulatório de Endocrinologia do Hospital Universitário Evangélico de Curitiba, na forma de coorte retrospectiva, com análise dos valores laboratoriais de valores glicêmicos, HbA1c e teste de função e tireoide por um período de 5 consultas. Estratificando por quartil de TSH e T4 livre e suas faixas de referência contempladas na literatura (TSH 0,5 a 4,5 e T4 0,7 a 1,8). **Resultados:** Há relação significativa entre o menor intervalo da faixa de referência do TSH (< 0,5 mU/L) e o desenvolvimento de pré-diabetes (RR 2,05; 95% IC; 1,23 – 3,40; p = 0,005). O mesmo não foi encontrado em relação à T2D. **Conclusões:** O controle intensivo do hipotireoidismo é capaz de aumentar o risco de T2D. **Endocrinol diabetes clin exp 2018 2045 - 2049.**

INTRODUCTION

Among all thyroid diseases, the hypothyroidism has , currently, important prevalence. The type 2 Diabetes (T2D) also fits within the most common chronic diseases of the world. The increase in the prevalence of these two diseases can lead to their concomitance in a single patient raising their morbidity (1).

There are several studies comparing the connections between these two diseases, mainly between hypothyroidism and type 1 Diabetes (T1D). The T2D reviews are scarce and contradictory when concerning relevance and frequency (1). To known the consequences of these associations is relevant because blood levels of thyroid hormones and TSH may interfer with the metabolic alterations present in Diabetes. So, changes in the thyroid function compromises the glycemic control (1).

Therefore, the present study aims to contribute to the study of the association between autoimmune hypothyroidism and T2D, since the results of these endocrinopathies are still scarce and discordant. We also present an extensive review the literature in the association of DM and thyroid disease.

LITERATURE REVIEW

Hypothyroidism is a metabolic disease diagnosed when reduced the thyroid hormones (T3 and T4) and increased the thyroid stimulating hormone (TSH) are found . It presents itself in two different ways. The primary form that is caused by the destructive autoimmune process or drugs and/or damage resulted from radiation (2). Secondary hypothyroidism, in turn, arises from a disorder in the production or secretion of the TSH or the release of TRH in the hypothalamus. There is also the subclinical hypothyroidism, which is diagnosed by the increased concentration of TSH, without the reduction of the T3 and T4 levels (2). In USA, the primary form of the disease presents itself in 4,6% of the population, while the positivity of anti-peroxidase antibodies (anti-TPO), without the presence of clinical hypothyroidism or subclinical, reaches 13%. Thus, the autoimmune shown is most common (3). The incidence of subclinical hypothyroidism ranges from 4 to 10%, more commonly seen in women, caucasians and residents of regions with iodine deficiency, with progressive increase of prevalence as age advances (4).

The clinical presentation is highly variable due to the great performance of thyroid hormones (TH) in the cellular metabolism. We can observe symptoms and clinical signs, linking them the positive predictive value (PPV+) in the following order: bradycardia (PPV+ = 3,88), lentified ankle reflex (PPV+ = 3,4), obstipation (TP+ = 3,6), thick and dry skin (PPV+ = 2,3), eyelids oedema (PPV+ = 4,0), pretibial oedema (PPV+ = 1,13), increased sensibility to cold (PPV+ = 3,5), slow motion (PPV+

[1]Faculdade Evangélica do Paraná (FEPAR) - Curitiba PR - Brazil
[2]Discipline of Endocrinology at Faculdade Evangélica do Paraná (FEPAR) - Curitiba PR - Brazil
[3]Discipline of Rheumatology at Faculdade Evangélica do Paraná (FEPAR) - Curitiba PR - Brazil
E-mail: fer.s.duarte@hotmail.com and luis_borges_44@hotmail.com

= 1), memory disturbance (PPV+ = 2,6), hoarseness (PPV+ = 5,2) and thicker voice (PPV+ = 7,1), (1).

Thyroid ultrasonography (US) is widely used as an assistance method to diagnose the disease. It can show decreased echogenicity in clinical and subclinical hypothyroidism. Hypoechoic lesions and thyroid US with irregular patterns were significantly associated with higher levels of TSH, even in individuals without evident thyroid disease, suggesting a possible use of thyroid US to early detection and subclinical thyroid disease. In a study, the PPV+ value of thyroid echogenicity reduction as an indicator of autoimmune thyroiditis, was of 88,3%, while the negative predictive value of this finding was 93%. Thyroid US can also be useful to identify patients with subclinical hypothyroidism with a higher risk of developing hypothyroidism, especially when evaluated in the presence of positive anti-TPO(1). As a valuable instrument, it was included in our study.

T1D is an autoimmune syndrome that destroys the pancreatic beta cells, causing insulin secretion insufficiency. It has an acute presentation and is often diagnosed as diabetic ketoacidosis (2).

The T2D is the predominant form of diabetes, accounting for 90% of global cases. The overall prevalence of this disease for 2033 is 11,1%, affecting 600 million people (2). It is diagnosed through fasting blood glucose and glycated hemoglobin elevated degree. The pathogenesis is founded by three mainstays: (1)- insulin resistance in peripheral tissues, liver, muscle and adipose tissue; (2)- decreased insulin secretion, particularly in response to glucose stimulation; (3)- increased glucose production by the liver, and decreased insulin production. Puberty, pregnancy, sedentary lifestyle and excessive dietary intake leading to weight gain are some of the main factors that impose a secretory burden on the pancreatic beta cell. It is important to emphasize that there is also the predisposing genetic factor; however it is responsible for less than 10% of the risk (2). The insulin resistance manifests as a reduction in glucose transport and metabolism, stimulated by insulin in adipocytes and skeletal muscle and for compromised suppression of hepatic glucose debit (2).

Insulin resistance, rises as the fat tissue increases. However, the adiposity most associated with insulin resistance and cardiovascular morbidity is the visceral central one. This risk is increased when associated to other independents factors, such as smoking, elevated LDL cholesterol and sedentarism (2).

The clinical presentation is heterogeneous,: the age of beginning varies widely as well as the severity of hyperglycemia and the degree of associated obesity. Common findings include blurred vision, infections and nocturia. However, many patients remain asymptomatic until they present target organ damage (2).

Organ damage results from macro or micro angiopathic damage, with endothelial dysfunction predisposing to atherosclerosis. The mechanisms of endothelial damage that occur in diabetes disease are beyond this study's area of discussion (2).

Thyroid hormone is a great metabolism and energy expenditure modulator and it is directly related to insulin secretion and glucose homeostasis. Patients with hypothyroidism have increased insulin secretion; high levels of free T3 are related to a better performance on insulin secretion in prediabetic people (5). However, the excess of T3 and T4 are associated to increased hepatic gluconeogenesis, increased peripheral resistance to insulin and glucose intolerance (5). Paradoxically, the reduction of thyroid hormone is also related to reduced peripheral insulin sensibility and glucose intolerance. Once corrected the thyroid dysfunction, the glucose balance returns to its physiological state (5).

In the literature, the association between hypothyroidism and insulin dependent diabetes mellitus is clear, mainly to Hashimoto's thyroiditis, as both present autoimmune characteristics (6). Patients with T1D and elevated TSH levels have shown elevation of microsomal thyroid antibody titre in 85-88% of cases. If the patient does not have elevate TSH, this prevalence falls to 19% (7).

The genetic relationhip of T1D is linked to the HLA locus types, the DR-2 form being the main one, whereas the DR-3 form is described only in Caucasians and Afrodescendents. In the case of hypothyroidism there is an association accordingly to the form. If it is hypertrophy with palpable goitre and increased antibody titer, it associates with HLA DR-5. If the patient is Caucasian and shows thyroiditis (atrophic or with goitre), there is correlation with HLA DR-3 (7).

Some physiopathological hypotheses about the relation between DM and hypothyroidism have recently been described. They involve mostly genetic, inflammatory and metabolic mechanisms.

Autoimmune hypothyroidism and T2D can have common genetic background. One link is the polymorphism of the deiodinase type 2 gene, whose functions are to transform T4 into T3 and maintain the intracellular levels of T3. The intracellular thyroid hormones positively modulate GLUT4, so when there is insufficiency, there is a lower glucose absortion by muscles. When the substitution from threonine to alanine in codon 92 occurs, there is a reduction of 20% of glucose uptake by the muscle. If this mutation is homozygous, the insulin resistance is even higher (8,9).

