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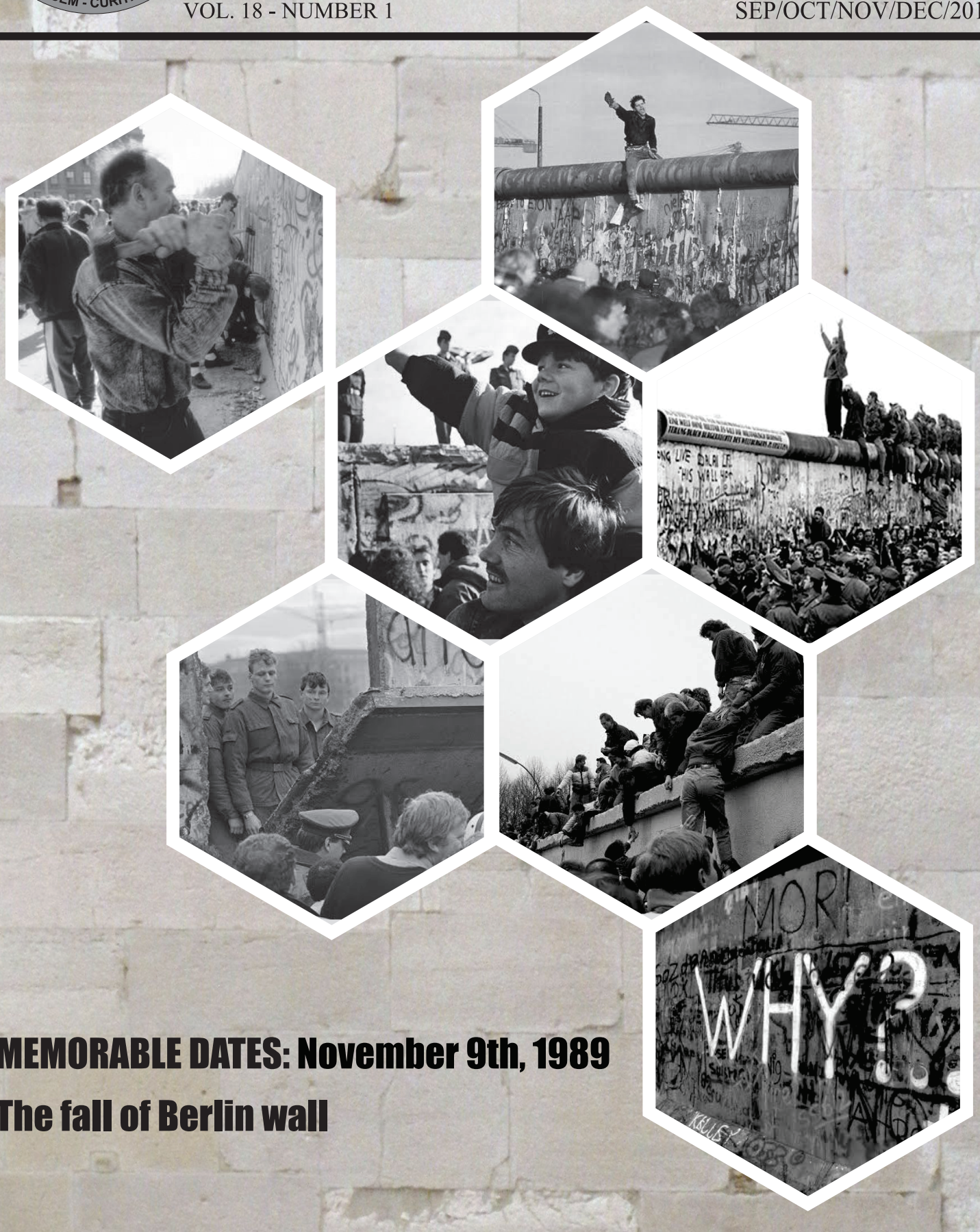

MEMORABLE DATES: November 9th, 1989

The fall of Berlin wall

EDITORIAL

MEMORABLE DATES
November 9th, 1989 The fall of Berlin wall

A symbol of the Cold War, Berlin Wall, by 28 years, separated the communist Eastern side of Berlin from democratic Western side. It was built in 1961 after the World War II, when Germany was divided into two parts – East Germany Zone and West Germany Zone, among the four allies that defeated the nazism

Berlin capital of Germany was shared by the allies being that : Soviet Union controlled East Berlin, while France, Great Britain and America controlled West Berlin.

The wall separated East from West, but there were a number of checkpoints that allowed passage to the two sides. The most famous was Checkpoint Charlie, a checkpoint separating the American-controlled zone of West Berlin from the Soviet-controlled East Berlin. The guard house for Checkpoint Charlie is now situated the Allied Museum in Berlin. The remnant of Checkpoint Charlie, in East German was demolished in 2000. Berlin Wall was called of 'wall of shame'. The East continued to rebuild the wall, making it further long. It reached a length of 103 miles, 4 feet high and 12 feet high. Guards and dogs were then added at check points to keep a watch on anyone trying to cross the wall. The East side was very poor .The Western part was growing and their economy become better day by day, while in the East the Soviets had full control with limited freedom to the citizens. Thus, the people living in East Germany did not want to live under the control of the Soviets and started to move to the Western border. The effects of the Berlin Wall were separation of whole families, loss of work and the comfortable life they enjoyed before the war

In November 9, 1989 an announcement was made which that relocation on the two sides can be done through all border checkpoints. So, all germanies celebrated the end of divided Germany by the wall and tearing down the wall with theirs hands and hammers. It was only on October 3, 1990 that Germany was officially recognized as one and was unified as a single country. under the name the Federal Republic of Germany.

References

www.history.com/News

https://edition.cnn.com/2013/09/15/world/europe/berlin-wall-fast-facts

Mirnaluci Paulino Ribeiro Gama

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Photo: Goolge (MEMORABLE DATES : November 9th, 1989)

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ORIGINAL ARTICLE
ANTITYROID ANTIBODIES IN GRAVE`S DISEASE: AN ANALYSIS OF A BRAZILIAN COHORT
ANTICORPOS ANTITIROIDIANOS NA DOENÇA DE GRAVES: ANÁLISE DE COORTE BRASILEIRO

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Key words: Autoantibodies Graves' disease, Hyperthyroidism, Ophthalmopathy
Descritores: Autoanticorpos, Doença de Graves, Hipertireoidismo, Oftalmopatia.

Abstract

A predictor of response to treatment, such as TRAb and Anti-TPO, could save patients from long and complicated treatments such as antithyroid drugs with potentially serious side effects and facilitate the early indication of definitive treatment with surgery or radioiodine therapy. This study aims to evaluate the TRAb and ATPO autoantibodies as predictors of response to the different therapeutic modalities in Graves' disease through the analysis of data of patients attended at the State Institute of Diabetes Endocrinology Luiz Capriglione (IEDE). The levels of Anti-TPO in patients with Graves' ophthalmopathy were higher than of patients without ophthalmopathy, with a statistically significant difference between the two groups (p = 0.048), but the use of TRAb and Anti-TPO as predictors of response to treatment and relation with extra-thyroid manifestations is still a controversial subject and needs long-term studies and in different populations so that its use is recommended with greater safety. It was also observed that TRAb levels during follow-up were lower in patients who entered remission, being statistically significant (p = 0.049). There is still a lack of studies regarding the levels of TRAb and Anti-TPO and its relation with the response to treatment. **Endocrinol diabetes clin exp 2019 / 2148 - 2151.**

Resumo

Um fator preditor de resposta ao tratamento, como o TRAb e Anti-TPO, poderia poupar pacientes de longos e complicados tratamentos como DAT com efeitos colaterais potencialmente graves, poderia também facilitar a definição precoce de tratamentodefinitivo com cirurgia ou radioiodoterapia (RAI). Este estudo objetiva avaliar os autoanticorpos TRAb e ATPO como preditores de resposta as diferentes modalidades terapêuticas na Doença de Graves através da análise dos dados de pacientes atendidos no Instituto Estadual de Diabetes Endocrinologia Luiz Capriglione (IEDE). Os níveis de ATPO em pacientes com oftalmopatia de Graves, apresentaram uma média superior à de pacientes sem oftalmopatia, tendo uma diferença estatisticamente significativa entre os dois grupos (p=0,048), porém o uso do TRAb e Anti-TPO como preditores de resposta ao tratamento e relação com manifestações extra-tireoidianas ainda é um assunto controverso, necessita de estudos a longo prazo e em diferentes populações para que seu uso seja recomendado com maior segurança. Observou-se também que os níveis de TRAb durante todo seguimento foram inferiores nos pacientes que entraram em remissão, sendo estatisticamente significativo (p=0,049). Existe ainda uma carência de estudos a respeito dos níveis de TRAb e Anti-TPO e sua relação com a resposta ao tratamento. **Endocrinol diabetes clin exp 2019 / 2148 - 2151.**

INTRODUCTION

Thyroid function tests are part of the laboratory investigation in several medical areas, where different conditions can lead to thyroid hypofunction or hyperfunction (1).

The initial evaluation of hyperthyroidism is made by dosing serum levels of TSH and thyroid hormones. The thyrotrophin (TSH) determined by ultrasensitive assay is the most accurate method (2). In manifested hyperthyroidism, serum T4L and T3 are increased and in early stages, isolated T3 increase may occur (3).

Graves' disease (DG) is an autoimmune disease where the thyroid is stimulated by autoantibodies against the TSH receptor (TRAb). TRAb acts by binding to the TSH receptor (TSHR), leading to excessive production of thyroid hormones (HT) (4).

According to the guidelines of the Brazilian Society of Endocrinology and Metabolism, thyrotropin receptor antibodies (TRAb) dosage is not routinely indicated. The diagnosis of GD can be established with relative safety in patients with thyrotoxicosis and ophthalmopathy or diffuse goiter.

It is appropriate to determine TRAb's levels in pregnant women with GD or previous history, in order to evaluate the risk of neonatal thyrotoxicosis due to transplacental passage of antibodies, in the differential diagnosis of gestational thyrotoxicosis and in euthyroid individuals with exophthalmopathy (5,6).

The determination of TRAb promotes greater acuracy in the diagnosis of GD. Anti-thyroid peroxidase (anti-TPO), which is present in up to 80% of GD patients, can also be used in order to reveal the autoimmune nature (7).

The association of TRAb and ATPO levels as a predictor of response to treatment has been poorly studied, however, a study shows that it can provide greater acuracy in predicting response to treatment (8). There are some evidence that Anti-TPO levels do not change with treatment, however, further studies on the subject are needed. (9)

The relationship of TRAb and extrathyroidal manifestations has been extensively investigated. It is known that high levels of TRAb are associated with ophthalmopathy and dermopathy (1,10).

Antithyroid drugs (ATD) are associated with a high risk of relapse, despite the high efficacy and safety, particularly in the first year after the ADT interruption. It is worth mentioning that TRAb levels are correlated with the course of the disease (11).

The inability to predict the risk of relapse is a current problem in drug treatment. Therefore, TRAb dosage could help practioners with the choice of the most suitable treatment for the GD patient (12). In view of the foregoing, it is crucial to identify which patient is at risk to fail treatment with ATD (13). This large Brazilian cohort is of great importance for further discussions and studies, as well as better elucidation of the topic

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OBJECTIVES

This manuscript has as a Primary Objective, the analysis of TRAb and Anti-TPO in patients with GD, of the State Institute of Diabetes and Endocrinology Luiz Capriglione (IEDE) in the city of Rio de Janeiro, by evaluating the importance of these antibodies as predictors of response to treatment and the following Secondary Objectives: Analyze the association between ophthalmopathy and dermopathy with TRAb and Anti-TPO.

MATERIALS AND METHODS

Observational and retrospective study of patients attending an outpatient clinic of the IEDE Thyroid Service. A total of 297 patient's charts were reviewed. The inclusion criteria were: Suppressed TSH with elevated thyroid hormone, associated with the increase of one or more antibodies, ophthalmology and / or dermatopathy or after exclusion of other causes of hyperthyroidism, only patients who at some point were treated in IEDE.

Exclusion criteria were: patients with hyperthyroidism without diagnostic criteria for GD, patients who did not have TRAb or ATPO dosed, those with less than 2 visits to outpatient clinic and those who did not receive any type of treatment.

The research protocol was approved by the Research Ethics Committee.

The method used for the dosing of the TRAb, as well as the dosage of the ATPO, was Electrochemiluminescence, other methods were excluded from the analysis.

