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ORIGINAL RESEARCH

Insulin resistance is increased in adult patients with dermatomyositis

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OBJECTIVE: To evaluate insulinemia in glucocorticoid naïve patients with dermatomyositis and to evaluate insulin resistance using the homeostatic model assessment of insulin resistance (HOMA2-IR).
METHODS: This cross-sectional study included 25 dermatomyositis, non-diabetic glucocorticoid naïve patients. The control group consisted of 50 volunteers matched for age, gender, ethnicity, weight and height. The HOMA2-IR index was calculated from baseline insulin and glucose data. The International Myositis Assessment & Clinical Studies Group (IMACS) parameters were used to evaluate disease status.
RESULTS: Mean age of the patients was 43.5 years and these were predominantly females. Patients had low disease activity according to IMACS parameters. Higher body mass index and waist circumference were observed in the dermatomyositis group compared to the control group. Insulin level and HOMA2-IR were also higher in patients with dermatomyositis. Moreover, analyzing dermatomyositis alone, the HOMA2-IR index correlated positively with weight, body mass index and waist circumference and was independent on disease status parameters.
CONCLUSIONS: Patients with dermatomyositis had higher values for basal insulinemia, insulin resistance, body mass index and waist circumference. Moreover, HOMA2-IR moderately correlated with these anthropometric parameters. These metabolic abnormalities are related to the development of metabolic syndrome, one of the main comorbidities observed in dermatomyositis.

KEYWORDS: Glucose; insulin resistance; dermatomyositis; metabolic syndrome; myositis.

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INTRODUCTION

Dermatomyositis (DM) is a systemic autoimmune myopathy subtype associated with high morbidity and mortality. Clinical manifestations include symmetrical muscle weakness of limbs and cutaneous lesions, including heliotrope rash and Gottron's papules.[1-4] Moreover, extra-skeletal manifestations can also occur such as joint, pulmonary, gastrointestinal and/or cardiorespiratory involvement.[2-4]

Recent studies have shown a high prevalence of metabolic syndrome[5-8] and basal insulinemia[5,6] in systemic autoimmune myopathies. However, these parameters were assessed in patients with different glucocorticoid regimens. Since high serum levels of insulin are associated with resistance to the action of this hormone,[9] it is important to evaluate whether, as in other autoimmune diseases, patients with DM have increased insulin resistance and whether this parameter is associated with clinical manifestations of the disease.

The homeostatic model assessment of insulin resistance (HOMA-IR) is a mathematical model used to assess insulin resistance based on basal glycaemia and insulin.[10] This method is straightforward and affordable for use in routine clinical practice. Recently, the model was updated (HOMA2-IR) providing a more accurate index.[11] However, to our knowledge, no studies evaluating the potential of HOMA2-IR for identifying insulin resistance in DM patients have been reported.

Therefore, the objective of this study was to evaluate insulin resistance using the HOMA2-IR model in DM patients without glucocorticoid therapy regimens.

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MATERIALS AND METHODS

This cross-sectional study was performed at a single center and initially included 71 consecutive patients with DM (age ≥ 18 years) enrolled between January 2012 and July 2016 who fulfilled all of the Bohan and Peter criteria items[1] and were regularly followed at our Myopathy Unit.

As inclusion criteria, only patients who were glucocorticoid naïve or not in use of the medication for the last 3 months were included in the present study. Patients with clinically amyopathic DM, cancer-associated myositis, acute and/or chronic infections, liver and renal diseases, hypothyroidism, diabetes mellitus, in use of antimalarial drugs or statins were excluded. Therefore, 25 out of the initial 71 patients with DM were included in the study along with 50 volunteers matched for age, gender, ethnicity, weight and height, selected in the same period.

The study was approved by the institutional Ethics Committee (case # 01445312.3.0000.0068).

All participants underwent a clinical evaluation that included a standardized interview, and charts, which were extensively reviewed.

Demographic data included current age, age at disease onset, gender, ethnicity, disease duration, waist circumference, weight, height and body mass index (BMI: weight/height^2 - kg/m^2). Clinical data included cutaneous manifestations, such as heliotrope rash, Gottron's papules, Raynaud's phenomenon, "V-neck" sign, facial rash, vasculitis, ulcers, "shawl" sign and calcinosis. Comorbidities and lifestyle evaluation, such as systemic arterial hypertension and tobacco use were also recorded.