Recently, it was identified a protein tyrosine phosphatase non-receptor type 22 gene (PTPN22) that has association with autoimmune hypothyroidism and T2D. The product of this gene is a protein with strong activation of the suppressor of T lymphocytes proliferation. There are two physiopathological hypothesis linked to this genetic polymorphism. The first one is that T lymphocytes suppression reduces its signals, allowing self-reactive lymphocytes in the thymus to be released. The second is that this intense suppression can affect predominantly lymphocytes that protect from autoimmune diseases (10,9).

Another gene that acts in a similar way to PTPN22 is the CTLA4, which inhibits the secondary immune synapse, inhibiting the link of costimulatory signals between CD28 and B7. This gene mutation is encountered in T2D and Hashimoto's hypothyroidism (11,12).

Lymphocytes and macrophages activated during inflammation promote the release of proinflammatory cytokines, including IL-1β and TNF-α. The increase of these cytokines can activate Fas receptors and trigger apoptotic processes leading to thyroid and pancreatic tissues death (12-14).

The association between T1D , thyroiditis and adrenal autoimmune disease is part of type 2 polyglandular autoimmune syndrome or Schmidt Syndrome. The diagnose is given by symptomatic hypotension, presence of hyperpigmentation/ vitiligo, fatigue and severe intermittent hypoglycemia, the last one being prevalent among children with Addison's disease. When the patient has Addison's disease or diabetes mellitus, he has a high risk (about 3050 times higher), to develop another autoimmune disease that is also part of this syndrome. However, when we evaluate this risk on patients that have hypothyroidism appearance first, the risk of developing another diseases is much more uncommon (15).

An observational study showed a prevalence of thyroid dysfunction in 10,8% of the diabetic population. The benefits of thyroid dysfunction treatment include improvement on lipid profile, prevention of atrial fibrillation, osteoporosis and higher glycemic control (6).

An interesting relation found in a recent meta-analysis demonstrated elevated TSH levels, above maximum reference value, associated with higher risk of the development of diabetes complications, and higher prevalence of subclinical hypothyroidism in T2D. The adjusted odds ratio comparing subclinical hypothyroidism in type 2 diabetics and non-diabetics was of 1.93 (95% CI, 1.66 – 2.24). Subclinical hypothyroidism

increased the development of diabetic complications in general (OR 1.74, 95% CI, 1.35 – 2.54). Diabetic nephropathy also confirmed significate association with subclinical hypothyroidism (OR 1.74, 95% CI, 1.34 – 2.28). Regarding diabetic retinopathy, there was a significant relation with subclinical hypothyroidism (OR 1,42; 95% CI, 1,21 – 1,67). Observing correlation with coronary artery disease, there was not statistical significance (OR 1.59, 95% CI, 0.92 – 2.76). Analyzing association between peripheral arterial disease and subclinical hypothyroidism, there was statistical significance (OR 1.85, 95% CI, 1.35 – 2.54). About diabetic peripheral neuropathy, there was a significant connection with subclinical hypothyroidism (OR 1.87, 95% CI, 1.06 – 3.28). Among the population, clinical hypothyroidism is more prevalent in diabetics than in healthy people. There is an hypothesis that the these results were due to hyperinsulinemia and could influence the release of TRH, TSH and the leptin pathway, which is higher in diabetics, which in its turn can stimulate TSH synthesis. Therefore, increased TSH value may have a mixed nature, relating, in this case, to the leptin pathway mechanism (16).

There are some cross-sectional and some prospective studies analyzing the correlation between thyroid dysfunction and diabetes, with controversial results (17,18). Recently, another cohort work investigated the thyroid function and the risk of development and progression of diabetes with an average duration of 7.9 years. With an adjusted model to age, smoking and other confounding factors were studied with the reference range of TSH (0,4 – 4,0 UI/L) and free T4 (11 – 25 pmol/L ou 0.86 – 1,94 ng/dL). First, it demonstrated that higher levels of TSH, within the reference range near the limit of the veracity of the study, in both normoglycemic and patients with prediabetes, had a significant risk of development or progression of diabetes. Higher free T4 levels, within normal range, were associated to a protective effect against diabetes in both healthy and subjects with prediabetes. It was found that doubling TSH , healthy and patients with prediabetes had a significantly higher risk of developing diabetes mellitus (HR=1,09; 95% CI=1,06 to 1,12 and HR = 1,13; 95% CI= 1,03 to 1,24, respectively). The most interesting fact was that, when analyzing TSH tertiles within the reference range of patients with prediabetes, the highest tertile had a 44% (95% CI= 1,13 to 1,93) risk of developing diabetes compared to the lowest tertile, while in normoglycemic subjects this risk was slightly lower (HR = 1.14; 95% CI= 1,02 to 1,27). Regarding prediabetes patients, free T4 tertiles had an inverse effect, comparing the highest and lowest tertile, the diabetes progression risk was 37% lower (95% CI= 0,48 to 0,82). Adjusting the results with anti-TPO positivity, there was not any significate alterations of the results (18).

Disparately, the HUNT research among the population of Norway, with 34235 participants, also evaluated the relation between thyroid dysfunction and diabetes. There was a significant association between treated hypothyroidism and autoimmune diabetes, but only with the treated form of the disease. No association between hypothyroidism and autoimmune diabetes was found. Likewise, there was no significant correlation between the prevalence of hypothyroidism in population with T2D, when adjusted for age, smoking and patients with elevated body mass index. Regarding anti-TPO, there was a significant association of its positivity in autoimmune diabetic men (OR=3,00; 95% CI=1,54 to 5,85), but not in women. The relationship between T2D and the anti-TPO status was not presented (19).

Study with 15 female patients who underwent thyroidectomy for thyroid carcinoma the hypothyroidism was significantly associated to a basal insulin reduction, it was not observed different values of fasting serum insulin before and after the hormonal reposition therapy. The fasting glycaemia was significantly smaller on hypothyroidism state than after hormonal reposition therapy. This last one may be explained by the decrease of hepatic glucose production in hypothyroidism (20).

The association between T2D and hypothyroidism is a controversial issue and there is much room for debate and future clarification shoud take into account other factors such as smoking, age, statins use and others.

MATERIAL AND METHODS

This is a longitudinal retrospective cohort study. The study consists in the analysis corresponding to five medical appointments of 320 patient records of the endocrinology service of the Hospital Universitário Evangélico de Curitiba. This study was approved by the local Committee of Ethics in Research The sample size was determined with the use of logistic regression, using G*Power 3 software, with significant statistical power The significant statistical power of the study was 80%, while the statistical significance was <0.05.

It was evaluated: TSH serum concentration, anti-thyroid peroxidase antibody, fasting glycaemia, glycated hemoglobin. The TSH in our institution is measured by chemiluminescence method; the reference interval is between 0,5 – 4,5 mU/L. The free T4 was measured by chemiluminescence method, whose reference interval is between 0,7 – 1,8 ng/dL (9-23 pmo/L). The anti-thyroid peroxidase antibody (TPOab) was considered positive when value is > 35 UI/mL, using the chemiluminescence laboratory method. The fasting glycemia was evaluated by glucose oxidase ; the reference interval of 70 – 99 mg/dL. The glycated hemoglobin had reference interval of 4,8% - 5,7% and its measurement was made by high performance liquid chromatography. Epidemiological data (such as gender, age, time of hypothyroidism, previous or current history of smoking), use of medications, thyroid ultrasonography results , presence or absence of systemic arterial hypertension, statin use, and family history of thyroid disease, diabetes mellitus, and thyroid cancer was collected .

Patients with TSH > 4,5 mU/L and free T4 < 1,8 ng/dL (23 pmol/L), or the ones that use levothyroxine were diagnosed with hypothyroidism (1). Normoglycemics, impaired fasting glycemia (prediabetes) and T2D were determined by the American Diabetes Association criteria (21). They are: Normoglycemia is defined by fasting glycaemia < 100 mg/dL (< 6.0 mmol/L) or glycated hemoglobin < 5.7%. Impaired fasting glycaemia ≥ 100 mg/dL and ≤ 125 mg/dL (> 6.0 mmol/L and < 7.0 mmol/L) or glycated hemoglobin ≥ 5,7% and ≤ 6,4%, and diagnosis of diabetes by glycated hemoglobin measurements ≥ 6,5%, or two exams with positive values to diabetes (fasting glycemia or ≥126mg/dl) or use of metformin.

Laboratorial data (TSH, free T4, HbA1c, fasting serum) and clinical data were collected in tables and followed for five consults.