The criteria for GD remission used was TSH> 0.3 µUI / mL and T4L <1.9 ng / dL, which refers to the reference range, and no current treatment or use of levothyroxine (LT4) replacement. Since it is a retrospective study, without previous standard parameters, it was not defined a period without ATD, as well as minimum time of treatment.

Regarding the statistical analysis, a descriptive analysis was used for demographic, clinical and laboratory variables. Anderson-Darling test was used to use to determine if a data set is well-modeled by a normal distribution, and data are presented as mean and standard deviation (SD). The 95% Confidence Interval for the odds ratio were calculated by logistic regression to estimate associations between variables and outcomes. P values of less than 0.05 were considered statistically significant. All statistical analyzes were performed with Minitab® software (version 17.0).

An extensive bibliographical review was carried out in order to develop the theoretical foundations, the respective reference is available in the bibliography.

RESULTS

The study included 207 patients, and a total of 8565 data from medical records were evaluated and documented. The majority, 170 (82%) patients, were female and 37 (18%) were male. The mean age at diagnosis among women was 42 years (Variation: 10-91 years) and men was 38 years (Variation: 14-80 years). Among the medical records evaluated, 90% had no information on the ethnicity of the patient, the 10% of those who had this information were 4% white, 4% black and 1% brown (**Table 1**).

The average time between diagnosis and treatment was 6 months, although 178 patients (86%) started treatment with less than 12 months, the maximum delay was 168 months (14 years). The mean follow-up time was 2.89 years.

Ophthalmopathy was found in 70 patients (34%). The association of dermopathy and ophthalmopathy was present in 5 patients (2%), and isolated dermopathy was reported in 8 patients (4%).

During follow-up, 71 (34%) went into remission. Of these, 82% did not use any medication after remission and 18% developed hypothyroidism. 98% of the patients had used DAT at some time in the treatment, where 167 (81%) used Tapazole (TPZ), 14 patients (7%) used Propylthiouracil (PTU) and 22 (11%) used both ATD during medical follow-up, whereas 4 patients (2%) did not use DAT and went through surgery or therapeutic dose with I131.

From the total of 207 patients included in the study, there was no information of the initial laboratory tests of 71 patients who started treatment previously to the follow up in IEDE. Therefore, in 136 patients it was possible to have access to pre-treatment laboratory tests.

The mean duration of ATD was 19.64 months (1.63 years), which corresponds to 19.66 months (Variation: 1-118.7 months) of TPZ and 9.55 (Variation: 0.5-103.1 months) of PTU.

Among 207 patients, 164 (79%) presented positive TRAb. Evaluating the highest TRAb result of only individuals with positive TRAb, we had an average of 34.39 IU / L.

It was found that 34 (47%) of the 71 patients had TRAb within the normal range in the whole follow-up, 21 (30%) patients had TRAb positive and 16 (23%) had no TRAb assessed at any time.

In the group of patients who went into remission and presented positive TRAb at some point (30%), the average autoantibodies against the TSH receptor was 22.9 UI / L (Variation 1, 8-338; [DP: 53.5]). Including patients who entered remission, who had wheather positive TRAb or not, the mean was 14.69 IU / L (Variation: 0.3-338; [SD: 43.57]).

A total of 136 patients did not enter into remission, where 5 patients (4%) did not have TRAb measured. Among the non-remission patients, 35 (26%) had TRAb within normal range during follow-up and mean TRAb of 0.94 IU / L (Variation: 0.3-1.73), moreover, 96 (70%) had the positive test during follow-up.

Comparing only the positive TRAb levels during follow-up of patients who entered enter remission with those who did not (Mean: 22.9 and 29.31 respectively), the difference was not statistically significant (p = 0.31). **Figure 1**

Table 1

Gender	Prevalence	Age	Ethnicity
Female	170 (82%)	42 years old (10-91anos)	Black – 8 (4%) Brown – 3 (1%) White – 9 (4%) Not informed – 187 (90%)
Male	37 (18%)	38 years old (14-80 anos)	

Table 1 - Shows the demographic profile data of the patients

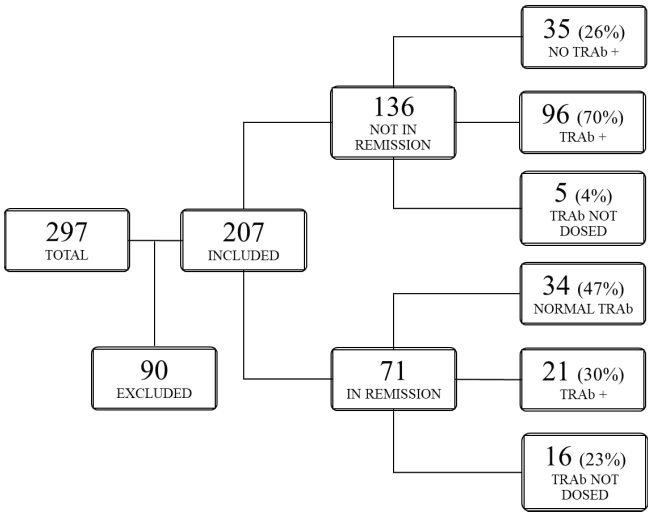

Figure 1 - Represents the patients evolution assessed and its TRAb during the treatment

In those patients who did not entered into remission the mean TRAb was 23.56 IU / L (Variation: 0.3-332, [SD: 45.7]). TRAb levels during follow-up were lower in remission patients when compared to non-remission patients, which was statistically significant (p = 0.049).

Evaluating specifically the moment of remission of the 71 patients, 32 patients did not have TRAb dosed the moment before the DAT suspension. Considering the 39 patients who entered remission and had TRAb specifically dosed at the time of drug withdrawal, 21 patients (54%) presented TRAb within the normal range, with a mean of 0.79 IU / L (SD: 0.40) and 18 patients (46%) had positive TRAb at drug suspension, with a mean of 19.11 UI / L (Variation: 2-111; [SD: 28.2]).

Among the 39 patients who had remission and TRAb dosed, 9 had recurrence (reintroduction of DAT, TSH suppressed and T4L above the normal range), of which 8 had positive TRAb (88%) and 1 negative TRAb at the time of DAT withdrawal (11%). It is notable that patients with positive TRAb at the time of drug withdrawal, 44% (8 of 18) had recurrence and patients with negative TRAb at the time of remission only 5% (1 of 21) had recurrence of the disease.

It was found that 56% of the patients who entered remission had positive ATPO (> 34U /mL) during follow-up with an average positive ATPO of 473U / mL (range: 38 to 4320 [SD: 509.5]). The mean ATPO of patients entering remission was 262.28 U / mL [SD: 291.6]), which was higher among subjects refractory to treatment with the mean ATPO of 383.93 U/ mL (SD: 465, 4).

Of those who did not go into remission, only 31 (23%) had ATPO within the normal range during follow-up (mean ATPO 13.43U / mL). When we compared the ATPO levels during follow-up between patients who entered and did not, we did not have a statistically significant difference between the two groups (p = 0.60).

Among the non-remission subjects (n = 136), 68 (50%) had positive ATPO during the follow-up and 37 (27%) did not have ATPO verified. The mean positive ATPO in this group was 546.27 (range: 38 to 4320 [SD: 614.9]). Comparing the positive levels of ATPO from the remission and non-remission group, we did not have a significant difference (p = 0.32). **Figure 2**.

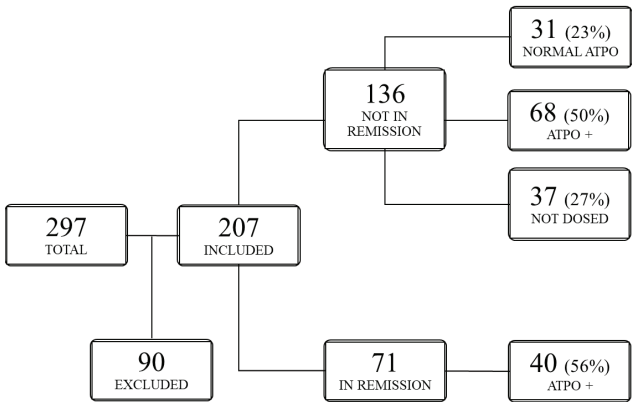

Figure 2 - Represents the patients evolution assessed and its ATPO during the treatment

Considering the 71 patients who has entered remission, 58 (82%) did not have ATPO dosed at the moment of drug withdrawal, among those who had, 8% had negative ATPO at the time of drug withdrawal and 92% had positive ATPO at this time. Among those with positive ATPO, 42% relapsed after suspension of the ATD.

Regarding the GO analysis, the mean TRAb in patients with ophthalmologic disorders related to GD was 23.95 IU / L (Variation: 0.3 to 228.0; [SD: 38.22]), higher than the mean of the patients without GO, 16.56 IU / L (Variation: 0.3 to 338.0, [DP: 45.18]), the difference was not statistically significant (p = 0.097). The levels of ATPO in patients with GO had an average of 429.99 U / mL (SD: 602.13), higher than the mean of patients without ophthalmopathy 295.63 U / mL, being statistically significant between the two groups (p =0.048).

In patients with Dermatopathy (DP), the mean TRAb was 30.52 IU / L (SD: 30.22), higher than the mean of patients without DP 19.42U / L (SD: 42.55), but with no statistical significance (p = 0.56). The mean ATPO in patients with DP was 419.3 U / mL (SD: 351.51) and without DP was 333.98 (SD: 506.58), similar to GO, also superior in patients with DP (p = 0.73).

DISCUSSION

In a recent review, which included 5 systematic reviews and Meta-analyzes with 52 observational studies, the peak incidence of Graves' disease was 30 to 60 years (14). In this study it was found an average age of 42 years for women and 38 years for men, in accordance with the systematic review. The incidence was about 4 times higher among women, being also in agreement with the literature (15).

It was found a 34% incidence of ophthalmopathy in physical examination, higher than some references, where about 25% of the patients had GO. Dermatopathy was present in 4% of the patients in this study, being present in only 1% of the patients in other studies. (16, 17).

Among the 207 patients, 98% used ATD as primary therapy, with a clear preference for drug treatment by endocrinologists in the city of Rio de Janeiro. Similar studies showed that 67-85% of endocrinologists worldwide have ATD as the initial treatment and only 40.5% of American endocrinologists initiate treatment with ATD. (14, 18).

The mean TRAb levels throughout the follow-up of patients who had remission were lower than the levels of patients who did not remission (p <0.05). Evaluating the 39 patients who had TRAb dosed at the time of remission, 21 (54%) had negative TRAb before ATD withdrawal, where 5% (1 of 21) had recurrence of the disease. It was observed a considerably lower rate of relapse than the literature, where 20-30% of patients with negative TRAb at the time of DAT had recurence in 3 to 5 years (19).

A possible explanation for such discordant results is the follow-up time after remission, there was no minimum follow-up established after drug withdrawal. However, 44% (8 of 18) of the patients with positive TRAb at remission had a recurrence, and according to the literature, approximately 50% of the patients who did not reach an immunological remission present recurrence (20,21).

A remission rate of 34% was found, lower than the 40-50% remission on literature. Patients treated with DAT may eventually develop hypothyroidism, occurring in 5-20% of cases, according to literature (22). The annual incidence of subclinical hypothyroidism in one study was 2.5% and hypothyroidism was 0.6%. (23). In this Brazilian study, the incidence of hypothyroidism after DAT was 18%, significantly higher than that found in another Brazilian cohort, where only one patient out of 127 patients developed spontaneous hypothyroidism after the interruption of the DAT. (24)

Approximately 80-90% of the patients with GD have positive ATPO (25, 26). A lower incidence was found in this study, where 56% of the patients who entered remission had positive ATPO and 77% those who did not entered remission had positive ATPO. The mean of ATPO was higher among patients who had no remission. We also observed that 92% had positive ATPO at the time of DAT suspension, of which 42% relapsed.

The mean TRAb of patients with ophthalmological alterations related to GD was higher than the mean of patients without GO, but not statistically significant (p = 0.097). On the other

hand, the ATPO levels in patients with GO, the mean levels was higher than of patients without ophthalmopathy, with a statistically significant difference between the two groups (p = 0.048). The results were not in accordance to a study published in February 2014 where the risk of ophthalmopathy was higher in patients with elevated TRAb levels and low ATPO levels (27).