Laboratory evaluation. A blood sample (15 mL) obtained from each participant after a 12-hour overnight fast was collected and immediately (< 30 min) centrifuged at 3000 rpm for 10 minutes at 4°C, and processed. The following laboratory data were analyzed: serum levels of creatine phosphokinase (reference value: 26 - 192 U/L), aldolase (≤ 7.6 U/L), alanine aminotransferase (< 31 U/L), aspartate aminotransferase (< 31 U/L), lactate dehydrogenase (135 - 214 U/L), fasting blood glucose (≤ 100 mg/dL) and insulin (≤ 25 μU/mL). Insulin resistance was defined by the HOMA2-IR model.[11,12] Antinuclear antibodies were detected by indirect immunofluorescence using HEp-2 cells as substrate. Anti-Mi-2 autoantibody was determined using a commercial kit (Myositis Profile 3, Euroimmun, Germany) according to the manufacturer's protocol. The evaluation of the anti-Mi-2 results was based on the methods established in a previous study.[13]

Disease status. Was evaluated by the following questionnaires and scores: global assessment of the disease (by physician and patient) using the visual analogue scale (VAS),[14] Manual Muscle Testing (MMT-8)[15] Health Assessment Quality (HAQ)[16] and Myositis Disease Activity Assessment Visual Analogue Scales (MYOACT).[17] Therapy data included the use of immunosuppressive drugs.

Statistical analysis. The Kolmogorov-Smirnov test was used to evaluate the distribution of each parameter. Data were expressed as mean ± standard deviation (SD) for continuous variables or as frequencies and percentages (%) for categorical variables. The median (25^{th} - 75^{th} interquartile range) was calculated for continuous variables that were non-normally distributed. Comparisons between patient vs. control parameters were made using Student's *t*-test or the Mann-Whitney test for continuous variables; the Chi-squared test or Fisher's exact test were used to evaluate the categorical variables. Correlations among the parameters were analyzed by Spearman correlation. All of the analyses were performed using the SPSS 15.0 statistics software (Chicago, USA). A value of $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Twenty-five DM patients and 50 healthy controls were evaluated; controls were matched to patients for mean age, ethnicity, gender, weight and height distribution and thus were comparable between the two groups (Table 1). Mean age at disease onset was 40.7 years, with a median period of symptoms prior to diagnosis of 4 months.

Concerning anthropometric parameters, BMI and waist circumference were higher in DM patients compared to controls.

The main cutaneous involvement was heliotrope rash followed by: Gottron's papules, Raynaud's phenomenon, "V-neck" sign, facial rash, vasculitis, ulcers and "shawl" sign. There were no cases with calcinosis.

In general, the patients included in the present study had low disease activity, with median MMT-8 of 80, HAQ of 0.00, patient VAS of 1.0 cm, physician VAS of 0.0 cm, MYOACT of 0.4 and low serum level of muscle enzymes.

The presence of antinuclear and anti-Mi-2 antibodies was 60.0 and 12.0%, respectively.

There was no difference between groups regarding systemic arterial pressure or tobacco use.

Nine patients (36.0%) were using immunosuppressive azathioprine: 2 – 3 mg/kg/day and/or methotrexate: (15 - 20 mg/week) as monotherapy or in combination.

Higher serum levels of insulin and HOMA2-IR were observed in DM patients, compared to controls, with similar levels of glucose.

Further analysis of DM patients revealed that the HOMA2-IR was moderately correlated with weight, BMI and waist circumference (Figure 1).

DISCUSSION

The present study showed that the patients with DM had higher values of insulinemia and insulin resistance compared to healthy individuals. Moreover, analyzing

Table 1. General features of patients with dermatomyositis and healthy controls.

Parameters	DM (n = 25)	Control (n = 50)	*P* value
Current age (years)	43.5±15.2	43.4±11.2	0.968
White ethnicity	16 (64.0)	32 (64.0)	>0.999
Female gender	19 (76.0)	38 (76.0)	>0.999
Age at disease onset (years)	40.7±15.2	-	-
Duration: diagnosis - symptoms (months)	4.0 (2.3-7.8)	-	-
Anthropometric parameters			
Weight (kg)	76 (65-87)	66 (58-74)	0.087
Height (cm)	162 (158-168)	165 (157-168)	0.408
BMI (kg/cm^2)	28.9 (23.5-32.0)	24.2 (23.5-26.2)	0.037
Waist circumference (cm)	99.5 (85.0-107.0)	82.0 (78.0-90.0)	0.003
Cutaneous involvement			
Heliotrope rash	23 (93.0)	-	-
Gottron's papules	23 (92.0)	-	-
Raynaud' phenomenon	12 (48.0)	-	-
"V-neck" sign	9 (36.0)	-	-
Facial rash	15 (20.0)	-	-
Vasculitis	5 (20.0)	-	-
Ulcers	4 (16.0)	-	-
"Shawl" sign	3 (12.0)	-	-
Calcinosis	0	-	-
MMT-8 (0-80)	80 (74-80)		
HAQ (0.00-3.00)	0.00 (0.00-0.43)	-	-
Patient VAS (0-10 mm)	1.0 (0.0-5.0)	-	-
Physician VAS (0-10 mm)	0.0 (0.0-3.5)	-	-
MYOACT (0-70)	0.4 (0.0-2.0)		
Creatine phosphokinase (U/L)	155 (74-402	100 (72-146)	0.041
Aldolase (U/L)	5.1 (3.6-6.8)	3.6 (2.8-4.4)	<0.001
Lactic dehydrogenase (U/L)	400 (333-596)	359 (318-400)	0.036
Alanine aminotransferase (U/L)	22 (15-52)	16 (13-21)	0.003
Aspartate aminotransferase (U/L)	26 (19-43)	20 (17-23)	0.020
Antinuclear antibody	15 (60.0)	-	-
Anti-Mi-2 antibody	3 (12.0)	-	-
Systemic arterial hypertension	8 (32.0)	8 (16.0)	0.139
Tobacco use	2 (8.0)	9 (18.0)	0.318
Glucocorticoid	0	0	>0.999
Immunossupressive	9 (36.0)	0	-
Glucose (mg/dL)	85 (78-94)	80 (70-89)	0.084
Insulin (μU/mL)	11.4 (7.8-18.8)	6.4 (5.0-8.0)	<0.001
HOMA2-IR	2.35 (1.38-4.33)	1.20 (0.90-1.70)	<0.001