Patients were divided into quartiles of TSH and free T4, with the analysis of the highest (RR1) and the lowest (RR2) quartile in relation to the others, determining their relative risks of developing T2D2, or prediabetes, or even the progression from prediabetes to T2D2. Then, the Data was coillected in tables using Excel program and patients who developed Type 2 diabetes or prediabetes were compared during the study period, determining relative risk, using a 95% confidence interval with the statistical tests X^2 (chi-square) and Mann-Whitney. Continuous variables were expressed as mean ± standard deviation and analyzed statistically. All patients with missing data were excluded from the analysis.

The results were compaired with the information obtained from the literature review. We searched the following databases: Pubmed, Scielo and New England Journal of Medicine using the keywords "Type 2 Diabetes Mellitus and Hypothyroidism" “Type 2 Diabetes and Hypothyroidism", Auto Immune Type 2 Diabetes", "Hypothyroidism and Type 2 Diabetes", "Thyroid Function", "Insulin Resistance", "Thyroid Function and Diabetes" and other articles found in the referrals of the researched. In the elaboration of this study, the STROBE criteria of cohort

study were used.

Inclusion citeria: Were included patients with at least 18 years of age, diagnosed with hypothyroidism, confirmed through laboratorial exams and/or clinical reportssame analysis was performed, this time dividing the groups accordingly to the reference intervals proposed by the practical clinical guideline for the handling of hypothyroidism (TSH: 0,5 – 4,5; free T4: 0,7 – 1,8) (1).

Exclusion criteria: Patients under 18 years, with T1D, hypothyroidism and diabetes on first consult, liver disease, pregnant women, hypothyroidism after surgery, hypothyroidism post-radiation with I131, thyroid cancer, HIV, those who used corticoid, amiodarone, phenytoin, carbamazepine, furosemide, lithium carbonate, interferon alpha, and those without complete data were excluded.

RESULTS

About 320 patients were evaluated; only 120 fit the inclusion criteria. Further 20 were excluded for lack of data or because they fit into other exclusion criteria. Therefore, the analysis was based on the remaining 100 patients.

The mean age of participants was 57.3 years and 92% were female. The mean time of the diagnosis of Hashimoto's thyroiditis was 7.3 years.

The presence of statins (used by 31% of the sample), tabbaco exposure, family history of diabetes or thyroid cancer were not relate to alterations in glucose and HbA1c levels (all p=ns)

The occurrence of arterial hypertension showed significant association with T2D (p= 0,04), but not with prediabetes. Patients with prediabetes who progressed to diabetes, showed significant association with the presence of previous history of smoking (p= 0,004).

Anti-TPO positivity did not show influence over the development of any glycemic disturbed analyzed, neither the daily dose of oral levothyroxine, which mean was 80,08 mcg per day.(p=ns)

None of the ultrasound reports significantly affected the advent of any glycemic disorder studied.

During the studied period, 42 new cases of T2D and 49 new cases of prediabetes were detected, of which 8 progressed toT2D.

TYPE 2 DIABETES MELLITUS

When comparing the odds ratio (OR) of the last quartile and the first, towards the others, both the TSH parameter (< 1,93; 1,94 - 3,44; 3,45 - 5,04; > 5,05) and free T4 (< 0,79, 0,79 - 0,995; 0,956 - 1,20; > 1,20), no significant difference was found regarding the risk of developing diabetes. When analyzed referring its reference intervals, divided into 5 groups (TSH < 0,5; 0,5 - 1,83; 1,84 - 3.17; 3,18 - 4,5; >4,5 / free T4 < 0,7; 0,7 - 1,06; 1,07 - 1,43; 1,44 - 1,8; > 1,8), no higher or lower risk of developing diabetes was observed.

PRE-DIABETES

When examined the risk of developing pre-diabetes according to the TSH quartiles (< 1,93; 1,94 - 3,44; 3,45 - 5,04; > 5,05) or free T4 (< 0,79; 0,79 0,995; 0,956 - 1,20; > 1,20), no significant association was observed.

Analyzing the risk regarding their reference intervals divided into 5 groups (TSH < 0,5; 0,5 - 1,83; 1,84 - 3,17; 3,18 - 4,5; > 4,5 / free T4 < 0,7; 0,7 - 1,06; 1,07 1,43; 1,44 - 1,8; > 1,8), a higher risk of prediabetes development was observed only in the analysis of TSH. When analyzed the smallest interval (< 0,5), there was a significant increase in the risk of prediabetes (OR=2 1,83; 95% CI=1,11 - 3,03; p= 0,01).

The evaluation the number of pre diabetes according to these TSH interval, it was noted a significate reduction of prediabetes cases when compared to the smaller TSH interval (< 0,5),. Because of this finding, we chose to analyze the others TSH intervals comparing to the first one. Almost all of them showed a significant increased risk to develop prediabetes, excluding only the third interval (2º interval with OR= 0,34; 95% CI 0,14 to 0,82; p= 0,01; 3º interval with OR=0,56, 95% CI=0,30 to 1,07, p= 0,08; 4º interval with OR=0,47; 95% CI 0,23 to 2,38; p= 0,03; 5 interval with OR 0,51, 95% CI, 0,28 – 0,93, p= 0,02)

PROGRESSION OF PRE DIABETES TO DIABETES MELLITUS TYPE 2

When investigated the risk of prediabetes progression to Diabetes according to the TSH or free T4 quartiles, no significant association was found. When assessing the reference intervals in 5 groups, no significant change in the risk of progression was also observed.

DISCUSSION

We individually compared the extremes of the TSH and free T4 quartiles with the risk of developing T2D, prediabetes and the progression from prediabetes to T2D. The data obtained in this evaluation did not show any significant statistical value. (all p=ns)

Later, a comparison was made through the TSH and free T4 values taken from the practical guideline for the management of hypothyroidism, aiming to contextualize the work with clinical practice (1). It was not observed any relevant association between hypothyroidism and T2D , nor between the progression from prediabetes to T2D. However, the association of the lowest reference interval of the TSH was significantly related to the development of prediabetes (RR2 1,83, 95% CI, 1,11 - 3,03, p= 0,01). When comparing the other intervals with the smaller one, a significant reduction in the risk of prediabetes was seen except in the 3rd interval. (2nd: OR =0,34; 95% CI=0,14 to 0,82; p= 0,01; 3rd: OR=0,56, 95% CI= 0,30 to 1,07, p= 0,08; 4th: OR=0,47; 95 % CI=0,23 to 2,38, p= 0,03; 5th: OR= 0,51, 95% CI,=0,28 to 0,93, p= 0,02).

As type 2 diabetics have some risk factors already consolidated in the literature, such as male gender, family history of diabetes, hypertension, advanced age (over 40 years), sedentary lifestyle and high BMI (2) we studied these associations in our sample. All were not found to be significant, but relatively high risk for T2D in hypertensive hypothyroid patients (p= 0,04). However, no significance among those those with prediabetes was observed. In the case of prediabetes who progressed to diabetes, a high risk was observed in the presence of previous history of smoking (p= 0,004).

Ultrasonographic manifestations of hypothyroidism did not significantly influenced the diagnosis of diabetes, or prediabetes or progression to T2D. Glycemic changes in hypothyroidism are classically described as reduced glucose absorption from the gastrointestinal tract, prolonged accumulation of peripheral glucose, reduced hepatic glucose synthesis and reduced glucose clearance (22,23).

This work has some limitations such as the small sample size and the retrospective analyzis However, on the other hand, it has a longitudinal follow up (for five consults), the exclusion of non-Hashimoto hypothyroidism, the use of two laboratorial aspects for the glycemic evaluation and the use of thyroid ultrasonography.

Given that prediabetes should not be considered as an isolated entity, but rather a high-risk state for diabetes and cardiovascular disease (21), we may consider that when increased the risk of prediabetes, the risk of developing diabetes is indirectly increased.

Future researches are necessary to confirm the association between autoimmune hypothyroidism and type 2 diabetes mellitus and further clarification of its pathophysiological relationships.

CONCLUSION

By the present study, it was concluded that there is a

concomitance between the two diseases in the majority of the analyzed cases. It was demonstrated that the controlled presence of hypothyroidism leads to a higher risk of developing T2D, due to glycemic parameters elevation.

Furthermore, the comparison showed that age, male gender, diabetes and hypertension family history have influence in the risk of developing T2D. Maintaining TSH below 0.5 mU may place the patient at risk.