CONCLUSIONS

The Primary Objective was to analyze the evolution of TRAb and Anti-TPO in patients with GD, evaluating the importance of these autoantibodies as predictors of response to treatment. There was a higher frequency of positive TRAb in patients who did not remission when compared to patients who had remission during follow-up (63% X 30%). In 47% of the patients who entered remission the TRAb was within the normal value throughout the follow-up.

The levels of TRAb during follow-up were lower in remission patients, with statistical significance (p = 0.049), suggesting that TRAb may have value as a predictor of response to treatment. In 56% of the patients who entered remission, the ATPO was positive during follow-up; among patients who did not go into remission, 69% presented a positive ATPO during follow-up. The comparison of the ATPO levels between patients who entered and did not enter in remission, there was no statistically significant difference (p = 0.60).

Regarding the correlation between the evolution of ophthalmopathy with TRAb and Anti-TPO levels, the mean TRAb in patients with ophthalmic alterations was higher than the mean of patients without OG, however, this difference was not statistically significant (p = 0.097).

There was a higher mean ATPO level in patients ophthalmopathy with a statistically significant difference (p = 0.048). Considering the patients with Dermatopathy (DP), the mean of the TRAb was higher than the patients without DP (p = 0.56). The mean ATPO in patients with DP, similar to OG, was also higher in patients with DP (p = 0.73).

References

1. Gadelha, P S; Montenegro, R. Interpretação dos testes de função tireoidiana, Endocrinologia Clinica - Lucio Vilar, 2013; Sexta edição- Capítulo 22, pp 390-402.
2. De los Santos, Starich GH, Mazzaferri EL. Sensitivity, specificity, and cost-effectiveness of the sensitive thyrotropin assay in the diagnosis of thyroid disease in ambulatory patients. **Arch Intern Med**, 1989; 149:526-32.
3. Mariotti S, Martino E, Cupini C, et al. Low serum thyroglobulin as a clue to the diagnosis of hyperthyroidism factitia. **N Engl J Med**.1982; 307(7):410-412.
4. Vieira, JGH, Kasamatsu T, Hauache OM et. al. Anticorpos Anti-Tiróide: Aspectos Metodológicos e Importância Diagnóstica, **Arq Bras Endocrinol Metab** 2003 47(5): 612-621.
5. LiVolsi VA. Pathology. - Braverman LE, Utiger RD, eds. Werner and Ingbar's The Thyroid.8th ed. Philadelphia: Lippincort Williams & Wilkins 2000: 488-511.
6. Luton D, Le Gac I, Vuillard E, et al. Management of Graves' disease during pregnancy: the key role of fetal thyroid gland monitoring. **J Clin Endocrinol Metab**, 2005; 90(11): 6093-8.
7. Maia A, Vaisman M, et. al. Consenso brasileiro para o diagnóstico e tratamento do hipertireoidismo: recomendações do Departamento de Tireoide da Sociedade Brasileira de Endocrinologia e Metabologia. **Arq Bras Endocrinol Metab**, 2013; 57(3): 207-220.
8. Alnaqdy A.a·Al-Maskari M.b. Determination of the levels of anti-thyroid-stimulating hormone receptor antibody with thyroid peroxidase antibody in Omani patients with Graves' disease Medical principles and practice, 2005; 14(3): 209-292.
9. M. Schott, A. Eckstein, H. S. Willenberg, T.et. al. Improved prediction of relapse of Graves' thyrotoxicosis by combined determination of TSH receptor and thyroperoxidase antibodies. **Hormone and Metabolic Research**, 2007; 39 (1): 56–61.
10. Anja K. Eckstein, et. al. Morgenthaler Thyrotropin Receptor Autoantibodies Are Independent Risk Factors for Graves' Ophthalmopathy and Help to Predict Severity and Outcome of the Disease. **J Clin Endocrinol Metab**, 2006; vol.91(9): 3464-3471.
11. Hesarghatta Shyamasunder A1, Abraham P1. Department of Diabetes and Endocrinology, Aberdeen Royal Infirmary, Aberdeen, UK. Measuring TSH receptor antibody to influence treatment choices in Graves' disease. **Clin Endocrinol** (Oxf). 2017 May;86(5):652-657. doi: 10.1111/cen.13327.
12. Li J1, Cai Y2, Sun X1, Yao D1, Xia J1. Department of Endocrine, Ningbo No. 2 MiR-346 and TRAb as Predicative Factors for Relapse in Graves' Disease Within One Year. Hospital, Ningbo City, Zhejiang Province, China. **Horm Metab Res**. 2017 Mar;49(3):180-184. doi: 10.1055/s-0043-100116. **Epub** 2017 Feb 13.
13. Katahira M1, Ogata H. Aichi Prefectural University School of Nursing and Health, Japan. Thyroglobulin Autoantibodies Are Associated with Refractoriness to Antithyroid Drug Treatment for Graves' Disease. Intern Med. 2016; 55(12):1519-24. doi: 10.2169/internalmedicine.55.6095. **Epub** 2016 Jun 15.
14. Burch, MD; David S. Cooper. Management of Graves' Disease A Review **JAMA**, 2015; 314(23:):2544-2554. doi:10.1001/jama.2015.16535.
15. Stalberg P, Svensson A, et. al. . Surgical treatmentof Graves' disease: evidence based approach. **World J**, 2008; 32:1269-77.
16. Bartalena L, Fatourechi V. Extra thyroidal manifestations of Graves' disease: a 2014 update. **J Endocrinol Invest**, 2014; 37(8):691-700.
17. Perros P, Hegedüs, Bartalena L, Marcocci C, et. al. Graves' orbitopathy as a rare disease in Europe: a European Group on Graves' Orbitopathy (EUGOGO) position statement. Orphanet J Rare Dis. 2017 Apr 20;12(1):72. doi: 10.1186/s13023-13017-0625-1.
18. Bartalena L, Burch HB, Burman KD, Kahaly GJA. A 2013 European survey of clinical practice patterns in the management of Graves' disease. **Clin Endocrinol** (Oxf), 2016; Jan 84 (1):115-120.
19. Liu X, Qiang W, Liu X, et al. A second course of antithyroid drug therapy for recurrent Graves' disease: an experience in endocrine practice. **Eur J Endocrinol**, 2015; 172(3):321-326.
20. Barbesino G, and Tomer Y. Clinical Utility of TSH Receptor Antibodies. J Clin Endocrinol Metab, 2013; 98(6): 2247–2255.
21. Feldt-RasmussenU, Schleusener H, Carayon P. Meta-analysis evaluation of the impact of thyrotropin receptor antibodies on long term remission after medical therapy of Graves' disease. **J Clin Endocrinol Metab**, 1994; 78:98–102.
22. Tamai H1, Kasagi K, Takaichi Y, et. al. Development of spontaneous hypothyroidism in patients with Graves' disease treated with antithyroidal drugs: clinical, immunological, and histological findings in 26 patients.-**J Clin Endocrinol Metab**. 1989 Jul; 69(1):49-53.
23. B. A. LambergJ. SalmiG. WägarT. Mäkinen. Spontaneous hypothyroidism after antithyroid treatment of hyperthyroid Graves' disease - **Journal of Endocrinological Investigation** - October 1981; 4 (4): 399–402
24. Peixoto MC, Coeli CM, Vaisman M. Evaluation of the Medical treatment of Graves`disease (GD). **Arq Bras Endocrinol Metabol** 2005, Jun; 49(3):410-9.
25. Davies T. Pathogenesis of Hashimoto's Thyroiditis (chronic autoimmune thyroiditis). **Uptodate.com**. Outubro 2017.
26. Ogawa T1, Sakata S, Nakamura S, Takuno H, Matsui I, Sarui H, Yasuda K. - Thyroid hormone autoantibodies in patients with Graves' disease: effect of anti-thyroid drug treatment.- **Clin Chim Acta**. 1994 Aug; 228(2):113-22.
27. Bengt Hallengren, Tereza Planck, Peter Åsman, et al. Increased TRAb and/or low anti-TPO titers at diagnosis of graves' disease are associated with an increased risk of developing ophthalmopathy after onset. **Exp Clin Endocrinol Diabetes**; 2014; 122:113–117.

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ORIGINAL ARTICLE
AGREEMENT RATE AMONG FOUR DISEASE ACTIVITIES SCORES IN RHEUMATOID ARTHRITIS

CONCORDÂNCIA ENTRE QUATRO FORMAS DE MEDIDA DE ATIVIDADE DE DOENÇA EM ARTRITE REUMATÓIDE.

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Key words: Rheumatoid arthritis, Inflammatory activity, Disease activity indexes
Descritores: Artrite reumatoide, atividade inflamatória, Indices de atividade de doença.

Abstract

Background: Measurement of disease activity in Rheumatoid Arthritis (RA) is the important to guide therapeutic choices. Several indexes have been proposed to measure this activity. **Objective:** To study the concordance level among four disease activity indexes used in RA: DAS-28 ESR (disease activity index using 28 joints and erythrocyte sedimentation rate); DAS-28 CRP (same as before but using C reactive protein instead of ESR); SDAI (simplified disease activity index) and CDAI (Clinical disease activity index). **Material and Methods**: One hundred ninety and nine patients were included and had the four indexes measured simultaneously and classified in remission, low disease activity, moderated activity and high activity according each instrument. The concordance of results (were studied through Kappa (K) calculation. **Results:** The concordance of the four indexes measuring disease remission had K=0.658; low disease activity of 0.307; moderated activity of 0.437 and high disease activity of 0.641. **Conclusion:** There is a high degree of dissociation in the obtained results. The four indexes had best agreement while judging remission and high disease activity. **Endocrinol diabetes clin exp 2019 / 2152 - 2155.**

Resumo

Justificativa: A medida da atividade de doença em artrite reumatoide ´(AR) é fundamental para orientar as escolhas terapêuticas. Existem vários indices que se propõe a medir esta atividade. **Objetivo:** Estudar o grau de concordância entre 4 dos indices de atividade de doença utilizados em AR: DAS-28-VHS (Disease Activity index usando 28 articulações e velocidade de hemossedimentação), DAS-28-CRP (mesmo que o anterior mas usando Proteina C reativa ao invés da VHS), SDAI (simplified disease activity index) e CDAI (Clinical disease activity index). **Material e Métodos:** Cento e noventa e nove pacientes foram incluídos e os quatro indices foram medidos simultaneamente, classificando os pacientes em remissão, baixa atividade, atividade moderada e alta. A concordância dos resultados foi avaliada pelo cálculo de Kappa (K). **Resultados:** A concordância dos quatro indices ao medir remissão mostrou K=0,658; em baixa atividade, o K foi de 0,307; atividade moderada de 0,437 e alta atividade de 0,641. **Conclusão:** Existe alto grau de dissociação nos resultados obtidos. Os quatro indices têm melhor concordância ao medir remissão e alta atividade. **Endocrinol diabetes clin exp 2019 / 2152 - 2155.**

INTRODUCTION

The measurement of disease activity is the main guide the therapeutic approach in patients with rheumatoid arthritis (RA) (1,2). Nowadays there is an agreement that this is a disease to be "treat to target"- that is a strategy where no inflammation is allowed (1,2). So, the rheumatologist should always try to achieve the minimum inflammatory activity for each patient changing or increasing medication if necessary. This strategy aims to avoid musculoskeletal structural damage (1) and the cardiovascular consequences of chronic inflammation (3).

However, the measurement of disease activity in RA is not an easy task. Inflammatory markers such as ESR (erythrocyte sedimentation rate) and C reactive protein (CRP) are unspecific and may not reflect the real situation. To improve this measurement some instruments have been built such as DAS-28 ESR, DAS 28 CRP, CDAI and SDAI (4-7).

DAS-28-ESR or Disease activity Score using 28 joints and the ESR- is an index that takes into account the pain and swelling of 28 joints, a measurement in the visual analogic scale (VAS) that ranges from zero to 10 of patients perception of general health and the ESR (5). DAS-28-CRP- is a Disease Activity Score measured using the same parameters as DAS-28-ESR but replacing the value of ESR for those of CRP. The final score of DAS-28-ESR and DAS-28-CRP requires application of a quite complicated formula (5).

SDAI or Simplified Disease Activity Index uses CRP, the count of swollen and of tender joints, the patient's global health assessment (from 0=best to 10=worst) and the health care provider global health assessment (from 0=best to 10=worst). The final score is obtained just adding all the values (5).

CDAI or Clinical Disease Activity Index is measured like SCDAI but do not uses the CRP neither any other laboratory test (5).