Results expressed as mean ± standard deviation, median (25th - 75th interquartile range) or percentage (%).
DM: Dermatomyositis; BMI: Body Mass Index; HAQ: Health Assessment Questionnaire; HOMA2-IR: Updated version of Homeostatic Model Assessment of Insulin Resistance; MMT: Manual Muscle Testing; MYOACT: Myositis Disease Activity Assessment Visual Analogue Scales; VAS: Visual Analogue Scales.
Immunosuppressive agents: azathioprine (2 – 3 mg/kg/day) and/or methotrexate (15 - 20 mg/week).

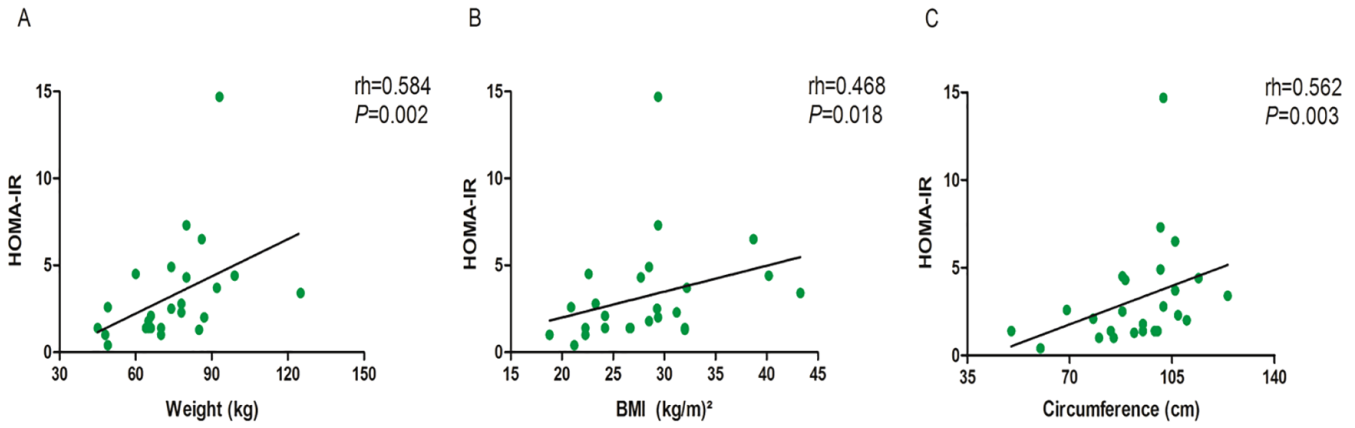

Figure 1. Correlation of HOMA2-IR with weight, body mass index (BMI) and waist circumference in patients with dermatomyositis. HOMA2-IR: Updated version of Homeostatic Model Assessment of Insulin Resistance; BMI: Body Mass Index.

patients with DM alone, the HOMA2-IR correlated significantly with weight, BMI and waist circumference.

Previous studies have shown a high prevalence of metabolic syndrome and basal insulinemia in DM.[5,6] However, these parameters were assessed in the patients with different glucocorticoid therapy regimens. By contrast, the present study included only patients who were glucocorticoid naïve, or not in use of the medication for the last 3 months.