References

1. Brenta, G. et al. Diretrizes clínicas práticas para o manejo do hipotiroidismo Clinical practice guidelines for the management of hypothyroidism. **Arq Bras Endocrinol Metab**, v. 57, n. 4, 2013.
2. Kronenberg, H. M. et al. **Williams Tratado de Endocrinologia**. Editora Elsevier, 11ª edição, cap. 12, 30 e 35, p. 318 – 376, 1058 – 1102 e 1235 - 1254, 2010.
3. Callegaro, C. F. et al. Associação de Tireopatias em Uma População com Diabetes. v. 49, n. **Arq Bras Endocrinol Metab**, p. 234–240, 2005
4. Pearce, S. H. S. et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. **European thyroid journal**, v. 2, n. 4, p. 215–28, 2013.
5. Rochon, C. et al. Response of glucose disposal to hyperinsulinaemia in human hypothyroidism and hyperthyroidism. **Clinical science (London, England** : 1979), v. 104, n. 1, p. 7–15, 2003.
6. Walkyria P. Pimenta G. et als. Associação de tireopatias em uma população de pacientes com diabetes, **Arquivos Brasileiros de Endocrinologia & Metabologia**, 49, 2, (234), (2005)
7. Mouradian M et als. Diabetes Mellitus and Thyroid Disease. **Diabetes care**, v. 6, n. 5, p. 512–520, 1983.
8. Dora, J. M. et al. Association of the type 2 deiodinase Thr92Ala polymorphism with type 2 diabetes: Case-control study and meta-analysis. **European Journal of Endocrinology,** v. 163, n. 3, p. 427–434, 2010.
9. Yalakanti, D., Dolia, P. B. Association of Type II 5′ Monodeiodinase Thr92Ala Single Nucleotide Gene Polymorphism and Circulating Thyroid Hormones Among Type 2 Diabetes Mellitus Patients. **Indian Journal of Clinical Biochemistry**, v. 31, n. 2, p. 152–161, 2016.
10. Bulut, F. et al. Protein tyrosine phosphatase non-receptor 22 gene C1858T polymorphism in patients with coexistent type 2 diabetes and Hashimoto's thyroiditis. **Balkan Medical Journal**, v. 31, n. 1, p. 37–42, 2014.
11. Itariu, B. K.; Stulnig, T. M. Autoimmune aspects of type 2 diabetes mellitus - A mini-review. **Gerontology**, v. 60, n. 3, p. 189–196, 2014.
12. Zaletel, K.; Gaberscek, S. Hashimotos Thyroiditis: From Genes to the Disease. **Current Genomics**, v. 12, n. 8, p. 576–588, 2011.
13. Guadarrama-López, A. L.; Valdés-Ramos, R.; Martínez-Carrillo, B. E. Type 2 diabetes, PUFAs, and vitamin D: Their relation to inflammation. **Journal of Immunology Research**, v. 2014, 2014.
14. Tong, H. Van et als. Adiponectin and pro-inflammatory cytokines are modulated in Vietnamese patients with type 2 diabetes mellitus. **Journal of Diabetes Investigation**, v. 8, n. 3, p. 295–305, 2017.
15. Eisenbarth, G. S.; Gottlieb, P. A. Autoimmune polyendocrine syndromes. **New England Journal of Medicine**, v. 350, n. 20, p. 2068–2079 12p, 2004.
16. Han, C. et als. Subclinical hypothyroidism and type 2 diabetes: A systematic review and meta-analysis. **PLoS ONE**, v. 10, n. 8, p. 1–22, 2015.
17. Khatiwada, S. et asl. Thyroid dysfunction and associated risk factors among Nepalese diabetes mellitus patients. International Journal of Endocrinology, v. 2015, p. 3–7, 2015.
18. Chaker, L. et als. Thyroid function and risk of type 2 diabetes: a population-based prospective cohort study. **BMC Medicine**, v. 14, n. 1, p. 150, 2016.
19. Fleiner, H. F. et als. Prevalence of thyroid dysfunction in autoimmune and type 2 diabetes: The population-based hunt study in Norway. **Journal of Clinical Endocrinology and Metabolism**, v. 101, n. 2, p. 669–677, 2016.
20. Stanická, S. et als. Insulin sensitivity and counter-regulatory hormones in hypothyroidism and during thyroid hormone replacement therapy. **Clinical Chemistry and Laboratory Medicine**, v. 43, n. 7, p. 715–720, 2005.
21. ASSOCIATION AMERICAN DIABETES. **Standards of Medical Care in Diabetes** - 2017. v. 40, n. January, 2017.
22. Wang, C. The relationship between type 2 diabetes mellitus and related thyroid diseases. **Journal of Diabetes Research**, v. 2013, 2013.

Received in: 09-04-2018
Reviewed in: 30-04-2018
Reviewed in: 15-05-2018
Accepted in: 09-07-2018
Conflict of Interest: No conflict of interest was declared by the authors.

Author adress: Fernanda Senechal Duarte
Avenida Iguaçu 2849, apto 92 Água Verde, Curitiba-PR, cep: 80240030

CASE REPORT
PANCREATIC STEATOSIS AND INSULIN RESISTANCE IN HEPATITIS C VIRUS INFECTION: A BRIEF CASE REPORT

ESTEATOSE PANCREÁTICA E RESISTÊNCIA INSULÍNICA EM INFECÇÃO PELO VÍRUS DA HEPATITE C – UM BREVE RELATO DE CASO

GABRIELA CORREIA MATOS DE OLIVEIRA[1]
RAYMUNDO PARANÁ[2]
ALCINA MARIA VINHAES BITTENCOURT[2]
LUÍS JESUÍNO DE OLIVEIRA ANDRADE[3]

Keywords: Pancreatic steatosis, Hepatitis C, Insulin resistance.
Descritores: Esteatose pancreática, Hepatite C, Resistência insulínica.

Abstract

The hepatitis C virus infection (HCV) is a risk factor for development of insulin resistance (IR), and visceral fat is an ectopic. Fat stored especially in the liver, pancreas and is associated with IR. We case a report of a woman with HCV, IR, and pancreatic steatosis. The patient was treated with fenofibrate, metformin, and current therapeutic scheme for HCV with improvement of pancreatic steatosis. . **Endocrinol diabetes clin exp 2018 2050 - 2051.**

Resumo

A infecção pelo vírus da hepatite C (HCV) é um fator de risco para o desenvolvimento de resistência insulínica (IR). A gordura visceral é ectópica, armazenada especialmente no fígado, pâncreas e associada a IR. Relatamos o caso de uma mulher com HCV, IR e esteatose pancreática. A paciente foi tratada com fenofibrato, metformina e o esquema terapêutico atual para HCV com melhora da esteatose pancreática. **Endocrinol diabetes clin exp 2018 2050 - 2051.**

CASE REPORT

A 50-year-old woman presented with a 1-year history of hepatitis C virus infection (HCV). Abdominal sonography revealed pancreatic steatosis level 2 (Figure A), and laboratory tests revealed elevated levels of glucose, insulin and triglycerides elevated. The insulin resistance evaluated by homeostatic model assessment index (HOMA-IR). Blood amylase and glycated hemoglobin levels were normal. The administration of fenofibrate and metformin was initiated, as well as current therapeutic scheme for HCV. On follow-up at 6 months, the patient had weight loss and normalization of laboratory tests levels with improvement of pancreatic steatosis (Figure B).

DISCUSSION

The HCV is a risk factor for development of insulin resistance (IR), and visceral fat is an ectopic fat stored especially in the liver, and pancreas, and is associated with IR (1). The transabdominal ultrasonography is diagnostic technique by imaging most used for quantifying the echogenicity grades of pancreatic steatosis, based in increase in echogenicity of the pancreas compared with the kidney (2). There is still no histological pattern for pancreatic steatosis diagnosis in function of limited tissue acquisition pancreatic and few studies in vivo demonstrate localized or diffused replacement of pancreatic parenchyma by mature adipose tissue (3). However, it has been demonstrated accumulation of fat within the pancreas in the interlobular, intralobular, and perilobular spaces, and islet hypertrophy in rats (4). The IR is a metabolic state in which the insulin produced by the pancreas does not produce adequate glycemic control, and your diagnosis is based on clinical findings associated with laboratory data (plasma glucose level, the fasting insulin level, and a lipid profile) (5).