It is debated which is the best index. If there is a good agreement of theses indexes in measuring high, moderate or low disease activity, the choice of the index would not influence the therapeutic strategy. In this work, we aimed to compared the four indexes of RA disease activity to see their degree of agreement in the classification of high, moderate or low activity.

MATERIAL AND METHODS

This study was approved by local Committee of Ethics in Research and all participants sign consent. This is a cross sectional study with a convenience sample of 199 RA patients

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from a single University Hospital Rheumatology Outpatient's Clinic. This number represents all RA patients that agreed to participate of the study in the period of six months. To be included the should fill at least 6 points in the American College of Rheumatology/European League against Rheumatism (ACR/EULAR) Classification Criteria from 2010 (8). We excluded patients with less than 18 years of age and those with disease onset prior to 16 years.

Charts patients were reviewed for epidemiological data (gender, age, ethnic background), clinical and serological data (presence of extra articular features, rheumatoid factor, measurement of ESR and CRP and used medications). After this, patients were submitted to the 28 joint count for tenderness and oedema. The included joints were proximal interphalangeal, metacarpophalangeal, wrists, elbows, shoulders and knees. DAS 28-ESR , DAS-28-CRP, CDAI and SDAI were calculated simultaneously using the online calculator RheumaKit available at https://www.rheumakit.com/en/calculators.

According to DAS 28-CRP or DAS-28 ESR patients were considered to have no disease activity when the score was between 0 and <2.6. Low activity corresponded to values of 2.6 to <3.2; moderate activity when between 3.2 and ≤5.1, while high activity was above 5.1 (5).

SDAI ranges from 0-86. Generally, remission is considered achieved if the score is between 0 and 5 included; low activity corresponds to >5 to 20 included; moderate activity is between >20 and 40 included, while high activity is strictly above 40 (5).

The CDAI scores range from 0 to 76. Remission is considered when the score is between 0 and 2.6 included; low activity corresponds to >2.6 to 10 included; moderate activity is between >10 and 22 included, high activity is above 22 (5).

The agreement of results (classified in degree of disease activity) were studied through Kappa (K) calculation. When k was <0 there was no agreement; from 0-0.19 – poor agreement, between 0.20-0.39- fair agreement, from 0.40 to 0.59 moderated agreement, from 0.60 to 0.79 substantial agreement and between 0.80-1.0 as almost perfect agreement. Calculus were done with help of on line calculator from Laboratory of Epidemiology and Statistics from University of São Paulo available at http://www.lee.dante.br/index.html.

RESULTS

One hundred ninety and nine patients were included. The studied sample had 179/199 females (89.9%) with age from 25 to 80 years (median of 56 years). Rheumatoid factor was present in 121/168 (61.1%) of them; nodules were found in 26/170 (15.2%). In this population: 25.3% were using antimalarials; 73.3% were on methotrexate; 45.2% were on leflunomide, 23.7% were on anti TNF drugs and 11.1% were using other biologicals.

In this sample the DAS-28-ESR went from 1.04 to 7.69 (median of 3.39); the DAS-28 CRP from 0.49-6.88 (median of 2.71);the CDAI went from 0-53 (median of 8) and the SDAI from 0-53.02 (median of 9.1).

The classification of disease activity according to each instrument is on **table 1**.

The agreement for each inflammatory category among the four indexes showed data on **table 2**.

Table 1- Classification of inflammatory activity in 199 rheumatoid arthritis patients according to the studied four instruments.

	DAS-28-ESR	DAS-28-CRP	CDAI	SDAI
Remission	42/194 (21.6%)	61/168 (36.3%)	46/198 (23.2%)	43/177 (24.2%)
Low activity	39/194 (20.1%)	21/168 (12.5%)	79/198 (39.8%)	59/177 (33.3%)
Moderate activity	82/194 (42.3%)	57/168 (33.9%)	41/198 (20.7%)	43/177 (24.3%)
High activity	31/194 (15.9%)	29/168 (17.2%)	32/198 (16.2%)	32/177 (18.0%)

Das-28-ESR- disease activity score using 28 joints and erythrocyte sedimentation rate;
DAS-28-CRP- disease activity score using 28 joints and C reactive protein;
CDAI- Clinical Disease Activity Index
SDAI= Simplified Disease Activity Index

Table 2- Kappa values of agreement of the four studied indexes according of the degree of inflammatory activity .

	Remission	Low activity	Moderate activity	High activity
Kappa value (5% confidence interval	0.72-0.59	0.36-0.24	0.49-0.37	0.70-0.57

DISCUSSION

Our results show that the four indexes cannot be used interchangeable. The best agreement was found in the classification of disease remission and in high disease activity and the lowest at low disease activity. All these indexes have been used to measure disease activity in daily practice and to justify escalation of RA therapy (mainly the use of biologicals) to insurers and regulators.

The only index that does not use any laboratory marker of inflammatory activity is the CDAI that relies only in joint counts (tenderness and oedema) and in the assessment of physician and patient of global activity (5). This index is the easiest to be used because relies only on clinical parameters. However, it has the problem of subjectivity, and this can affect the results. All others uses one biomarker of inflammation: two of them using CRP. CRP is considered a better indicator of inflammation than the erythrocyte sedimentation rate because it is more sensitive and responds more quickly to changes in the clinical situation (9). Several factor may cause dissociation of ESR and CRP while measuring inflammatory activity and justify the discrepancy of results found presently. ESR values can be affected by size, shape and number of red blood cells (9). Considering that active RA is commonly associated with chronic disease anemia (10), the ESR in this context may be falsely elevated Other known influences on ESR are plasma albumin concentration and presence of non-acute phase reaction proteins, mainly abnormal immunoglobulins (9). Renal failure, obesity, ageing and female sex are also associated with higher erythrocyte sedimentation rates (9). In a retrospective cohort study, discrepancies between C-reactive protein and erythrocyte sedimentation rate have been reported in 12.5% of patients (11). For the above-explained reasons indexes using CRP should be more reliable than those using ESR.

Fleischmann et al. (12) found that the percentage of patients who achieved remission or low disease activity was greater for DAS28-CRP versus DAS28-ESR regardless of patient population or treatment group and suggested that these two indexes should not use the same cut off points.

Taking into account the present results, it would interesting that a physician, while following a RA patient sequentially, uses always the same index while judging worsening or improvement of inflammatory activity in order to avoid misinterpretation.

CONCLUSION

Concluding, the four used indexes to measure disease activity index in rheumatoid arthritis do not shown a good concordance except while judging remission and high disease activity. A physician that treats rheumatoid arthritis should use always the same index while accompanying an individual patient.

References

1. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. **Ann Rheum Dis**. 2016; 75:3-15.
2. Owens GM. Optimizing Rheumatoid Arthritis Therapy: Using Objective Measures of Disease Activity to Guide Treatment. **Am Health Drug Benefits**. 2015; 8:354-60.
3. Ghosh-Swaby OR, Kuriya B. Awareness and perceived risk of cardiovascular disease among individuals living with rheumatoid arthritis is low: results of a systematic literature review. **Arthritis Res Ther**. 2019;21:33.
4. Dhaon P, Das SK, Srivastava R, Dhakad U. Performances of Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) appear to be better than the gold standard Disease Assessment Score (DAS-28-CRP) to assess rheumatoid arthritis patients. **Int J Rheum Dis**. 2018; 21(11):1933-39.
5. Pinheiro GRC. Pooled indices to measure rheumatoid arthritis activity - Why and how to use them. **Rev. Bras. Reumatol**. 2007; 47:362-365.
6. Anderson JK, Zimmerman L, Caplan L, Michaud K. Measures of rheumatoid arthritis disease activity: Patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score with 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Patient Activity Score (PAS) and Patient Activity Score-II (PASII), Routine Assessment of Patient Index Data (RAPID), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Chronic Arthritis Systemic Index (CASI), Patient-Based Disease Activity Score With ESR (PDAS1) and Patient-Based Disease Activity Score without ESR (PDAS2), and Mean Overall Index for Rheumatoid Arthritis (MOI-RA). **Arthritis Care Res (Hoboken)**. 2011;63 Suppl 11:S14-36.
7. Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. **Arthritis Care Res (Hoboken)**. 2012; 64: 640-7.
8. Goeldner I; Skarel T; Messias Reason IT, Utiyama SRR. Rheumatoid arthritis: a current view . **J. Bras. Patol. Med. Lab**. 2011;47:495-503.
9. Harrison M. Erythrocyte sedimentation rate and C-reactive protein. **Aust Prescr**. 2015 ; 38(3):93-4.
10. Goyal L, Shah PJ, Yadav RN, Saigal R, Agarwal A, Banerjee S. Anaemia in Newly Diagnosed Patients of Rheumatoid Arthritis and its Correlation with Disease Activity. **J Assoc Physicians India**. 2018;66:26-9.
11. Feldman M, Aziz B, Kang GN, Opondo MA, Belz RK, Sellers C. C-reactive protein and erythrocyte sedimentation rate discordance: frequency and causes in adults. **Transl Res** 2013;161:37-43.

12. Fleischmann R, van der Heijde D, Koenig A3, Pedersen R, Szumski 3, Marshall L, et al. How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? **Ann Rheum Dis**. 2015 ; 74:1132

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ORIGINAL ARTICLE
BALANCE AND FALLS IN FIBROMYALGIA
EQUILÍBRIO E QUEDAS EM FIBROMIALGIA

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Key words: Fibromyalgia, Balance, Falls.
Descritores: Fibromialgia, Equilíbrio, Quedas.

Abstract

Background: Fibromyalgia (FM) is a chronic disease that causes important impairment in patient's quality of life. **Objective:** To compare the fall risk in FM patients with that of rheumatoid arthritis (RA) patients and normal controls.**Material and Methods:** We studied 60 FM, 60 RA patients and 60 controls for fall frequency in one week, one month, six months and one year. Patients were submitted to body mass index determination and balance evaluation by the Berg scale. Data on disease impact and depression were collected in FM patients through the Fibromyalgia Impact Questionnaire (FIQ) and the Beck Questionnaire respectively. **Results:** FM patients had a higher frequency of falls than RA and control patients in one month ($p<0.0001$), in six months ($p<0.0001$) and in one year ($p<0.0001$). No relationship was found between falls with body mass index, pain and depression scores. Falls in 12 months were associated with higher FIQ values. **Conclusion:** FM patients fall more often than RA and control patients. **Endocrinol diabetes clin exp 2019 / 2156 - 2160.**

Resumo

Justificativa: A fibromialgia (FM) é uma doença crônica que causa comprometimento importante na qualidade de vida do paciente. **Objetivo:** Comparar o risco de queda em pacientes com FM com o de pacientes com artrite reumatóide (AR) e controles normais. **Material e Métodos:** Foram estudados 60 FM, 60 pacientes com AR e 60 controles para frequência de queda em uma semana, um mês, seis meses e um ano. Os pacientes foram submetidos à determinação do índice de massa corpórea e avaliação do equilíbrio pela escala de Berg. Os dados sobre o impacto e a depressão da doença foram coletados em pacientes com FM por meio do questionário de impacto fibromialgia (FIQ) e do questionário Beck respectivamente. **Resultados:** Os pacientes com FM apresentaram maior frequência de quedas do que RA e controle em um mês ($p < 0,0001$), em seis meses ($p < 0,0001$) e em um ano ($p < 0,0001$). Não foi encontrada relação entre quedas com índice de massa corporal, escores de dor e depressão. As quedas em 12 meses foram associadas com valores mais elevados de FIQ. **Conclusão:** Os pacientes de FM caem mais frequentemente do que os pacientes de AR controles. **Endocrinol diabetes clin exp 2019 / 2156 - 2160.**

INTRODUCTION

Fracture caused by falls is one of the factors that prevent chronic diseased people from living independently and there is a need to better know the risk factors in order to effectively prevent them (1). Among these are older age, poor vision, impaired general health, medications etc (1,2). Joint abnormalities are also included (2).

Fibromyalgia (FM) is a disease with widespread musculoskeletal pain but without anatomical or physiological evidence of dysfunction of the locomotor system (3). FM patient's complaints are not always taken seriously because of lack of objective signs. Despite absence of inflammatory articular damage it has been reported that FM patients have a higher frequency of falls. Jones et al (4) studying 34 FM patients and 32 controls found that the first group had a prevalence of 37 reported falls in six months against only 6 in the second group.