Insulin resistance is highly prevalent in autoimmune rheumatic diseases.[17-21] Waist circumference, BMI and obesity seem to be the main factors contributing to increased insulin resistance in these diseases.[22,23] For instance, BMI and waist circumference were found to be significantly associated with the HOMA2-IR in systemic lupus erythematosus.[22] In rheumatoid arthritis, obesity is the main determinant of insulin resistance, even more than the circulating pro-inflammatory cytokines levels.[23]

The present study corroborates the growing body of evidence suggesting that insulin resistance in autoimmune rheumatic diseases is independent of the diseases and is, instead, caused by associated risk factors.[22,23]

Several factors can contribute to the high BMI and waist circumference found in these patients. The use of glucocorticoids could be associated with an increase in visceral fat and waist circumference.[23] However, because patients on glucocorticoid therapy were not included in the present study, other factors may have contributed to the increased waist circumference and BMI seen in these patients.

In this scenario, patients with autoimmune rheumatic diseases show marked sedentary behavior and physical inactivity, risk factors which seem to be frequently overlooked in these patients.[24] This behavior, in turn, can lead to an increase in BMI and waist circumference, which further contributes to increased insulin resistance.[25] However, in the present study, we do not measure physical activity levels in the patients with DM, or if this outcome correlates with IR in these patients. Thus, more studies are necessary for further extrapolations. Increased BMI and waist circumference are associated with an increase in pro-inflammatory cytokines, such as TNF-α and IL-1β, two cytokines capable of impairing insulin signaling.[26-28] Furthermore, an increase in visceral fat and waist circumference is associated with activation of toll-like receptors (TLR).[29] TLR signaling pathways exacerbate the pro-inflammatory response, and might contribute to the development of obesity-associated insulin resistance.[29,30]

Recent studies have shown that metabolic syndrome is highly prevalent in patients with DM.[5,6] Metabolic syndrome, a clinically relevant condition, is defined as the presence of at least three risk factors for cardiovascular disease, including visceral obesity, dyslipidemia, hypertension and insulin resistance, with this last factor representing a central component of this disorder.[6]

The elevated levels of insulinemia and insulin resistance found in the present study, associated with the higher prevalence of metabolic syndrome, further confirm that patients with DM have a higher cardiovascular risk, independent of disease activity. Thus, strategies capable of attenuating this outcome, and consequently lowering cardiovascular risk, should be employed in this group of patients.

The present study has some limitations. A complementary analysis of the lipid profile, of acute reactant factors and also of some pro-inflammatory serum cytokines were not performed.

SUMMARY

Patients with DM show higher values of basal insulinemia and insulin resistance. Moreover, the HOMA2-IR correlates with weight, BMI and waist circumference in DM. These metabolic abnormalities are related to the development of metabolic syndrome, one of the main comorbidities observed in dermatomyositis.

AUTHOR CONTRIBUTION

D S Oliveira: reviewing literature, executing and writing the present article.

M G Silva: reviewing literature, executing and writing the present article.

S K Shinjo: planning, reviewing literature, executing and writing the present article.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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RESISTÊNCIA INSULÍNICA AUMENTADA EM PACIENTES COM DERMATOMIOSITE

OBJETIVO: Avaliar a insulinemia em pacientes com dermatomiosite virgens de glicocorticoide e avaliar a resistência insulínica, utilizando o modelo de avaliação da homeostase de resistência insulínica (HOMA2-IR).

MÉTODOS: Este estudo transversal incluiu 25 pacientes com dermatomiosites, não-diabéticos e sem uso prévio de glicocorticoides. Para o grupo de controle, 50 voluntários foram pareados por idade, gênero, etnia, peso e estatura. O índice HOMA2-IR foi calculado a partir de dados basais de insulina e glicose. Os parâmetros do International Myositis Assessment & Clinical Studies Group (IMACS) foram utilizados para avaliar o status da doença.

RESULTADOS: A méda de idade dos pacientes foi de 43,5 anos, predominantemente do sexo feminino. Os pacientes apresentaram baixa atividade de doença de acordo com os parâmetros do IMACS. O índice de massa corporal e a circunferência da cintura foram maiores no grupo da dermatomiosite em comparação com o grupo controle. O nível de insulina e o HOMA2-IR também foram maiores em pacientes com dermatomiosite. Além disso, analisando a dermatomiosite isoladamente, o índice HOMA2-IR correlacionou-se positivamente com o peso, o índice de massa corporal e a circunferência da cintura e foi independente dos parâmetros de status da doença.

CONCLUSÕES: Pacientes com dermatomiosite apresentam valores mais elevados de insulinemia basal, resistência à insulina, índice de massa corporal e circunferência da cintura. Além disso, o HOMA2-IR está moderadamente correlacionado com esses parâmetros antropométricos. Essas anormalidades metabólicas estão relacionadas ao desenvolvimento da síndrome metabólica, uma das principais comorbidades observadas na dermatomiosite.

PALAVRAS-CHAVE: Glicose; resistência a insulina; dermatomiosite; síndrome metabólica; miosite.

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