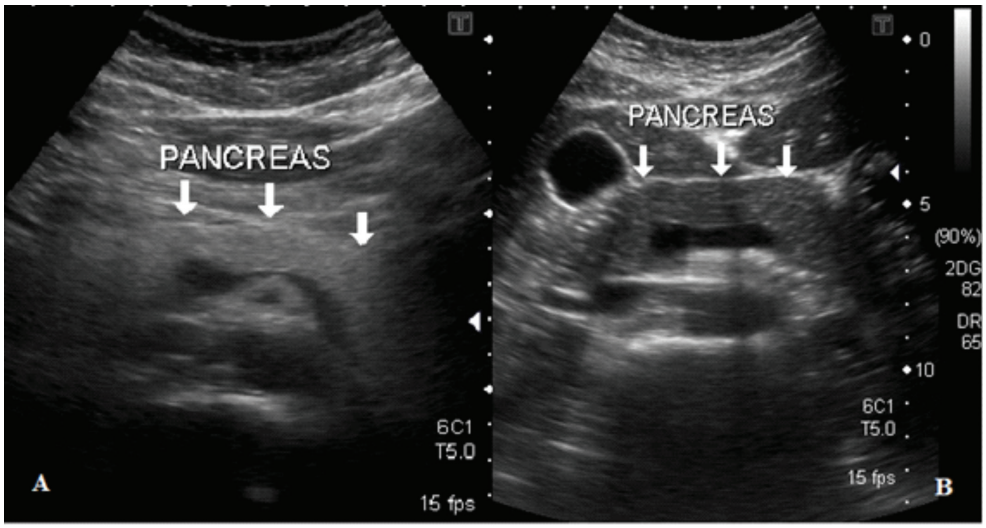


Figure 1. A - Difuse steatosis pancreatic B. Normal pancreas

[1] Faculdade de Medicina – Unime – Lauro de Freitas, Bahia, Brazil.
[2] Faculdade de Medicina – Universidade Federal da Bahia – Salvador, Bahia, Brazil.
[3] Programa de Pós-graduação em Ciências da Saúde – Universidade Estadual de Santa Cruz – UESC – Ilhéus, Bahia, Brazil.
E-mail: luis_jesuino@yahoo.com.br

CONCLUSION

The pancreatic steatosis is associated with pancreatic β-cell function dysfunction, correlating with higher metabolic risk secondary to IR.5 Thus, HCV infection may interfere in the normal functioning of beta cells taking to IR that induces pancreatic steatosis.

References

1. Kralj D, Virović Jukić L, Stojsavljević S, Duvnjak M, Smolić M, Čurčić IB. Hepatitis C Virus, Insulin Resistance, and Steatosis. **J Clin Transl Hepatol**. 2016;4(1):66-75.
2. Jeong HT, Lee MS, Kim MJ. Quantitative analysis of pancreatic echogenicity on transabdominal sonography: correlations with metabolic syndrome. **J Clin Ultrasound**. 2015;43(2):98-108.
3. Altinel D, Basturk O, Sarmiento JM, Martin D, Jacobs MJ, Kooby DA, et al. Lipomatous pseudohypertrophy of the pancreas: a clinicopathologically distinct entity. **Pancreas**. 2010;39(3):392-7.
4. Frantz ED, Crespo-Mascarenhas C, Barreto-Vianna AR, Aguila MB, Mandarim-de-Lacerda CA. Renin-angiotensin system blockers protect pancreatic islets against diet-induced obesity and insulin resistance in mice. **PLoS One**. 2013;8(7):e67192.
5. Eguchi Y, Mizuta T, Ishibashi E, Kitajima Y, Oza N, Nakashita S, et al. Hepatitis C virus infection enhances insulin resistance induced by visceral fat accumulation. **Liver Int**. 2009;29(2):213-20.

Received in: 25-06-2018
Accepted in: 04-07-2018
Conflicts of interest:
The authors declare no conflicts of interest.

Corresponding Author:
Luis Jesuino de Oliveira Andrade
Departamento de Ciências da Saúde
Universidade Estadual de Santa Cruz – UESC – Ilhéus – Bahia,

CASE REPORT
MACRO-ASPARTATE AMINOTRANSFERASE AFTER TSH-RECOMBINANT USE - CASE REPORT.

MACRO-ASPARTATO AMINOTRANSFERASE APÓS USO DE TSH-RECOMBINANTE – RELATO DE CASO.

GABRIELA CORREIA MATOS DE OLIVEIRA[1]
RAYMUNDO PARANÁ[2]
ALCINA MARIA VINHAES BITTENCOURT[2]
GUSTAVO MAGNO BAPTISTA[3]
ROSEANE MONTARGIL ROCHA[3]
LUÍS JESUÍNO DE OLIVEIRA ANDRADE[3]

Keywords: Macroenzyme, Macro-aspartate aminotransferase, TSH-recombinant.
Descritores: Macroenzima, Macro-aspatato aminotransferase, TSH-recombinante.

Abstract

Case report of an asymptomatic teenage girl with an isolated and persistent increase in serum levels of aspartate aminotransferase (AST), after recombinant human thyrotropin use for stimulated thyroglobulin levels analysis five years after initial treatment of thyroid cancer. The diagnosis of macro-AST was suggested and confirmed based on reduction of more than 50% of the level serum in dosage performed after storage of the same sample between 2-8 °C by five days. **Endocrinol diabetes clin exp 2018 2052 - 2053.**

Resumo

Relato de caso de uma adolescente assintomática, com aumento isolado e persistente dos níveis séricos de aspartato aminotransferase (AST), após uso de tirotrofina humana recombinante para análise de níveis de tireoglobulina estimulada, cinco anos após o tratamento inicial do câncer de tireoide. O diagnóstico de macro-AST foi sugerido e confirmado com base na redução de mais de 50% do nível plasmático de AST na dosagem realizada após o armazenamento da mesma amostra entre 2-8 ° C por cinco dias. **Endocrinol diabetes clin exp 2018 2052 - 2053.**

INTRODUCTION

Aspartate aminotransferase (AST) is an enzyme used in the study of liver diseases, and the increase in the levels of serum commonly reflects the various degrees of hepatic injury (1). The AST is expressed in cells of various tissues, such as skeletal and cardiac muscle, erythrocytes, kidney, and hepatocytes, among others. Therefore, although its elevation is generally related to liver disease, the differential diagnosis shall include other pathologies with this laboratory alteration (2). A rare cause and benign of the isolated elevation AST (macro-AST) is existence of circulating macroenzymes. Macro-AST corresponds to complexes of high molecular weight formed by multiple enzymatic molecules linked by immunoglobulins (3).

We describe a case of macro-AST in teenage girl. Current concepts on macro-AST and their clinical implications are discussed. Besides that, we apply an in silico simulation of molecular docking between AST and immunoglobulin.

CASE REPORT

An asymptomatic teenage girl, with laboratory and image testing previously normal, in whom an isolated AST elevation was discovered after recombinant human thyrotropin (TSH--recombinant) use for stimulated thyroglobulin levels serum analysis 5 years after treatment of thyroid cancer. The abdominal ultrasound was normal, and control liver function tests evaluated were within the reference interval, except the isolated elevation and persistent of the AST.

In 3 years clinical follow-up the patient remained asymptomatic. The diagnosis of macro-AST was suggested and confirmed. The protocol described by Baser et al. (4) was used, and method is based on the decrease in the plasma AST level after storage of the macroenzyme at 2-8 °C for 5 days, and has the advantages of low cost, reliability, and practicality at any health center. The AST activity at day 6 had decreased by more than 50% from day 1.

Macro-AST is a complex between normal AST (Figure 1) and an immunoglobulin (Figure 2) in the circulation that manifests as isolated elevation of AST. Thus, we applied molecular docking with *in silico* simulation, and were observed sites ligand between structure of aspartate aminotransferase (PDB ID: 1IVR) and structure of immunoglobulin (PDB ID: 1IGT) (Figure 3). The specific enzyme binding site is mostly on the Fab and F(ab1)2 fragment of the immunoglobulin molecule.