In order to examine this problem, in the present study we analyzed fall frequency in FM patients comparing them with rheumatoid arthritis patients - who have objective inflammatory articular impairment - and healthy controls. We also tried to evaluate if falls in FM patients are related to balance impairment, depression, weakness and body mass index. We also studied its relation to overall pain and quality of life.

MATERIAL AND METHODS

This study was approved by the local Committee of Ethics in Research and all included participants signed a written consent.

We studied 180 participants: 60 with FM and 60 with RA diagnosed according to the American Rheumatology Classification Criteria for FM (5) and RA (6) respectively and 60 healthy controls. Data on the three studied group are in **table 1**. We excluded patients that could not stand up alone, had severe vision or auditive impairment, known vestibular diseases, diabetes mellitus, polyneuropathy, dementia, history of head injury and secondary fibromyalgia.

The FM participants were selected according to the appointment sequence and willingness to participate in the study; RA patients and healthy controls were chosen according appointment order and matched for age and sex. Healthy controls were invited among physiotherapy professionals and students.

In the RA group, 52/60 (86.6%) were using prednisone; 45/60 (75%) were using methotrexate; 35/60 (58.3%) were using antimalarials; 23/60 (38.3%) were on leflunomide use; 7/60 (11.6%) on sulphasalazine and 3/60 (5%) on anti-TNF use. The DAS-28 4v (or disease activity score using 28 joints- 4th version) (7) (varied from 0.7 to 7.0 (mean 3.26±1.40) and there were 32/60 patients in functional class (8) 1 (53.3%); 22/60 (36.6%) in class 2 and 6/60 (10%) in class 3. Disease duration varied from 8 to 372 months (mean 121.6± 92.5; median 96 months).

After obtaining demographic data, data on weight and height for body mass index (BMI) determination, all participants were asked to recall the number of falls in the last week, month, six months and one year. BMI index was calculated according to standard formula (9). Patients were divided according to BMI in four groups: < 20 kg/m2; 21-25 kg/m2 ; 26-30 kg/m2 and >30 kg/m2.

Falls were defined as an unintentionally coming to rest on the floor or low surface such as chair or bed. (10)

All participants were submitted to the Berg test (11). This is

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an instrument that analyses functional balance through common tasks such as trying to reach for an object, to change from one place to another, to stay, to rise, to turn etc all of which involve static and dynamic balance. These tasks are scored according to a Likert scale (from zero to four) with a total maximum of 56 points. Lower scores indicate a poorer balance. This instrument has 82-91% sensitivity and 70-95% specificity in fall risk evaluation (11).

RA and FM patients were asked to fill a VAS (visual analogic scale) from zero to 10 on overall pain.

Patients with FM were also submitted to a Fibromyalgia Impact questionnaire (FIQ) for determination of disease impact and the depression Beck scale. FIQ (12) is a 10 item instrument that measures physical impairment, severity of specific symptoms such as pain, stiffness, fatigue, disability and overall well-being during the last week. The severity of each symptom is measured on a scale from 0 (absence of symptoms) to 10 (very severe). Total FIQ score range from 0 to 100, with higher scores indicating greater impairment. The Beck depression scale (13) has 21 items graded in scores of four (1= absent, 2=light, 3=moderate and 4=severe) ranging from 0 to 84 with higher scores translating more depressive state. This scale evaluates symptoms that are usually present in depression independent of its cause. Inquired items concern humor, fatigue, anhedonia, health worries, libido alterations among others.

Obtained data were grouped in frequency and contingency tables. We applied Mann-Whitney and Kruskall-Wallis test for comparing tests of numeric data and chi-squared for nominal data. For correlation studies we used the Spearman test. Statistical analysis was done with help of the software Graph Pad Prism 4.0 adopting a significance of 1%.

Table 1 - shows the pairing data of the 3 studied groups: FM, RA and controls.

RESULTS

Studying the number of falls in the three samples, we found the data in **table 2 and figure 1** that reveal a higher number of falls in FM patients that in controls and RA. RA patients have more falls than controls but without reaching statistical significance.

Table 1- Pairing data of fibromyalgia (FM), rheumatoid arthritis (RA) and healthy control group.

		FM (n=60)	RA (n=60)	Control (n=60)	P
Mean age		51.80±9.97	49.98±10.93	50.35±10.31	0.60
Gender (Female/male)		55/5	55/5	55/5	1,0
BMI (kg/m2)	<20	0	6	2	
	20-25	21	16	23	
	26-30	17	24	22	
	>30	22	14	13	0,052

BMI= body mass index

Table 2- Number of falls in fibromyalgia (FM), rheumatoid arthritis (RA) and healthy control groups

	FM(n=60)	RA (n=60)	Healthy control (n=60)	P
Falls in one week (mean)	0.13±0.34	0.07±0.31	0.02±0.13	0.0332
Falls in one month (mean)	0.65±1.10	0.13±0.50	0.07±0.25	<0.0001
Falls in six month (mean)	1.65±3.15	0.42±1.15	0.25±0.51	<0.0001
Falls in one year	2.43±3.77	0.67±1.62	0.55±1.35	<0.0001

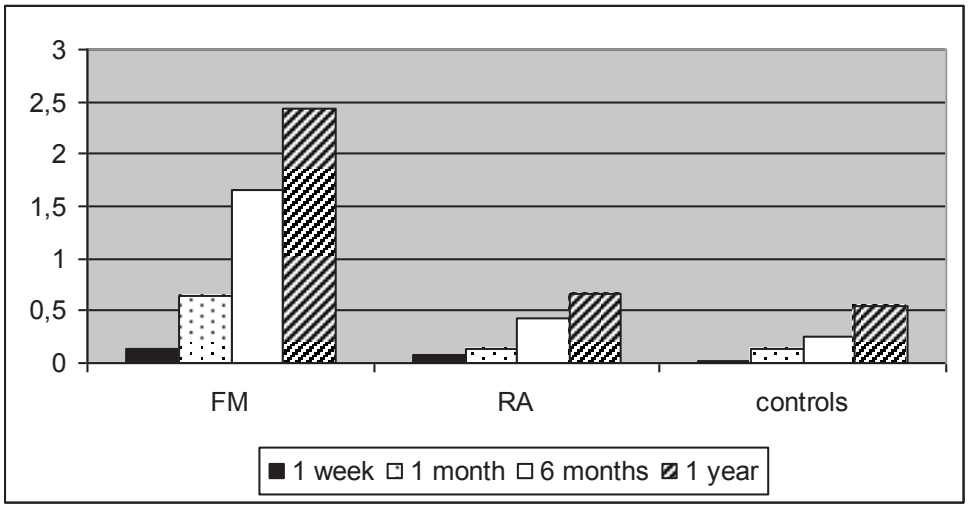

Figure 1 - Mean fall frequency (per person) in Fibromyalgia (FM), Rheumatoid Arthritis (RA) patients and healthy controls in one week, one month, six months and one year.

1 week - FM X RA p=0.42 ; FM X healthy control p= 0.31; Healthy control X RA with p=0.86
1 month - FM X RA p=0.012; FM X healthy control p= 0.0062; Healthy control X RA with p=0.85
6 months -FM X RA p= 0.003; FM X healthy control p=0.0001; Healthy control X RA with p=0.94
1 year - FM X RA p< 0.0001; FM X healthy control p <0.0001; Healthy control X RA p=0.64

Studying the Berg values in the three groups we found that in the FM group: 2/60 had values between 21-40 and 58/60 had values between 41-56; in the RA patients: 1/60 had values between 21-40 and 58/60 between 41-56 and all the controls (60/60) were in the group between 41-56 (p=0.36).

The relationship of Berg values and fall numbers was found in the FM group at 1 and 6 months and 1 year according to data in **table 3**.

No influence of BMI in the number of falls could be found in the three studied groups as shown in **table 4**.

Table 3- Relationship of berg scale and number of falls in rheumatoid arthritis (RA) fibromyalgia (FM) and healthy controls.

	1 week		1 month		6 months		1 year	
	p	Spearman r	P	Spearman r	P	Spearman r	p	Spearman r
FM	0.054	-0.175	0.001	-0.296	0.0009	-0.299	<0.0001	-0.353
RA	0.21	-0.162	0.92	0.0012	0.74	-0.042	0.55	-0.07
Controls	0,57	0,074	0,93	0,010	0,30	-0,13	0,05	-0,24

Table 4- Number of falls in rheumatoid arthritis (RA) and fibromyalgia (FM) and healthy controls according to body mass index

	1 week		1 month		6 months		1 year	
	p	Spearman r	P	Spearman r	P	Spearman r	p	Spearman r
FM	0.47	-0.065	0.44	0.071	0.07	0.161	0.12	0.141
RA	0.22	0.160	0.25	0.150	0.61	0.066	0.90	-0.016
Controls	0.11	0.206	0.22	0.158	0.56	0.076	0.53	0.082

Mean values of EVA (or visual analogic scale) for pain were 7.80 ±2.10 in FM and 4.63±2.77 in RA patients (p=0.00001).

Analyzing the number of falls in relation to pain, Beck and FIQ in the FM group, we found the results in **table 5**.

Table 5: Correlation between falls and pain, depression (by Beck scale) and fibromyalgia impact questionnaire (FIQ).

	EVA pain		BECK		FIQ	
	p	Spearman r	p	Spearman r	p	Spearman r
1 week	0.98	0.002	0.69	0.051	0.24	0.15
1 month	0.60	0.067	0.68	0.053	0.11	0.20
6 months	0.16	0.180	0.87	0.020	0.08	0.22
1 year	0.018	0.302	0,87	-0,020	0.005	0.35

If we isolate the item on "feeling weak" from the FIQ, we find that FM patients have an EVA on weakness from 01 to 8.5 (mean 6.29±1.99) and no relationship could be found between feeling of weakness and falls in one week (p=0.67); one month (p=0.57), 6 months (p=0.24) or one year (p=0.09).

DISCUSSION

Our results demonstrate that FM patients have a mean fall frequency higher than that of RA and normal controls. The incidence of falls in 6 months was 1.75 falls/person, a higher value than that found by Jones et al (4), (1.15 falls/person).

Rheumatic disease may cause falls if they induce loss of balance, muscle weakness and alterations in the gait pattern. Loss of balance and falls have been linked to muscle weakness in RA and in FM. Yet in our study, balance by the Berg scale was the same in RA and FM patients even though these two patient groups had different fall frequency.

According to Nørregaard et al (14), FM patients have a reduction in muscle strength per area unit of about 35%. These authors claimed that this finding may be secondary to physical inactivity or neuroendocrine factors. Others have found that the improvement of muscle strength predicts benefits on postural balance of FM patients (15). However if one is to credit falls just to loss of muscle strength, how is it possible to explain that the RA group have different fall frequencies than the FM group? Pierroynoswski et al (17) observed that FM patients exhibit a different gait pattern when compared to healthy controls. They found that FM patients preferentially power gait using hip flexors while normal controls use ankle plantar flexors. The pattern used by FM patients is similar to that used for healthy controls when walking fast. These authors claim that this could explain the fatigue feeling experienced by these patients; one could also implicate this finding in the fall frequency. Decreased ankle flexibility, decreased plantar tactile sensitivity and toe plantar strength are considered as contributors to fall in elderly people without arthritis (17). Another finding by Bazzichi et al (18), who studied electroneuromyographic findings, is that FM patients have median spectral frequency, conduction velocity and fatigue index significantly lower than controls, suggesting that they may have different fiber recruitment or type 2 fiber atrophy. These alterations impair muscle relaxation and cause an activation pattern of motor unit similar to that seen in patients with Parkinson's disease. Auditory brainstem function is also found to be abnormal in FM patients (20).

In elderly people, depression is considered a significant predictor of being a "faller" at 12 months (21). The underlying mechanism is not well known but it is thought to be mediated through loss of self confidence and anxiety in performing daily tasks. Also association of gait unsteadiness and depression has been demonstrated as these patients have greater swing time and stride time variability. In the present study, we could not assign falls to depression in FM patients.

We found an association of number of falls at 12 months with FIQ and a trend to association with pain severity showing that falls are more common in people with higher disease impact even though a causal relationship cannot be inferred.