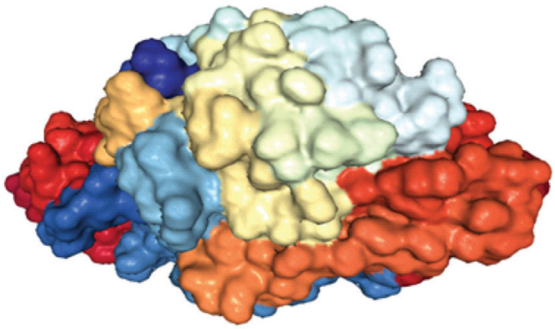


Figure 1. Structure of Aspartate Aminotransferase

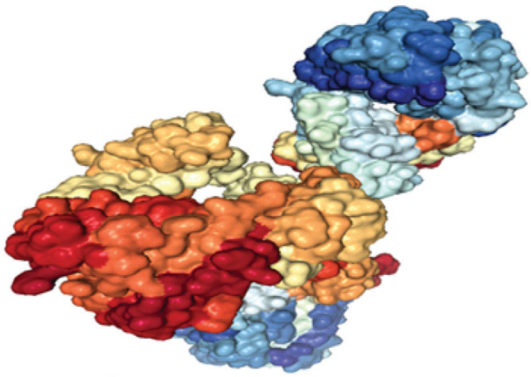


Figure 2. Structure of Immunoglobulin - Without Ligant

[1] Faculdade de Medicina – UNIME – Lauro de Freitas – Bahia – Brazil.
[2] Faculdade de Medicina – UFBA – Salvador – Bahia – Brazil
[3] Programa de Pós-Graduação em Ciências da Saúde – UESC – Ilhéus – Bahia – Brazil.
E-mail: luis_jesuino@yahoo.com.br

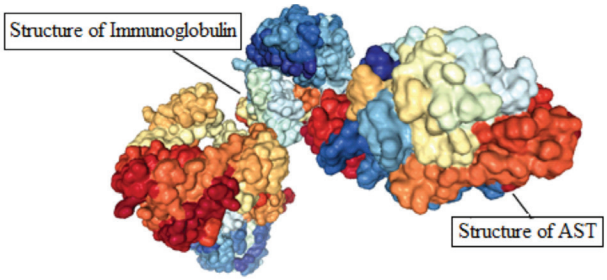


Figure 3. Immunoglobulin-complexed AST: Macro-AST

DISCUSSION

The serum AST activity is one of the basic biochemical parameters used in the diagnosis of several disease, because there are a series of conditions that elevate AST, because has been a low specificity and can originate in different cellular reservoirs including liver, heart, red blood cells, muscle and kidney (5).

Macroenzymes were described for the first time in 1964, and are resulting of polymerization or formation of complexes with other plasma constituents leading to the formation of high molecular weight compounds. Macro-AST is a complex of high-molecular weight formed by docking between normal AST and an immunoglobulin (usually IgG, rarely IgA or IgM) or proteins, that in circulation if manifests as isolated elevation of AST (6,7). The macro-AST due to high-molecular weight (250 kDa) presents renal clearance reduced without there being an increase in its release from the cells (8).

Enzymatic macro-complexes can be measured with different techniques. The most frequently used is the polyethylene glycol method (PEG) based on the principle that macromolecules can be precipitated and thus is measured the activity before precipitation and the remaining activity in the supernatant (9). Another method used alternatively is electrophoresis or gel chromatography (10). We used the laboratory protocol described by Baser et al. (4), based on the studies of Davidson and Watson and Castiella et al. (11), that is based on the reduction in the plasma AST level after storage of the macroenzyme at 2-8°C for 5 days, and with the advantages of low cost, reliability, and practicality at any health center, and becoming unnecessary other tests after diagnosis.

Macro-AST is a relatively rare and benign phenomenon, with a prevalence of 0.014% among a general population, and 9.09% of gastroenterological patients and those with isolated increased AST without liver abnormalities (9). Occurs more often in young people, and your pathogenesis is unknown, but a deregulation of the immune tolerance that would lead to the binding of immunoglobulins is postulated (12). Has been shown occurs heterogeneous responses of TSH-recombinant human receptor to immunoglobulins from patients with thyroid disease (13). The mechanisms of the immune complex formation are unclear, but may be due to autoimmunity, with immunoglobulins targeting enzymes as antigens via molecular mimicry (14).

CONCLUSION

vation of macro-AST associated with the use of human TSH-recombinant. Thus, the administration of human TSH--recombinant could increase levels of immunoglobulins with molecular docking to AST with an isolated increase of AST levels. Additionally, it was demonstrated in silico simulation docking molecular between AST structure and immunoglobulin structure, underlying the formation of high-molecular-weight serum macro-AST.

References

1. Torruellas C, French SW, Medici V. Diagnosis of alcoholic liver disease. **World J Gastroenterol**. 2014;20(33):11684-99.
2. Kawamoto R, Kohara K, Kusunoki T, Tabara Y, Abe M, Miki T. Alanine aminotransferase/aspartate aminotransferase ratio is the best surrogate marker for insulin resistance in non-obese Japanese adults. **Cardiovasc Diabetol**. 2012;11:117.
3. Bustamante V, Arab JP, Terc F, Poggi H, Goycoolea M, Arrese M, et al. Persistent elevation of aspartate aminotransferase (AST) due to the presence of macro-AST: Report of one case. **Rev Med Chil**. 2016;144(8):1078-1082.
4. Beşer OF, Laçinel S, Gülcü D, et al. An easy method for diagnosing macro-aspartate aminotransferase: a case series. **Turk J Gastroenterol**. 2014;25(5):568-70.
5. Davidson DF, Watson DJ. Macroenzyme detection by polyethylene glycol precipitation. **Ann Clin Biochem**. 2003; 40 Pt 5): 514-20.
6. Galasso PJ, Litin SC, O'Brien JF. The macroenzymes: A clinical review. **Mayo Clin Proc**. 1993;68(4):349-54.
7. Wener RR, Loupatty FJ, Schouten WE. Isolated elevated aspartate aminotransferase: a surprising outcome for clinicians. **Neth J Med**. 2012;70(3):136-8.
8. Chtioui H, Mauerhofer O, Gunther B, Dufour JF. Macro-AST in an asymptomatic young patient. **Ann Hepatol**. 2010; 9(1): 93-5.
9. Patteet L, Simoens M, Piqueur M, Wauters A. Laboratory detection of macro-aspartate aminotransferase: case report and evaluation of the PEG-precipitation method. **Clin Biochem**. 2012;45(9):691-3.
10. Chung YW, Sohn JH, Baek CH, et al. Macro-aspartate aminotransferase in a patient with chronic hepatitis **C. Korean J Gastroenterol**. 2006;47(3):229-32.
11. Castiella A, Aguayo FJ, Rueda M, Fernandez J, Zapata E. Macroaspartate aminotransferase (Macro-AST) a rare cause of hipertransaminasemia: another way to diagnosis? **J Clin Gastroenterol**. 2006;40(7):655.
12. Plebani M, Wu AH. Circulating macrocomplexes: old wine in new bottles? **Clin Chem Lab Med**. 201;49(5):759-60.
13. Endo T, Ohmori M, Ikeda M, Anzai E, Onaya T. Heterogeneous responses of recombinant human thyrotropin receptor to immunoglobulins from patients with Graves' disease. **Biochem Biophys Res Commun**. 1992;186(3):1391-6.
14. Remaley AT, Wilding P. Macroenzymes: biochemical characterization, clinical significance, and laboratory detection. **Clin Chem**. 1989;35(12):2261-70.

Received in: 22-052018
Accepted in: 04-06-2018
Conflict of Interest: No conflict of interest was declared by the authors.
Corresponding Author
Luís Jesuíno de Oliveira Andrade
Departamento de Ciências da Saúde
Universidade Estadual de Santa Cruz – UESC
CEP 45662-900. Ilhéus-Bahia, Brazil.

TOPICS IN MEDICAL CLINIC
CASE REPORT
PYOMIOSYTIS OF THE STERNOCLEIDOMASTOID MUSCLE IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

PIOMIOSITE DO MÚSCULO ESTERNOCLEIDOMASTOIDEO EM PACIENTE COM LUPUS ERITEMATOSO SISTÊMICO

BETÂNIA LONGO*
JHÉSYCA FLÁVIA SOUSA CASTAMAN STÉDILE*
THELMA LAROCCA SKARE*

Key words: Systemic lupus erythematosus, pyomyositis, infection, immunossupression.
Descritores: Lupus eritematosos sistêmico, piomiosite , infecção, imunossupressão.

Abstract

Introduction: Pyomyositis is a condition defined as an infectious disease of bacterial etiology which attacks the skeletal musculature. It is linked to conditions that lead to immunosuppression, such as systemic lupus erythematosus (SLE). **Case description:** MFVO, female, 61 years, diagnosed with SLE 20 years ago, was admitted at the emergency room, with a seven day history of a painful and hard bulge of the left anterior cervical region, next to the gonial angle, of approximately 3 cm, associated with localized redness and warmth. The patient presented with restricted neck mobility and fever (38.9°C). Laboratory exams showed 11,310 leukocytes/mm³, with 3% of band cells, C reactive protein (CRP) of 9.46 mg/L, and erythrocyte sedimentation rate (ESR) of 75 mm. Computed tomography (CT) of the cervical region demonstrated an image compatible with pyomyositis of the left sternocleidomastoid muscle. Treatment was done with antibiotic therapy for 7 days, with good clinical and laboratorial evolution and no need for surgical drainage. **Conclusion:** Pyomyositis must be remember as cause of fever and mass enlargement in a systemic lupus patient. **Endocrinol diabetes clin exp 2018 2054 - 2055.**

Resumo

Introdução: Piomiosite é uma condição descrita como doença infecciosa de origem bacteriana que afeta a musculatura esquelética. Está associada com situações que levam a imunossupressão como o Lúpus Eritematoso Sistêmico (LES). **Descrição do caso:** MFVO, feminina, 61 anos, tem diagnóstico de LES há 20 anos. Foi admitida na sala de emergência com a história de 7 dias de aparecimento de uma massa dura na região cervical próximo ao ângulo da mandíbula, de 3 cm, avermelhada e quente. A paciente apresentava redução da mobilidade em coluna cervical e febre (38.9oC). Exames de laboratório mostravam 11.310 leucócitos/mm3 com 3% de células imaturas; proteína C reativa de 9,46 mg/L e VHS (velocidade de eritrossedimentação) de 75mm. Uma tomografia computadorizada (TC) da região cervical mostrou imagem compatível com piomiosite do esternocleidomastoideo à esquerda. Tratamento foi instituído com antibióticos por 7 dias com boa resposta clínica e laboratorial, sem necessidade de drenagem cirúrgica. **Conclusão:** Piomiosite deve ser lembrada como causa de febre e aumento de volume em pacientes com lupus sistêmico. **Endocrinol diabetes clin exp 2018 2054 - 2055.**

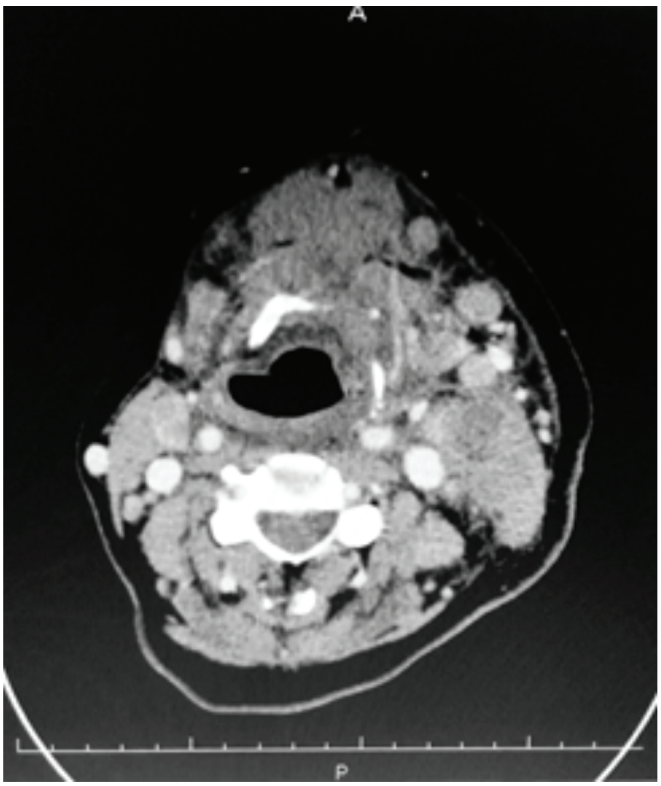
INTRODUCTION

Pyomyositis is a condition defined as an infectious disease of bacterial etiology that involves skeletal musculature and frequently stems from hematogenic dissemination (1). It often presents through abscess formation (2), single or multiple (1,3). Pyomyositis is linked to immunosuppression situations such as rheumatologic disorders, use of immunosuppressors, HIV (human immunodeficiency virus), malignancy, and diabetes mellitus (1).

Herein, we report a case of pyomyositis of rather unusual location: in the sternocleidomastoid muscle of a patient with SLE.

CASE DESCRIPTION

MFVO, female, 61 year old, diagnosed with SLE 20 years ago, showing articular, cutaneous and renal impairment (class-V glomerulonephritis). The patient also had arterial hypertension, with previous history of myocardial infarction and generalized osteoarthritis. She was taking methotrexate 10 mg/week, pred-



*Rheumatology Unit, Hospital Universitário Evangélico de Curitiba - Curitiba, PR, Brazil
E-mail: betania_1301@hotmail.com

nisone 5 mg/day, captopril 100 mg/day and acetylsalicylic acid (ASA) 100 mg/day.

This patient was admitted to the emergency room having, for 7 days, a painful and hardened bulge of the left anterior cervical region, next to the gonial angle, up to the wishbone, with a length of approximately 3 cm. This enlargement was red and warm. The patient presented restricted neck mobility, and fever (38.9°C), with no complaints of dyspnea or dysphagia. Physical examination confirmed the presence of lymphadenomegaly on the right submandibular region, left retroauricular region, and left inguinal region, with no focus of infection in the oral cavity. Laboratory exams showed white cell count of 11,310 leukocytes/mm³ and 3% of band cells, C reactive protein of 9.46 mg/L and erythrocyte sedimentation rate of 75 mm. A CT scan of the cervical region revealed an image compatible with pyomyositis of the left sternocleidomastoid muscle (Figure 1). Treatment with endovenous antibiotics (cefepime and clindamycin) was administered for 7 days, with improvement of the clinical and laboratorial picture and no need for surgical drainage.

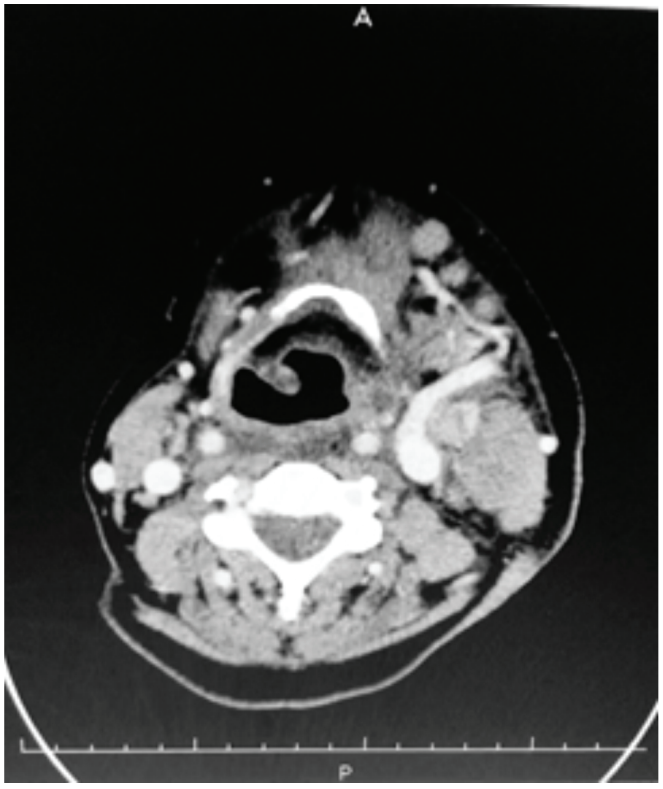


Figure 1: Well-defined hypodense collection in the lower left parotid gland, measuring 2.2 x 1.8 cm in the axial axes.

DISCUSSION

Pyomyositis can be classified into three clinical stages: invasive, suppurative, and advanced. Invasive stage is characterized by non-specific symptoms and low fever. In the suppurative stage, deep, single or multiple muscular abscess occurs, with fever and increasing pain. If the proper treatment is not applied, it can evolve into advanced stage, with high fever, signs of toxicity, risk of sceptic shock and death (1-4). The most frequently reported causal organism in cases of pyomyositis is Staphylococcus aureus (1,3). The patient from this report was probably in the invasive stage, which explains the prompt response to the antibiotic therapy.

The clinical manifestations and laboratorial exams are non-specific (1,5). The evidence of inflammatory activity is usually high, and the muscle enzymes usually within normal range (3,5). In diagnostic investigation, early image evaluation is of vital importance (5). Ultrasonography contributes to diagnosis, although it might not detect early lesions (2). The most sensible method is magnetic resonance imaging (MRI) (5), which is capable of detecting bone and adjacent joint involvement (2). The CT scan is useful when a guide fluid aspiration is needed (5).

Due to the insidious clinical picture and non-specific manifestations, diagnosis is often late (3,4), and this is related to worst prognosis, increase in morbidity and mortality rate (5), that, according to the literature ,varies from 0.5 to 2% (3).