CONCLUSION

Concluding, our findings suggest that FM patients have higher fall frequency than RA patients and normal controls. In the studied sample, no relationship of falls with BMI, depression or pain could be demonstrated. Patients with more frequent falls in 12 months have a poorer quality of life. Even though this is a retrospective study with all the recall bias involved in such a design it highlights the higher prevalence of falls in FM patients and suggests that more studies should be done in order to understand the pathophysiology of falls in this population

References

1. Oswald AE, Pye SR, O'Neill TW, Bunn D, Gaffney K, Marshall T et al. prevalence and associated factors for falls in women with established inflammatory polyarthritis. **J Rheumatol** 2006; 33:690-4.
2. Smulders E, Schreven C, Weerdesteyn V, van den Hoogan FH, Laan R, Lankveld WV. Fall Incidence and fall risk factors in people with rheumatoid arthritis. **Ann Rheum Dis** 2009; 68: 1795-6.
3. Arias M. Es la fibromialgia una enfermidad neurological? **Neurologia** 2008; 23: 593-601.
4. Jones KD, Horak FB, Winters-Stone K, Irbine JM, Bennet RM. Fibromyalgia is associated with impaired balance and falls. **J Clin Rheumatol** 2009;15: 16-21.
5. Dadabhoy D, Clauw DJ. The fibromyalgia syndrome. In Klippel JH, Stone JH, Crofford LJ, White PH. (Eds) **Primer on the Rheumatic diseases**. 13th Ed, Springer Science , N York, 2008, p.87-93.
6. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. **Arthritis Rheum**. 1988; 31:315-24.
7. Fransen J, van Riel PLCM. DAS remission cut points. **Clin Exp Rheumatol** 2006; 24 (S-43):S29-S32.
8. Klippel JH, Dieppe PA. Selected measures for outcome assessment of rheumatic diseases. In Klippel JH, Dieppe PA (Eds). **Rheumatology** 1998, 2nd Ed, Mosby, London, vol.2, S-A:1-12.
9. Department of Health and Human Services, National Institutes of Health, Obesity Education Iniative. BMI Calcultor. Captured at http://www.nhlbisupport.com/bmi/, in 2nd February 2010.
10. Kaz Kaz H, Johnson D, Korry S, Chinappen U, Tweed K, Patel S. Fall-related risk factors and osteoporosis in women with rheumatoid arthritis. **Rheumatology** 2004; 43: 1267-71.
11. Miyamoto ST, Lombardi Jr I, Berg KO, Ramos LR, Natour, J. Brazilian version of the Berg balance scale. **Braz J Med Biol Res** 2004; 37:1411-21.
12. Marques AP, Santos AMB, Assumpção AMLA, Lage LV, Pereira CAB. Validation of the Brazilian version of the Fibromyalgia Impact Questionnaire (FIQ). **Rev Bras Reum**.2006; 46: 24-31.
13. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory

for measuring depression. Arch Gen Psychiatry 1961; 4: 561-71.
14. Nørregard J, Büllow PM, Danneskiold-Samsøe B. Muscle strength, voluntary activation, twitch properties and endurance in patients with fibromyalgia **J Neurol Neurosurg Psychiatry** 1994;57: 1106-11.
15. Tomas-Carus P, Gusi N, Häkkinen A, Häkkinen K, Raimundo A, Ortega-Alonso A. Improvement of muscle strength predicted benefits in HRQOL and postural balance in women with fibromyalgia: an 8-month randomized controlled trial. **Rheumatology** 2009; 48:1147-51.
16. Pierrynowski MR, Tiidus PM, Galea V. Women with fibromyalgia walk with an altered synergy. **Gait Posture** 2005; 22:210-8.
17. Menz HE, Morris ME, Lord SR. Foot and ankle risk factors for falls in older people: a prospective study. **J Gerontol A Biol Sci Med Sci** 2006, 61:866-70.
18. Bazzichi L, Dini M, Rossi A, Corbianco S, De Feo F,giacomelli et AL. Muscle modifications in fybromyalgic patietns revealed by surface electromyography (SEMG) analysis. **BMC Musculskelet Disord** 2009; 10: 36-42.
19. RosenhallU, Johansson G, Orndahl G. Eye motility dysfunction in chronic primary fibromyalgia with disesthesia. **Scand J Rehabil Med** 1987;19:147-52.
20. Sai AJ, Gallagher JC, Smith LM, Logsdon S. Fall predictors in the community dwelling elderly: a cross sectional and prospective cohort study. **J Musculoskelet Neuronal Interact** 2010;10 :142-50.

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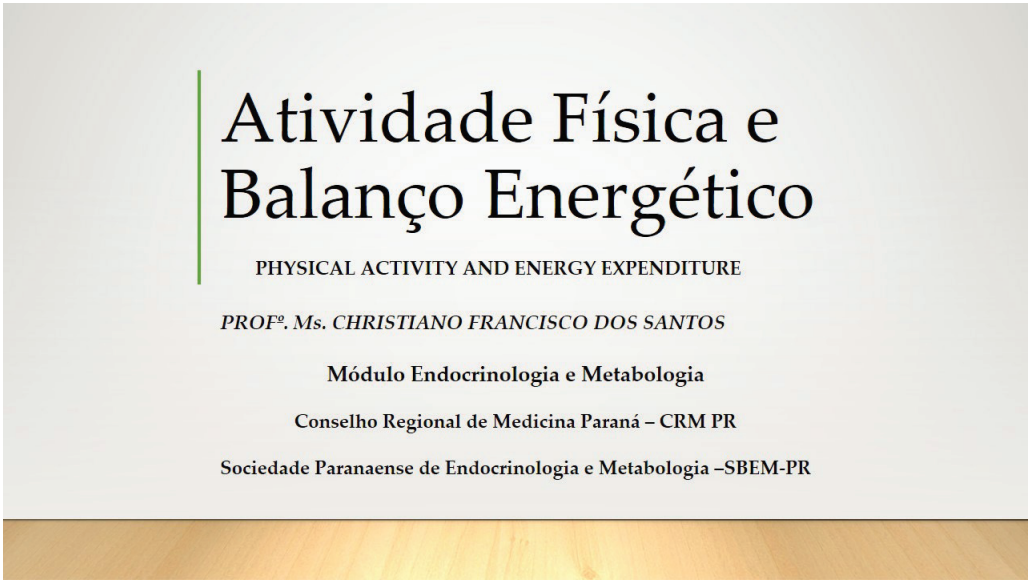
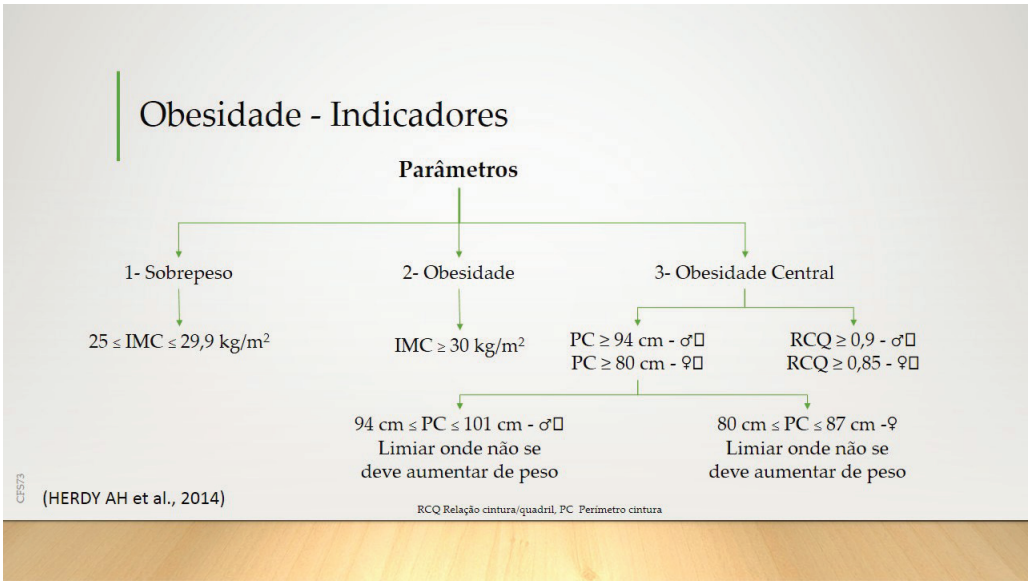
LECTURE
PHYSICAL ACTIVITY AND ENERGY EXPENDITURE
EXERCISE SEEMS TO PREVENT THE RETURN OF WEIGHT GAIN

PROFº. MS. CHRISTIANO FRANCISCO DOS SANTOS





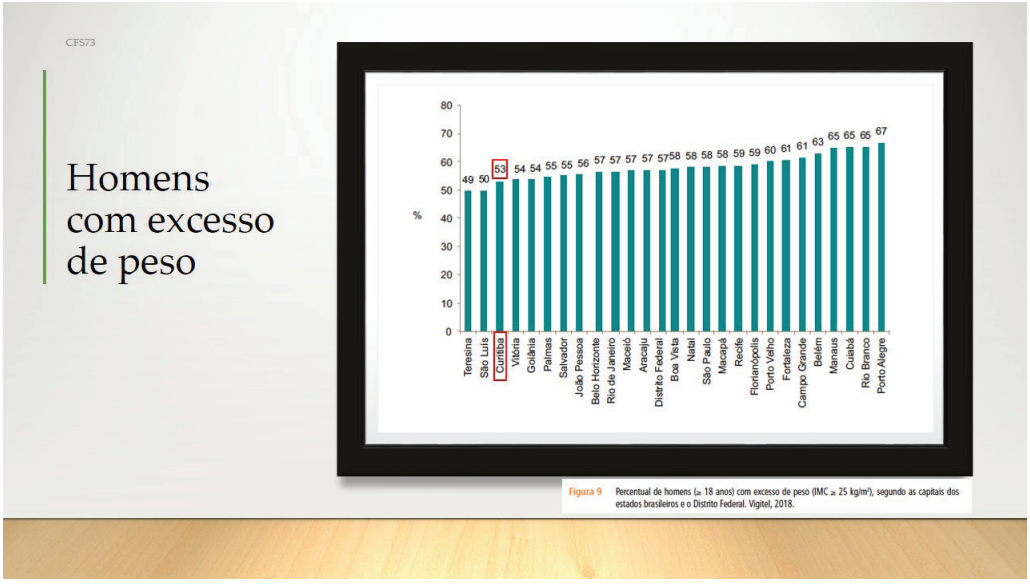


Figura 9 Percentual de homens (≥ 18 anos) com excesso de peso (IMC ≥ 25 kg/m²), segundo as capitais dos estados brasileiros e o Distrito Federal. Vigitel, 2018.

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Homens com obesidade

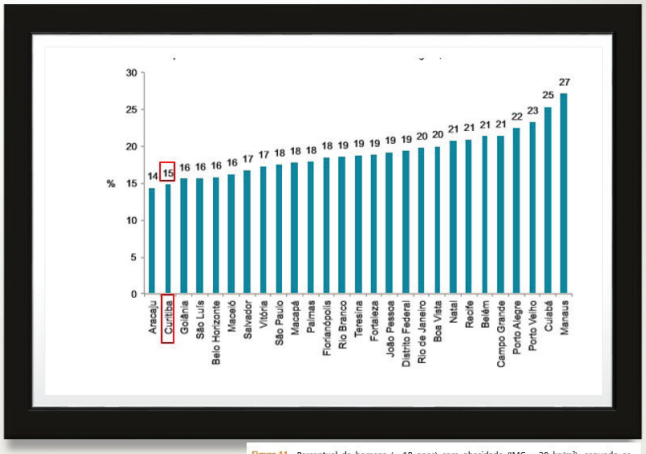

Figura 11 Percentual de homens (≥ 18 anos) com obesidade (IMC ≥ 30 kg/m²), segundo as capitais dos estados brasileiros e o Distrito Federal. Vigitel, 2018.

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Mulheres com excesso de peso

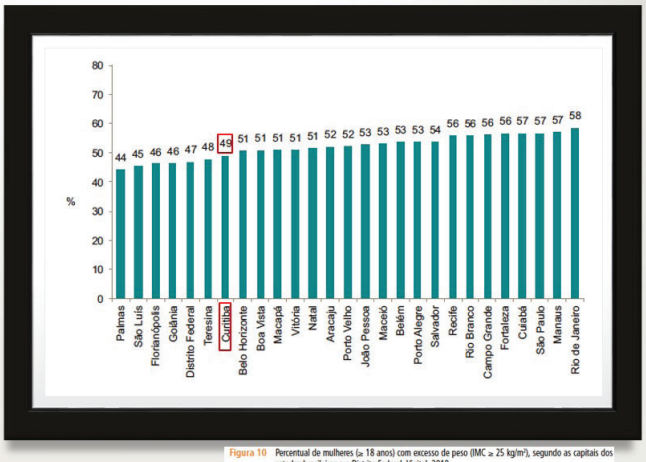

Figura 10 Percentual de mulheres (≥ 18 anos) com excesso de peso (IMC ≥ 25 kg/m²), segundo as capitais dos estados brasileiros e o Distrito Federal. Vigitel, 2018.

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Mulheres com obesidade

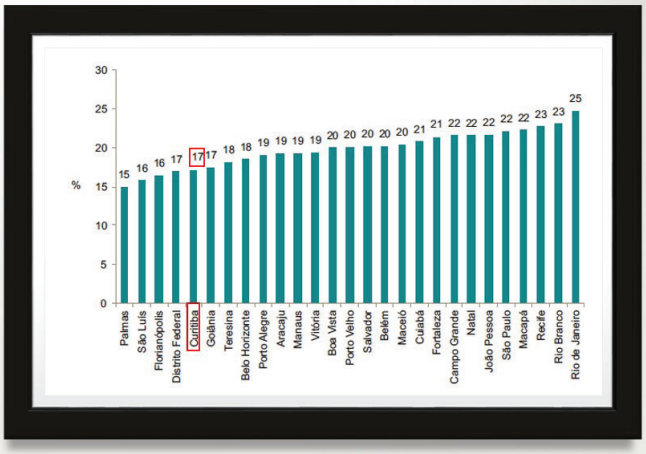

Figura 12 Percentual de mulheres (≥ 18 anos) com obesidade (IMC ≥ 30 kg/m²), segundo as capitais dos estados brasileiros e o Distrito Federal. Vigitel, 2018.

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Homens que praticam atividade física pelo menos 150′/sem.

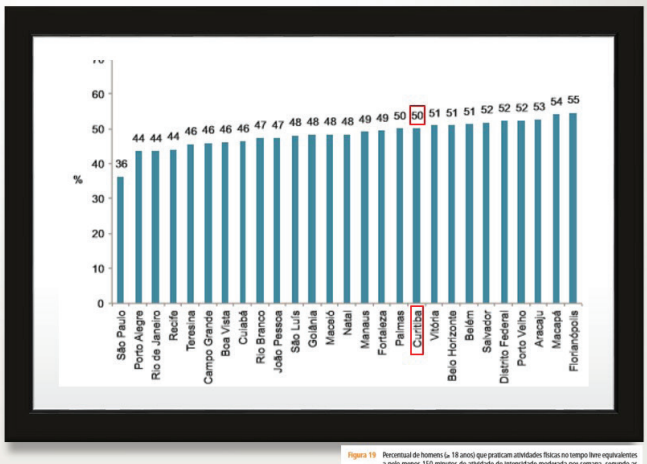

Figura 19 Percentual de homens (≥ 18 anos) que praticam atividades físicas no tempo livre equivalentes a pelo menos 150 minutos de atividade de intensidade moderada por semana, segundo as capitais dos estados brasileiros e o Distrito Federal. Vigitel, 2018.

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Mulheres que praticam atividade física pelo menos 150′/sem.

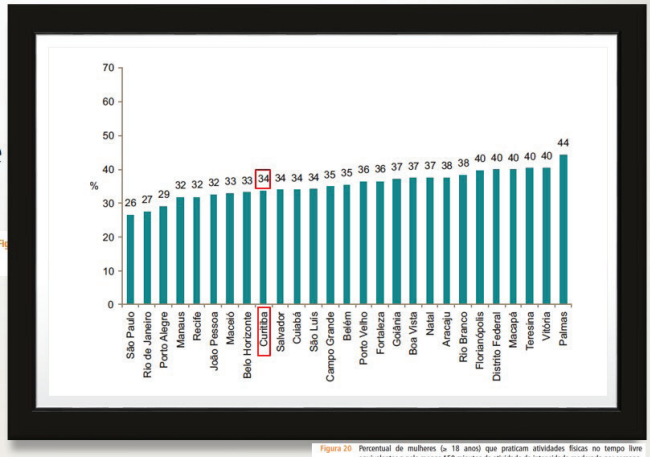

Figura 20 Percentual de mulheres (≥ 18 anos) que praticam atividades físicas no tempo livre equivalentes a pelo menos 150 minutos de atividade de intensidade moderada por semana, segundo as capitais dos estados brasileiros e o Distrito Federal. Vigitel, 2018.

Obesidade – Comorbidades Associadas

Obesidade

- Doenças Cardiovasculares
- Diabetes Mellitus
- Câncer
- Problemas Musculoesqueléticos

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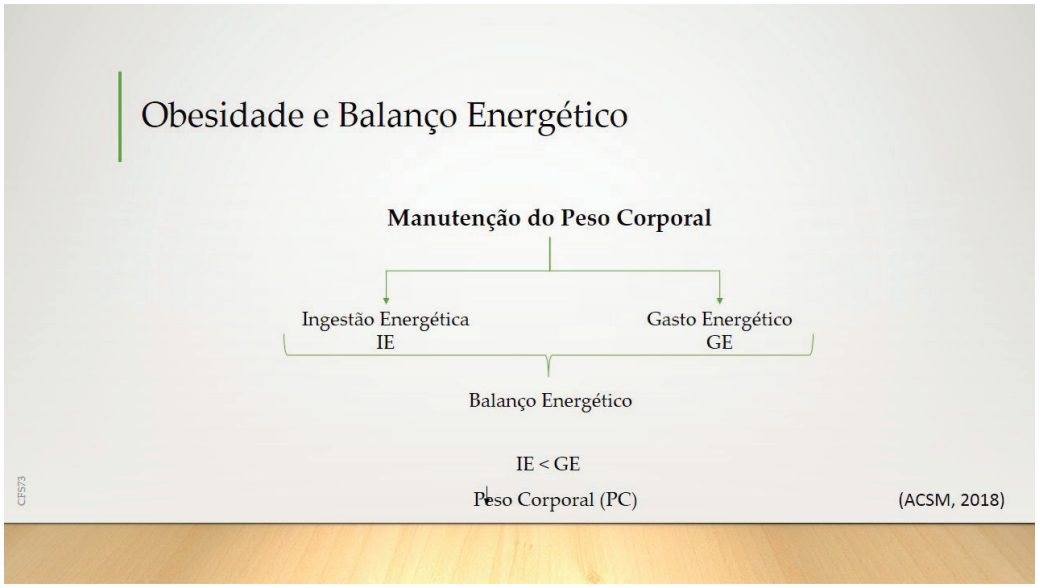
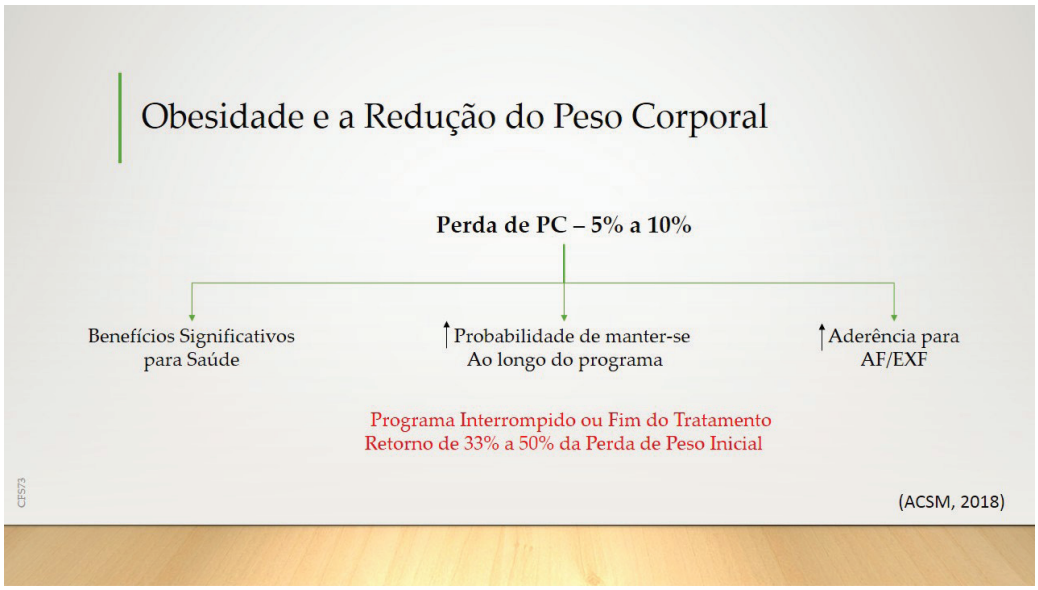
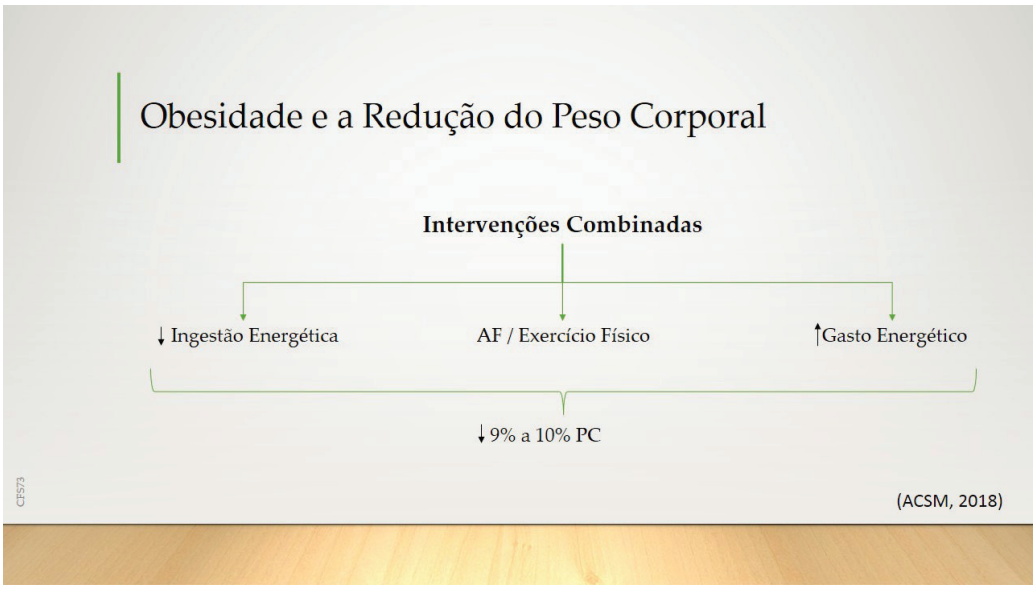
(HERDY AH et al., 2014)


Obesidade e Balanço Energético
Manutenção do Peso Corporal
Ingestão Energética
IE
Gasto Energético
GE
Balanço Energético
IE < GE
Peso Corporal (PC)
(ACSM, 2018)


Obesidade e a Redução do Peso Corporal
Perda de PC – 5% a 10%
Benefícios Significativos
para Saúde
Probabilidade de manter-se
Ao longo do programa
Aderência para
AF/EXF
Programa Interrompido ou Fim do Tratamento
Retorno de 33% a 50% da Perda de Peso Inicial
(ACSM, 2018)


Obesidade e a Redução do Peso Corporal
Intervenções Combinadas
Ingestão Energética
AF / Exercício Físico
Gasto Energético
9% a 10% PC
(ACSM, 2018)

Obesidade e o Programa de Intervenção

Início do Programa de Intervenção

↓Ingestão Energética → Mais determinante

Exercício Físico → Impacto Modesto

IE Moderada + E. Físico Moderada/Vigoroso = Maximiza a Perda de Peso em Indivíduos com sobrepeso e Obesos

(ACSM, 2018)

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Obesidade e o Programa de Intervenção

Porém, o Exercício Físico Parece Impedir o Retorno do Sobrepeso e da Obesidade

(ACSM, 2018)

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Prescrição de Exercícios

FITT

- **Frequência:** 5x Semanais.
- **Intensidade:** 40% a 60% VO2res. / FCres >= 60% VO2res. / FCres.
- **Tempo**: 30´ - 60´/ dia
- **Tipo:** Aeróbios - GM Exercícios de Força, Equilíbrio e Flexibilidade

Liberação Médica: Teste de Esforço

Avaliação

- Clínica.
- Antropométrica.
- Funcional

(ACSM., 2018)

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Manutenção da Perda de Peso

Tempo: > 250′

Frequência: 5 a 7x Semana

Duração: 30′ dia → 250′dia.