Treatment depends on the stage of the disease, and must be applied as early as possible. When the patient is in the suppurative or advanced stage, the first line is broad-spectrum endovenous antibiotic therapy (1), with percutaneous or surgical abscess drainage, as needed (4).

Possible complications include compartmental syndrome, septic arthritis (depending on the location), septicemia in more severe cases, osteomyelitis, cerebral and pulmonary abscesses, pericarditis, myocarditis and endocarditis (5). Some of the differential diagnoses include contusion, muscle rupture and hematoma, cellulitis, muscular osteosarcoma (3).

Early clinical suspicion and proper handling are critical for satisfactory progression of the clinical picture (4).

CONCLUSION

Pyomyositis diagnosis must be considered whenever an immunosuppressed patient, such as the one described in this report, presents with localized muscular pain, with or without changes in muscular enzymes.

References

1. Blay G, Ferriani MPL, Buscatti IZ, França CMP, Campos LMA, Silva CA. Piomiosite no lúpus eritematoso sistêmico juvenil. **Braz Ver Reumatol**. 2016;56(1):79-81.
2. Agarwal V, Chauhan S, Gupta RK. Pyomyositis. **Neuroimag Clin N Am**. 21(2011)975-983.
3. Chauhan S, Jain S, Varma S, Chauhan SS. Tropical pyomyositis (myositis tropicans): current perspective. **Postgrad Med J**. 2004;80:267-70.
4. Souza HCB, Carvalho BN, Morais MGV, Monteiro GZ, Emori FT, Latorre LC. Piomiosite tropical em paciente com lúpus eritematoso sistêmico e infecção por HTLV 1/2. **Braz Ver Reumatol**. 2011;51(1):97-103.
5. Nikolopoulos DD, Apostolopoulos A, Polyzois I, Liarokapis S, Michos I. Obturador internus pyoyositis in a Young adult: a case report and review of the literature. **Cases J**. 2009,2:8588.

Received in: 16-072018
Reviewed in:20-07-2018
Accepted in: 27-07-2018
Conflict of interest: None
Source of funding: None
Corresponding author: Betânia Longo
Rua Luiz Leitner, 50 – Bigorrilho – Curitiba (PR) – Brasil

Instructions for the publication of the Journal Endocrinology & Diabetes Clinical and Experimental

The journal follows the International Committee of Medical Journal Editors

01 All the manuscripts will be published in English. The journal accepts original articles, preliminary notes, case reports, review articles, updates and letters to editor. There a topic dedicate to internal medicine linking endocrinology and medical clinic. The journal strongly encourages on line submissions of manuscripts. Those should be accompanied by a title, keywords and an abstract in English for the purposes of international registration. Abstracts in other languages may also be attached.

02 The articles received by the Editor will be analyzed with the Assistance of the Editorial Board. Minor changes to "copy desk" can be effective with the purpose of standardizing the articles, without substantial changes in original text.

03 Manuscripts can be sent on CD or via on line to publicacao@revistaendocrino.com. The text should be typed on pages containing 20 to 24 rows and rows with 70 to 75 spaces, with the objective of enabling the diagramming the calculation of space required for each article. The word processor used must be either Microsoft Windows compatible program (Word, Write etc.).

05 The article must have title, full name of the authors; quote from site (full address) where out performed the work; full titles of authors, key words (or "keywords") without exceeding a limit of 250 words; introduction; material or material and methods or description of the case; results; discussion and/or comments (when applicable); conclusions (when applicable); summary (summary in English), consisting in the correct version of the summary, not exceeding 250 words; references (as quoted below in item 08) in alphabetical order; the accompanying illustrations must follow appropriate rules, described in item 07.

06 Illustrations are of figures and graphs referred to in Arabic numerals (example: fig. 3, graph 7), in the form of ink drawings photographs ECG EEG etc. When possible must be submitted in original form. The illustrations will be accepted only allow good reproduction. Should not be glued in the middle of the article text and it must be attached with the respective legends typed on the bottom of the same (one sheet for each illustration). Must take care to number each illustration on the back of the same and indicate the correct place where should be introduced. Tables and frames are specified in Arabic numerals, consisting always the respective title, accurately. Tables and frames without its description in the text and are intended to summarize the article. The units used to express the results (m, g, g/100 ml, etc.) will appear at the top of each column. It will be up to the Editor to judge excessive illustrations (figures, tables, graphs, tables etc.), deleting the redundant.

07 The references must follow the alphabetical order or the order of appearance in the text. Showing them all authors cited in the text. It must be contain: name of author, name of the journal abbreviated in accordance with the criteria used in the Index Medicus (www.nlm.nih.gov/tsd/serials/lji.html). Papers accepted but not yet published may be included in the references. You should avoid using as reference poster or free themes from conferences unless they are of high relevance. Articles published online may be cited in the references and should bear the name of the site as well as the date of access.Chapter of Book: Ruch, TC.Somatic Sensation. In Ruch T C et al. Neurophysiology. Philadelphia Saunders 1963; 330-332 Journal article: R.W.G Gruessner, Sutherland D.E.R, Najarian j. S, et al. Solitary pancreas transplantation for non uremic patients with insulin-dependent diabetes mellitus labile. Transplantation 1997; 64: 1572-77.

08 The names of drugs cited in the text (names of fantasy, officers, patented, and acronyms of chemical research) shall comply with corresponding regulations of the World Health Organization, according to rules summarised by KOROLKOVAS, a.-Regulatory Editorial Nomenclature-Names of drugs (Drug Nomen--clature). Rev. Bras. Clin. Terap. 5: 1976 (February).

09 The authors will receive ten copies of the issue in which their work was published (for reprints), which will be sent directly to the place where the work performed. Reprints must be ordered and previously combined with the Commercial Direction.

10 The manuscripts that don't fit the standards or that does not suit the needs of the journal editorials may be forwarded to the authors to carry out the necessary adjustments that will be indicated in the personal letter from the Editor. Will be mentioned the dates of receipt and approval of work for publication, in order to safeguard the interests of the author's priority. In the case of re-routing of work to adapt to our rules for publication, the date cited is always receive the first forwarding of work. The content of the articles is the responsibility of the authors. The link between the author (s) and pharmaceutical laboratories, as well as another source that is generating resources must always be quoted by author (s). The copyright of the manuscripts are of the magazine in question.

11 Will be given top priority in the publication of articles and/or notes that they concerned about matters directly or indirectly related to the basic purpose of the journal Endocrinology & Diabetes Clinical and Experimental

12 Studies that involve animals, research or human, should obey the rules of the Helsinki Declaration of 1979 and revised in 2000. The authors is entitled to explanation, if your search is not in accordance with the rules of the Declaration of Helsinki. In addition, when the study involves humans must be approved by the Ethics Committee of your institution.

13 Mailing address of the main author must appear at the end of the article. Your article is your own responsibility, and the same answer for your account both within the medical ethics as in legal proceedings.

14 Structural definition of the main types of articles: Original articles: Articles Are produced through scientific research, presenting original data scientific findings with respect to experimental or observational aspects of Medical Biochemistry and social feature. Includes descriptive analysis and data inferences or own. In its structure should contain the following items: Introduction, Material and methods, results obtained and studied by an appropriate statistical method discussion and conclusion. Review articles: Are articles that seek to summarize, analyze, evaluate or synthesize research already published in scientific journals. The revisions are expected to be commissioned by the editors, except in case of scientific relevance for the medical class. Articles from Update or disclosure: These report updated information of interest to the magazine or a new technique or laboratory research. This topic is distinct in its account of the review article. Case report: Present descriptive data about a pathology with academic relevance in relation to the disease, treatment, laboratory or association with another pathology

15 The Journal of Endocrinology & Diabete clinical and Experimental use the peer review form of review the manuscripts Peer review is an important process for all authors to understand. Ultimately, peer review was created to protect scientific integrity and promote the sharing of research with other colleagues. It can help authors discover problems and helps to strengthen the credibility of their research. The extensive amount of published material relating to peer review can be overwhelming for readers to sort through, and this paper provides a relevant guide for authors regarding the peer-review process. The necessity of having quality control measures for published work is important to the scientific community, and without such measures, the quality of published work would not be what it is today. Peer review is necessary to identify scientific manuscripts worthy of publication and to improve the quality of published research


ENDOCRINOLOGIA & DIABETES CLÍNICA E EXPERIMENTAL
FEPAR - HUEC - CURITIBA - BRASIL