Realizar múltiplas sessões ao longo do dia de 10′

Exercícios de Força
↑ Força Muscular
↑ Capacidade Funcional
↓ Risco de doenças crônicas não transmissíveis

Mudança de Comportamento no Estilo de Vida - Incluir mais AF ao longo do dia

CFS73

(ACSM., 2018)

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Take Home Message

- Mínimo de 5% a 10% PC ;
- Abordagem Multiprofissional;
- Mudança de Comportamento – Hábitos Saudáveis;
- Redução da Ingestão Energético;
- Exercício Físico por no mínimo 150′semanais – Até alcançar 250′;
- Exercícios Multicomponentes
  - Aeróbio, Força, Equilíbrio e Flexibilidade.

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OBRIGADO

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ENDOCRINOLOGY AND DIABETES SERVICE PROTOCOL OF HOSPITAL UNIVERSITÁRIO EVANGÉLICO MACKENZIE DE CURITIBA-PR - BRAZIL - FOR DIAGNOSIS OF MATURITY ONSET DIABETES OF THE YOUNG

PROTOCOLO DO SERVIÇO DE ENDOCRINOLOGIA E DIABETES DO HOSPITAL UNIVERSITÁRIO EVANGÉLICO MACKENZIE DE CURITIBA-PR - BRASIL - PARA DIAGNÓSTICO DO DIABETES TIPO MODY

THAMARABATISTELLA
JAMILLE LUNKES
MIRNALUCI PAULINO RIBEIRO GAMA

MODY 1	MODY 2	MODY 3	MODY 4	MODY 5
CROMOSSOMO 20q HNF 4ALFA	**CROMOSSOMO 7p GLUCOQUINASE**	**CROMOSSOMO 12q HNF 1ALFA**	**CROMOSSOMO 13q PDX-1 OU IPF-1**	**CROMOSSOMO 17q HNF 1BETA**
FENÓTIPO: SEMELHANTE MODY 3 DEFEITO PRIMÁRIO: PÂNCREAS, PODE TER ALTERAÇÃO EM NÉFRON	FENÓTIPO: DIABETES DE FÁCIL CONTROLE, ASSINTOMÁTICOS, PODEM PASSAR A VIDA SEM DIAGNÓSTICO DEFEITO PRIMÁRIO: FÍGADO E PÂNCREAS	FENÓTIPO: DM2 PRINCIPALMENTE, MAS PODE SE ASSEMELHAR AO DM1. ALTA PENETRÂNCIA. DEFEITO PRIMÁRIO: RIM (SGLT2), PÂNCREAS (GENE INSULINA), FÍGADO (PCR)	FENÓTIPO: SEMELHANTE A MUTAÇÃO DO HNF 1ALFA DEFEITO PRIMÁRIO: PÂNCREAS	FENÓTIPO: VARIÁVEL, DISFUNÇÃO DE CÉLULA BETA E INSULINO RESISTÊNCIA SEM OBESIDADE DEFEITO PRIMÁRIO: RIM, PÂNCREAS FÍGADO E TRATO GENITAL
APOA1, APOA2 E HDL ↓ LDL DISCRETAMENTE ↑ TOTG: ↑ DESPROPORCIONAL	PODE ABRIR COMO DMG ALTERAÇÃO DO *SET POINT* DE LIBERAÇÃO DE INSULINA	PODE ABRIR O QUADRO MAIS TARDIAMENTE (ATÉ 55 ANOS)	PODE CURSAR COM AGENESIA PANCREÁTICA	HIPERINSULINEMIA, ↑ TG E ↓ HDL
BIFÁSICO: HIPERINSULINEMIA INTRA ÚTERO (MACROSSOMIA + HIPOGLICEMIA TRANSITÓRIA AO NASCER) E HIPOINSULINEMIA DURANTE A VIDA (PROGRESSIVA DISFUNÇÃO DE CÉLULA BETA)	GLICADA 5,5 – 8% GJ 100 – 145 TOTG ↑ < 50MG/DL APÓS 2H AUTO ANTICORPOS NEGATIVOS PEPTÍDEO C + INCAPACIDADE DE FAZER GLICOGÊNESE	INÍCIO: JEJUM NORMAL, PÓS PRANDIAIS ALTERADAS TOTG ↑ 80MG/DL APÓS 2H *** GLICOSÚRIA*** GLISOSÚRIA PRESENTE MESMO COM GLICEMIA BAIXA (145MG/DL)		PODE CURSAR COM ATROFIA PANCREÁTICA, CISTOS RENAIS, PROTEINÚRIA LEVE, ESTENOSE URETERAL, INSUFICIÊNCIA RENAL DIABETES PÓS TRANSPLANTE RENAL(*PTDM*), MÁ FORMAÇÃO UTERINA, DISFUNÇÃO HEPÁTICA *** SEMPRE SOLICITAR ECOGRAFIA ABDOMINAL ***
MACROANGIOPATIA PODE SER MAIS PRESENTE	RETINOPATIA: CUIDAR, PRINCIPALMENTE APÓS 40 ANOS ASSOCIAÇÃO COM DCV	MENOR RISCO DCV PELA MENOR ATIVIDADE SIMPÁTICA HDL MAIOR PORÉM NÃO CARDIOPROTETOR		ASSOCIA-SE TAMBÉM A RETARDO MENTAL, DÉFICIT DE CRESCIMENTO, HIPERURICEMIA E DEFICIÊNCIA EXÓCRINA DO PÂNCREAS. PARECE TER MAIOR RISCO DE CA DE PRÓSTATA
RESPONDE A SULFONILUREIA, MAS MENOS QUE O TIPO 3	QUANDO NECESSÁRIO TRATAMENTO, DOSES MAIORES QUE O HABITUAL DE INSULINA SÃO NECESSÁRIAS	RESPONDE MUITO A SULFONILURÉIA!!!! INICIAR COM 20 – 40MG *RISCO DE HIPOGLICEMIA*		NÃO RESPONDE A SULFONILUREIA, DETERIORAÇÃO IMPORTANTE DE CÉLULAS BETA, INSULINOTERAPIA PRECOCE, RISCO DE *CETOACIDOSE*
DISLIPIDEMIA: TRATAR COMO OUTROS DIABÉTICOS	GESTAÇÃO: FETO COM BAIXO PESO: PROVÁVEL PORTADOR DA MUTAÇÃO, NÃO TRATAR A MÃE. FETO NORMAL: TRATAR A MÃE	PIORA PROGRESSIVA POR PERDA DE FUNÇÃO DA CÉLULA BETA NECESSIDADE DE INSULINIZAÇÃO TARDIA E NA GESTAÇÃO		CRIANÇA COSTUMA NASCER COM BAIXO PESO, 800G ABAIXO DO NORMAL, PELA ↓ SECREÇÃO DE INSULINA

E-mail:mirnaluci.gama@yahoo.com

MODY 6	MODY 7	MODY 8	MODY 9	MODY 10	MODY 11
NEURO D1	**KLF 11**	**CEL**	**PAX 4**	**GENE DA INSULINA**	**BLK**
DEFEITO NA TRANSCRIÇÃO DA INSULINA E NO DESENVOLVIMENTO PANCREÁTICO	FATOR DE TRANSCRIÇÃO DO PÂNCREAS, REGULADOR NEGATIVO DO CRESCIMENTO CELULAR EXÓCRINO	ATUA NA FUNÇÃO EXÓCRINA E ENDÓCRINA DO PÂNCREAS. GENE EXPRESSO NOS TECIDOS ACINARES PANCREÁTICOS E CÉLULAS LACTOTRÓFICAS	DISFUNÇÃO QUE AFETA O DESENVOLVIMENTO DA CÉLULA BETA DURANTE O DESENVOLVIMENTO EMBRIONÁRIO, LEVANDO A REDUÇÃO DA MASSA DAS CÉLULAS ADULTAS E DA SUA PROLIFERAÇÃO	FENÓTIPO: DESDE DIABETES LEVE E HIPERINSULINEMIA, POR ↓ DA ATIVIDADE BIOLÓGICA DA MOLÉCULA DE INSULINA, A DOENTES MODY COM MUTAÇÕES QUE REDUZEM A ESTABILIDADE ESTRUTURAL DA INSULINA E ATÉ DIABETES NEONATAL POR MUTAÇÕES QUE CAUSAM DEFEITOS GRAVES NA BIOSSÍNTESE DA MOLÉCULA DE INSULINA	GENE DA FAMÍLIA SRC DE PROTO ONCOGENES. EXPRESSO NAS CÉLULAS B, PROMOVE A SÍNTESE E SECREÇÃO DE INSULINA EM RESPOSTA À GLICOSE, PELO *UPREGULATION* DOS FATORES DE TRANSCRIÇÃO PDX-1 E NKX-6
REGULA EXPRESSÃO DA INSULINA	DEIXA AS CÉLULAS PANCREÁTICAS MAIS SUSCETÍVEIS AO ESTRESSE OXIDATIVO POIS ATIVA O PROMOTOR DA CATALASE 1, REDUZ O CLEARANCE DE RADICAIS LIVRES, AUMENTANDO ASSIM SUA APOPTOSE	ENZIMA CARBOXYL ESTER LIPASE – CEL É UMA LIPASE DEPENDENTE DE SAIS BILIARES, ATUANDO NA HIDRÓLISE E ABSORÇÃO DE COLESTEROL E VITAMINAS LIPOSSOLÚVEIS		SUA MUTAÇÃO CAUSA DIABETES NEONATAL PERMANENTE, MAS RARAMENTE PODEM CAUSAR MODY	ATUA A NÍVEL DE SINALIZAÇÃO CELULAR, ESTANDO ENVOLVIDOS EM ADESÃO, CRESCIMENTO, MOVIMENTO E DIFERENCIAÇÃO CELULARES
		LIPOMATOSE PANCREÁTICA E DISFUNÇÃO EXÓCRINA PRECOCES			

CRITÉRIOS SUGESTIVOS – MODY

IDADE DE INÍCIO DE DIABETES ANTERIOR AOS 25 ANOS	GLICOSÚRIA OBSERVADA INAPROPRIADAMENTE COM EUGLICEMIA OU HIPERGLICEMIA MODERADA, NA AUSÊNCIA DE ALBUMINÚRIA E DIABETES MAL CONTROLADO (BAIXO LIMIAR RENAL QUE RESULTA EM GLICOSURIA É UMA CARACTERÍSTICAS TÍPICA DE MODY3)	DIABETES MODERADO NA APRESENTAÇÃO, SEM CETOSE SIGNIFICATIVA
CARACTERÍSTICAS INCONSISTENTES COM OUTROS TIPOS DE DIABETES: 1. SEM OBESIDADE SIGNIFICATIVA, 2. AUSÊNCIA DE ACANTOSE NIGRICANS 3. EVIDÊNCIA DE RESISTÊNCIA À INSULINA EM DM TIPO 2 DE INÍCIO PRECOCE 4. HISTÓRIA FAMILIAR DE DIABETES 5. AUSÊNCIA DE AUTO-ANTICORPOS PANCREÁTICOS.	NECESSIDADE REDUZIDA DE INSULINA MESMO FORA DO PERÍODO DE "LUA DE MEL", A NECESSIDADE DE INSULINA EM MODY É INFERIOR A DM TIPO 1.	RAÇA: ALGUNS AUTORES SUGEREM QUE MODY É MAIS FREQUENTE EM EUROPEUS, MAS ESTA PATOLOGIA FOI IDENTIFICADA EM TODAS RAÇAS, APESAR DE MENOS FREQUENTES.
- HISTÓRIA FAMILIAR DE DIABETES EM PELO MENOS DUAS GERAÇÕES, COM TRANSMISSÃO AUTOSSÓMICA DOMINANTE - NOTA: OS MEMBROS DA FAMÍLIA PODEM TER SIDO MAL DIAGNOSTICADOS COMO DM TIPO 1 OU TIPO 2	SENSIBILIDADE MARCADA A SECRETAGOGOS DE INSULINA (SULFONILUREIAS). SUBTIPOS HNF 1ALFA E HNF 4ALFA	MODY2 PODE SE APRESENTAR COMO DM GESTACIONAL EM GESTANTE COM HIPERGLICEMIA MODERADA EM RASTREIO PRÉ-NATAL, PORTANTO, A HISTÓRIA FAMILIAR DEVE SER TIDA EM CONSIDERAÇÃO.

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


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